ALNYLAM PHARMACEUTICALS, INC.
Form 424B5
November 13, 2017
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The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-217688

Subject to completion, dated November 13, 2017

Preliminary Prospectus Supplement

(To Prospectus dated May 5, 2017)

$675,000,000

Common Stock

We are offering up to $675,000,000 of our common stock.

Our common stock trades on The Nasdaq Global Select Market under the trading symbol ALNY . On November 10, 2017, the last reported sale price of our common stock on The Nasdaq Global Select Market was $139.98 per share.

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

We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to an additional $101,250,000 of our common stock at the public offering price, less the estimated

underwriting discounts and commissions.

We estimate the expenses of this offering, excluding underwriting discounts and commissions, will be approximately $400,000.

Investing in our common stock involves risks. See Risk Factors beginning on page S-7 of this prospectus supplement.

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

The underwriters expect to deliver the shares to purchasers on or about November , 2017.

Joint book-running managers

Goldman Sachs & Co. LLC **J.P. Morgan** **Barclays**

Lead manager

Credit Suisse

November , 2017

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About this prospectus supplement

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

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

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

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless the context otherwise indicates, references in this prospectus to Alnylam, we, our, us, the Company and s designations refer, collectively, to Alnylam Pharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiaries. Alnylam is a trademark of Alnylam Pharmaceuticals, Inc. Our logo, trademarks and service marks are

property of Alnylam. All other trademarks or service marks appearing in this prospectus supplement are the property of their respective holders.

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Special note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical facts, that we include in this prospectus supplement, the accompanying prospectus and in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus may be deemed forward-looking statements for purposes of the Securities Act and the Exchange Act. We use words such as believe, expect, anticipate, may, could, intend, will, plan, target estimate, project, will, would and similar expressions to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These statements appear throughout this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus and are statements regarding our current intent, belief or expectation, primarily with respect to our operations and related industry developments. Examples of these statements include, but are not limited to, statements regarding the following: our views with respect to the potential for RNAi therapeutics; the progress of our research and development programs; our current and anticipated clinical trials and expectations regarding the reporting of data from these trials; our expectations regarding potential product characteristics of, market size for, and the successful commercialization of, the product candidates we are developing; the timing of regulatory filings and interactions with regulatory authorities and our ability to obtain and maintain regulatory approval, pricing and reimbursement for our products; the status of our manufacturing operations and the construction of our manufacturing facility; our progress in establishing a commercial and ex-United States infrastructure; our ability to manage our growth and operating expenses; our expectations regarding our STAr pipeline growth strategy and our Alnylam 2020 guidance for the advancement and commercialization of RNAi therapeutics; our corporate collaborations, including potential future licensing fees and milestone and royalty payments; protection of our intellectual property; the outcome of litigation; the sufficiency of our cash resources; the timing and likelihood of regulatory approvals; and our operations and legal risks. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and, accordingly, you should not place undue reliance on our forward-looking statements. There are a number of important factors that could cause actual results or events to differ materially from those expressed or implied by these forward-looking statements, including those discussed under Risk factors and elsewhere in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

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

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Prospectus supplement summary

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

Alnylam Pharmaceuticals, Inc.

Our business

We are a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for selectively silencing and regulating the expression of specific genes. Our research and development strategy focuses primarily on the use of our proprietary N-acetylgalactosamine, or GalNAc-conjugate platform for delivery of small interfering RNAs, or siRNAs the molecules that mediate RNAi toward genetically validated, liver-expressed target genes involved in the cause or pathway of human diseases.

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 innovative medicines, and that this potential new drug class is similar to the opportunity created with other major biological discoveries such as recombinant DNA and monoclonal antibodies. Using our intellectual property and expertise, we are developing what we believe to be a reproducible and modular platform to develop RNAi therapeutics for a variety of human diseases. Our development strategy is focused on clinical indications where there are high unmet needs, early biomarkers for the assessment of clinical activity in Phase 1 clinical studies, and a definable path for drug development, regulatory approval, patient access and commercialization.

Specifically, our broad pipeline of investigational RNAi therapeutics is focused in three Strategic Therapeutic Areas, or STArs: Genetic Medicines, with multiple product candidates for the treatment of rare diseases; Cardio-Metabolic Diseases, with product candidates directed toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases; and Hepatic Infectious Diseases, with product candidates designed to address the major global health challenges of hepatic infectious diseases, beginning with hepatitis B and hepatitis D viral infections. We are focused on advancement of our *Alnylam 2020* strategy for the development and commercialization of RNAi therapeutics as a potential new class of innovative medicines. Specifically, our goal is to achieve, by the end of 2020, a company profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArs. Our most advanced investigational RNAi therapeutic, patisiran, targets the transthyretin, or TTR, gene for the treatment of patients with hereditary TTR-mediated amyloidosis, or hATTR amyloidosis. In early November 2017, we reported positive complete results from our APOLLO Phase 3 study of patisiran. Based on the positive APOLLO data, we plan to submit our first new drug application, or NDA, in the United States for patisiran by the end of 2017, where Fast Track Designation has been granted. We also intend to file a marketing authorization application, or MAA, in the European Union, or EU, around the end of 2017. The Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, has granted an accelerated assessment for patisiran. In addition, our partner, Sanofi Genzyme, the specialty care global business unit of Sanofi, is currently preparing for regulatory filings for patisiran in Japan, Brazil and other countries, beginning in the first half of 2018. Pending regulatory approvals, we intend to commercialize patisiran in the United States, Canada and Western Europe, with Sanofi Genzyme commercializing the product in the rest of the

world.

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We are also advancing fitusiran, an investigational RNAi therapeutic targeting antithrombin (AT) in development for the treatment of hemophilia and rare bleeding disorders. In July 2017, we announced the initiation of our ATLAS Phase 3 program for fitusiran. This global, multicenter clinical program is designed to evaluate the safety and efficacy of fitusiran in three separate trials, including patients with hemophilia A and B with or without inhibitors. In September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic serious adverse event, or SAE, and agreement with regulatory authorities on a risk mitigation strategy. In November 2017, we announced that we have reached alignment with study investigators and the United States Food and Drug Administration, or FDA, on safety measures and a risk mitigation strategy to enable resumption of dosing in clinical studies with fitusiran, including our Phase 2 open label extension, or OLE, study and the ATLAS Phase 3 program. Following regulatory and institutional review and approval of amended study protocols and other clinical materials implementing these measures, we intend to resume our fitusiran studies as soon as possible. In addition, in November 2017, we announced that we have initiated our ENVISION Phase 3 clinical study of givosiran for the treatment of acute hepatic porphyrias. Finally, in November 2017, our partner The Medicines Company, or MDCO, announced that it has initiated its Phase 3 program to study inclisiran, an investigational RNAi therapeutic targeting PCSK9 in development for the treatment of hypercholesterolemia, in patients with atherosclerotic cardiovascular disease, or ASCVD.

Based on our expertise in RNAi therapeutics and broad intellectual property estate, we have formed alliances with leading pharmaceutical and life sciences companies to support our development and commercialization efforts, including Sanofi Genzyme, the specialty care global business unit of Sanofi, MDCO and Vir Biotechnology, or Vir.

Commercial Operations

After years successfully meeting challenges such as discovering a new product platform technology, solving drug delivery, and developing a potential new class of innovative medicines while retaining broad commercial rights, we now embark on the next part of the journey - introducing our RNAi therapeutics to as many eligible patients in need as possible. To meet that new challenge, we have started to build a global commercial operation which will be fully integrated and ready to sequentially manage the potential of multiple product launches across multiple geographies. As a commercial-stage biopharmaceutical company, we intend to leverage the internal knowledge accumulated at Alnylam as well as hire talented individuals from the industry to commercialize our products ourselves in as many countries as possible. The conduct of these commercial activities will be dependent upon regulatory approvals and on agreements that we have made or may make in the future with strategic collaborators, currently as follows with respect to our late-stage clinical programs:

- For patisiran, if approved by regulatory authorities, we have rights to commercialize in the United States, Canada and Western Europe while Sanofi Genzyme has rights to commercialize in the rest of the world;

- For fitusiran, if our ATLAS Phase 3 trials are positive following resumption of patient dosing, we have rights to co-commercialize with Sanofi Genzyme in the United States, Canada and Western Europe, and Sanofi Genzyme has rights to commercialize in the rest of the world;

- For givosiran, we retain global rights to commercialize; and

For inclisiran, we have granted MDCO global rights to commercialize.

Throughout the development of our product candidates, we have remained focused on keeping patients at the center of everything we do. This patient focus will continue as we transition towards commercialization. Moreover, the late stage programs we are commercializing are focused on orphan diseases, and these patients and their families are often in need of more than just a product. It is our goal to identify information, education solutions and services that benefit these patients and their families, and to have a rich patient services approach in these orphan diseases. In addition, we are focused early in the product development cycle on establishing evidence that we can bring to payors about the overall burden of disease and pharmacoeconomic opportunities that our product candidates represent to ensure access for patients.

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Planning ahead of regulatory approval, we are assembling the key components of a commercial organization with a focus on preparation for the potential commercial launch of patisiran in 2018, assuming regulatory approval is obtained. We have started assembling a focused commercial team with broad experience in marketing, sales, patient access, patient services, distribution and product reimbursement, in particular for orphan diseases. As we continue to prepare for a potential patisiran commercial launch in the United States, Canada and Western Europe, we plan to continue to expand our commercial organization over the next six to twelve months. This expansion will include incorporation of appropriate quality systems, compliance policies, systems and procedures, implementation of internal systems and infrastructure in order to support commercial sales, and establishment of patient-focused programs. In the coming months, we will also continue to expand our footprint in major European markets with the hiring of country general managers, medical experts, market access professionals and marketing and sales professionals. Our objective is to be ready on time to execute successful product launches. For some territories/countries, we may also elect to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products.

Company information

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

The offering

Common stock offered	shares
Common stock to be outstanding after this offering	shares
Option to purchase additional shares offered to the underwriters	The underwriters have an option to purchase a maximum of an additional $101,250,000 of our common stock from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus supplement.
Use of proceeds	We intend to use the net proceeds from this offering for general corporate purposes, including clinical trial costs and other research and development expenses, continued growth of our manufacturing, quality, commercial and medical affairs capabilities to support our transition toward a commercial-stage biopharmaceutical company, the anticipated commercial launches of patisiran, givosiran and fitusiran across several continents, assuming favorable regulatory reviews, the expected commercial expansion beyond the United States, Canada and Western Europe for givosiran and other potential future products, the potential expansion of patisiran commercialization efforts in mixed phenotype populations, assuming consistent product labelling, potential repayment of outstanding indebtedness, potential acquisitions, investments or licenses in businesses, products or technologies that are complementary to our own, working capital, capital expenditures and general and administrative expenses. See Use of proceeds.

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Risk factors	You should read the Risk factors section of this prospectus supplement beginning on page S-7 for a discussion of factors to consider before deciding to purchase shares of our common stock.
The Nasdaq Global Select Market symbol	ALNY

The number of shares of our common stock to be outstanding after this offering is based on 92,730,812 shares outstanding as of October 31, 2017, and excludes:

- 11,647,871 shares of common stock issuable upon the exercise of outstanding stock options at a weighted-average exercise price of $60.20 per share as of October 31, 2017;
- 158,326 shares of common stock reserved for issuance upon settlement of restricted stock units as of October 31, 2017; and
- an aggregate of 4,250,212 additional shares of common stock reserved for future issuance under our 2009 stock incentive plan, our 2004 stock incentive plan and our 2004 employee stock purchase plan as of October 31, 2017.

Except as otherwise noted, we have presented the information in this prospectus supplement assuming no exercise by the underwriters of the option to purchase up to an additional $101,250,000 of our common stock in this offering.

Sanofi Genzyme, one of our existing stockholders and collaboration partners, had a right to purchase directly from us, in a concurrent private placement, the number of shares needed to maintain its current ownership percentage of our common stock of approximately 11 percent at the public offering price, but has informed us that it has elected not to exercise this right.

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Risk factors

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

Risks Related to Our Business

Risks Related to Being a Clinical Stage Company

Although we have product candidates in late stage clinical development, there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies in the biopharmaceutical industry.

Although we have product candidates in late stage clinical development, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

- execute product development activities using unproven technologies related to both RNAi and to the delivery of siRNAs to the relevant tissues and cells;
- build and maintain a strong intellectual property portfolio;
- gain regulatory acceptance for the development and commercialization of our product candidates and market success for any products we commercialize;
- develop and maintain successful strategic alliances; and
- manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

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

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

We have concentrated our efforts and therapeutic product research and development on RNAi technology and our future success depends on the successful development of this technology and products based on it. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is still limited. Skepticism as to the feasibility of developing RNAi therapeutics has been expressed in scientific literature. For example, there are potential challenges to achieving safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response. In addition, decisions by other companies with respect to their RNAi development efforts or their adoption of different or related technologies and the potential success of any such different or related technologies may increase skepticism in the marketplace regarding the potential for RNAi therapeutics.

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Relatively few product candidates based on these discoveries have ever been tested in humans. siRNAs may not naturally possess the inherent properties typically required of drugs, such as the ability to be stable in the body, or the ability to enter cells within relevant tissues in order to exert their effects. We currently have limited data to suggest that we can introduce these properties into siRNAs. We have spent and expect to continue to spend large amounts of money developing siRNAs that possess the properties typically required of drugs, and to date, we have only taken one product candidate through Phase 3 development. In addition, these compounds may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies, and they may interact with human biological systems in unforeseen, ineffective or harmful ways. For example, in October 2016, we discontinued development of revusiran, an investigational RNAi therapeutic that was in development for the treatment of patients with cardiomyopathy due to hATTR amyloidosis, due to safety concerns. We conducted a comprehensive evaluation of the revusiran data and reported the results of this evaluation in August 2017, however, our investigation did not result in a conclusive explanation regarding the cause of the mortality imbalance observed in the ENDEAVOUR Phase 3 study. We may not succeed in developing products that gain regulatory approval and succeed in the marketplace, we may not become profitable and the value of our common stock will decline.

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

Risks Related to Our Financial Results and Need for Financing

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

We have experienced significant operating losses since our inception. At September 30, 2017, we had an accumulated deficit of $2.01 billion. To date, we have not received regulatory approval to market or sell any products nor generated any revenues from the sale of products. Further, we do not expect to generate any product revenues until at the earliest 2018, assuming we receive marketing approval for patisiran. We expect to continue to incur annual net operating losses over the next several years and will require substantial resources over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics. Until we are successful in obtaining regulatory approval for our product candidates and successful in commercializing such products, we anticipate that a significant portion of any revenues we generate over the next several years will be from alliances with pharmaceutical and biotechnology companies, but cannot be certain that we will be able to maintain our existing alliances or secure and maintain new alliances, or meet the obligations or achieve any milestones that we may be required to meet or achieve to receive payments. We anticipate that revenues derived from such sources will not be sufficient to make us consistently profitable.

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

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

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development, including pre-clinical testing and clinical trials of our product candidates, and

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to manufacture, market and sell any products that are approved for commercial sale. Because we cannot be certain of the length of time or activities associated with successful development of our product candidates, we are unable to estimate the actual funds we will require to develop and commercialize them.

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

- our progress in demonstrating that siRNAs can be active as drugs and achieve desired clinical effects;
- progress in our research and development programs, as well as what may be required by regulatory bodies to advance these programs;
- the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, if any;
- our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;
- the resources, time and costs required to successfully initiate and complete our pre-clinical and clinical studies, obtain regulatory approvals, prepare for commercialization of our product candidates and obtain and maintain licenses to third-party intellectual property;
- our ability to establish, maintain and operate our own manufacturing facilities in a timely and cost effective manner;
- our ability to manufacture, or contract with third parties for the manufacture of, our product candidates for clinical testing and commercial sale;
- the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;
- the costs associated with legal activities, including litigation, arising in the course of our business activities and our ability to prevail in any such legal disputes; and
- the timing, receipt and amount of sales and royalties, if any, from our potential products.

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

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

In April 2016, our subsidiary, Alnylam U.S., Inc., entered into an aggregate of $150.0 million in term loan agreements, for which we are the guarantor, related to the build out of our new drug substance manufacturing facility, that mature in April 2021. Interest on the borrowings is calculated based on LIBOR plus 0.45 percent. During an event of default under either agreement, the obligations under such agreement will bear interest at a rate per annum equal to the interest rate then in effect plus two percent. The obligations under the term loan agreements are secured by cash collateral in an amount equal to, at any given time, at least 100 percent of the principal amount of all term loans outstanding under the credit agreements at such time. The agreements include restrictive covenants that could limit our flexibility in conducting future business activities and further limit our ability to change the nature of our business and, in the event of insolvency, the lenders would be paid before holders of equity securities received any distribution of corporate assets. If an event of default occurs, the interest rate would increase and the lenders would be entitled to take various actions, including the acceleration of amounts due under the loan. Our ability to satisfy our obligations under these agreements and meet our debt service obligations will depend upon our future performance, which will be subject to financial, business and other factors affecting our operations, many of which are beyond our control.

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In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our existing stockholders will result. In addition, as a condition to providing additional funding to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Moreover, our investor agreement with Sanofi Genzyme provides Sanofi Genzyme with the right, subject to certain exceptions, generally to maintain its ownership position in us until Sanofi Genzyme owns less than 7.5 percent of our outstanding common stock, subject to certain additional limited rights of Sanofi Genzyme to maintain its ownership percentage. In accordance with the investor agreement, to date, Sanofi Genzyme has exercised its right to purchase an additional 344,448 shares of our common stock in connection with our acquisition of Sirna in March 2014, an aggregate of 401,281 shares of our common stock based on its 2014 and 2015 compensation-related rights and an aggregate of 1,042,067 shares of our common stock in connection with our public offerings in January 2015 and May 2017. These purchases allowed Sanofi Genzyme to maintain its ownership level of our outstanding common stock. Sanofi Genzyme currently holds approximately 11 percent of our outstanding common stock. While the exercise of these rights by Sanofi Genzyme has provided us with an additional $147.7 million in cash to date, and while any exercise of these rights by Sanofi Genzyme in the future will provide us with further additional cash, these exercises have caused, and any future exercise of these rights by Sanofi Genzyme will also cause further, dilution to our stockholders. In January 2017, Sanofi Genzyme elected not to exercise its 2016 compensation-related right and in November 2017, Sanofi Genzyme informed us that it has elected not to exercise its right to purchase additional shares in connection with this public offering. In November 2016, Sanofi Genzyme elected to expand its regional rights for fitusiran and opt-in to co-develop and co-commercialize fitusiran in the United States, Canada and Western Europe, in addition to developing and commercializing the product in the rest of the world. In connection with the exercise of this right, Sanofi Genzyme paid us in January 2017 for its incremental share of co-development costs incurred from January 2016 to September 2016, in accordance with the 2014 Sanofi Genzyme collaboration. Going forward, Sanofi Genzyme will share in 50 percent of certain development and sales and marketing costs for fitusiran, which will result in increased expense reimbursement to us. Sanofi Genzyme also has a right to elect a co-development/co-commercialize license for ALN-TTRsc02.

If we are unable to obtain additional funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs or undergo future reductions in our workforce or other corporate restructuring activities, and our ability to achieve our strategy for 2020 may be delayed or diminished. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own.

If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements prove inaccurate, our actual results may vary from those reflected in our projections and accruals.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct.

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

At September 30, 2017, we had $999.8 million in cash, cash equivalents and fixed income marketable securities, excluding the $150.0 million of restricted investments related to our term loan agreements. We historically have

invested these amounts in high grade corporate notes, commercial paper, securities issued or sponsored by the U.S. government, certificates of deposit and money market funds meeting the criteria of our investment policy, which is focused on the preservation of our capital. Corporate notes may also include foreign bonds denominated

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in U.S. dollars. These investments are subject to general credit, liquidity, market and interest rate risks. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our consolidated financial statements. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition.

Risks Related to Our Dependence on Third Parties

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

We currently are developing capabilities for sales or distribution and also have early capabilities for marketing, sales and market access, as well as limited capacity for drug development due to our growing pipeline of RNAi therapeutic opportunities. Accordingly, we have entered into alliances with other companies and collaborators that we believe can provide such capabilities in certain territories, and we intend to enter into additional such alliances in the future. Our collaboration strategy is to form alliances that create significant value for us and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Sanofi Genzyme in 2014 pursuant to which we retain development and commercial rights for our current and future Genetic Medicine products in the United States, Canada and Western Europe, and Sanofi Genzyme has the right to develop and commercialize our current and future Genetic Medicine products principally in the rest of the world, subject to certain broader rights. With respect to our Cardio-Metabolic Disease pipeline, we intend to seek future strategic alliances for these programs, under which we may retain certain product development and commercialization rights, or we may structure as global alliances, as we did in our collaboration with MDCO to advance inclisiran. In October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic hepatitis B virus infection.

In such alliances, we expect our current, and may expect our future, collaborators to provide substantial capabilities in clinical development, regulatory affairs, and/or marketing, sales and distribution. Under certain of our alliances, we also may expect our collaborators to develop, market and/or sell certain of our product candidates. We may have limited or no control over the development, sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties. For example, we will rely entirely on (i) Sanofi Genzyme for the development and commercialization of patisiran, fitusiran and potentially other of our Genetic Medicine programs in territories outside of the United States, Canada and Western Europe, and (ii) MDCO for all future development and commercialization of inclisiran worldwide. If Sanofi Genzyme and/or MDCO are not successful in their commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected. Sanofi Genzyme has a right to elect a co-development/co-commercialize license for ALN-TTRsc02. Sanofi Genzyme also has the right to elect one global license for a future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of our 2014 collaboration. Sanofi Genzyme could elect its global license for lumasiran (ALN-GO1), an investigational RNAi therapeutic targeting glycolate oxidase for the treatment of primary hyperoxaluria type 1. If Sanofi Genzyme elects to take a global license to lumasiran or another of our programs, we will no longer control the development of such program and any revenues we receive will depend solely on the success of Sanofi Genzyme s efforts. In addition, Sanofi Genzyme may elect not to opt into one or more of our Genetic Medicine programs. For example, during 2016, Sanofi Genzyme elected not to take a regional license for our givosiran and cemdisiran (ALN-CC5) programs. While we intend to advance these programs independently, retaining global development and commercial rights, our ability

to advance these programs and successfully develop and commercialize these product candidates may be adversely affected as a result of Sanofi Genzyme s decision.

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We may not be successful in entering into future alliances on terms favorable to us due to various factors, including our ability to successfully demonstrate proof of concept for our technology in humans, our ability to demonstrate the safety and efficacy of our specific drug candidates, our ability to manufacture or have third parties manufacture RNAi therapeutics, the strength of our intellectual property and/or concerns around challenges to our intellectual property. For example, our decision in October 2016 to discontinue development of revusiran could make it more difficult for us to attract collaborators due to concerns around the safety and/or efficacy of our technology platform or product candidates. In addition, our decision in September 2017 to temporarily suspend dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE and agreement with regulatory authorities on a risk mitigation strategy could, notwithstanding the alignment reached with the FDA on a risk mitigation strategy in November 2017, contribute to further concerns about the safety of our therapeutic candidates. Even if we do succeed in securing any such alliances, we may not be able to maintain them if, for example, development or approval of a product candidate is delayed, challenges are raised as to the validity or scope of our intellectual property, we are unable to secure adequate reimbursement from payors or sales of an approved drug are lower than we expected.

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

For certain product candidates that we may develop, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with Sanofi Genzyme and MDCO. We may not, however, be able to enter into additional collaborations for certain other programs, and the terms of any collaboration agreement we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to one or more of our product candidates, we may not have sufficient funds to develop that or other product candidates internally, or to bring our product candidates to market. If we do not have sufficient funds to develop and bring our product candidates to market, we will not be able to generate revenues from these product candidates, and this will substantially harm our business.

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

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

Our current collaborations allow, and we expect that any future collaborations will allow, either party to terminate the collaboration for a material breach by the other party. In addition, our collaborators may have additional termination rights for convenience with respect to the collaboration or a particular program under the collaboration, under certain circumstances. For example, Sanofi Genzyme has the right to terminate our collaboration on a product-by-product basis in the event of certain safety concerns. If Sanofi Genzyme were to terminate a particular program, we may have to expend significantly more on the development and commercialization of such product candidate. Moreover, our agreement with MDCO relating to the development and commercialization of inclisiran worldwide may be terminated by MDCO at any time upon four months prior written notice. If we were to lose a commercialization collaborator, we would have to attract a new collaborator or develop expanded sales, distribution and marketing capabilities internally, which would require us to invest significant amounts of financial and management resources.

In addition, if we have a dispute with a collaborator over the ownership of technology or other matters, or if a collaborator terminates its collaboration with us, for breach or otherwise, or determines not to pursue the research,

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development and/or commercialization of RNAi therapeutics, it could delay our development of product candidates, result in the need for additional company resources to develop product candidates, require us to expend time and resources to develop expanded sales and marketing capabilities outside of the United States and EU on a more expedited timeline, make it more difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities. For example, in March 2011, Arbutus Biopharma Corporation, or ABC (formerly Tekmira Pharmaceuticals Corporation) and Protiva Biotherapeutics, Inc., a wholly owned subsidiary of ABC, and together with ABC, referred to as Arbutus, filed a civil complaint against us claiming, among other things, misappropriation of its confidential and proprietary information and trade secrets. As a result of the litigation, which was settled in November 2012, we were required to expend resources and management attention that would otherwise have been engaged in other activities. In addition, in August 2013, we initiated binding arbitration proceedings to resolve a disagreement with Arbutus regarding the achievement by Arbutus of a $5.0 million milestone payment under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. The Arbutus arbitration hearing was held in May 2015. In March 2016, the arbitration panel ruled in our favor and as a result, no milestone payment is due to Arbutus at this time. Arbutus did not appeal this ruling.

Moreover, a collaborator, or in the event of a change in control of a collaborator or the assignment of a collaboration agreement to a third party, the successor entity or assignee, could determine that it is in its interests to:

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

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

- if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates developed without us.

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

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

We rely on independent clinical investigators, contract research organizations, or CROs, and other third-party service providers to assist us in managing, monitoring and otherwise carrying out our clinical trials. We have contracted, and we plan to continue to contract with, certain third parties to provide certain services, including site selection, enrollment, monitoring, auditing and data management services. Although we depend heavily on these parties, we control only certain aspects of their activity and therefore, we cannot be assured that these third parties will adequately perform all of their contractual obligations to us in compliance with regulatory and other legal requirements and our internal policies and procedures. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with good clinical practice, or GCP, requirements, which are regulations and guidelines enforced by the FDA and comparable foreign

regulatory authorities for all of our product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations.

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If our third-party service providers cannot adequately and timely fulfill their obligations to us, or if the quality and accuracy of our clinical trial data is compromised due to failure by such third party to adhere to our protocols or regulatory requirements or if such third parties otherwise fail to meet deadlines, our development plans and/or regulatory reviews for marketing approvals may be delayed or terminated, including, for example, review of our planned NDA and MAA filings for patisiran. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

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

We have limited manufacturing experience. In order to develop our product candidates, apply for regulatory approvals and commercialize our products, if approved, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Historically, our internal manufacturing capabilities were limited to small-scale production of material for use in *in vitro* and *in vivo* experiments that is not required to be produced under current good manufacturing practices, or cGMP, standards. During 2012, we developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late stage clinical trial use and commercial supply. In addition, in April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts, where we have commenced construction of a cGMP manufacturing facility for drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use.

We may manufacture limited quantities of clinical trial materials ourselves, but otherwise we currently rely on third parties to manufacture the drug substance and, with the exception of patisiran, the finished product we will require for any clinical trials that we initiate and to support the commercial launch of our first several products. There are a limited number of manufacturers that supply synthetic siRNAs. We currently rely on a limited number of contract manufacturing organizations, or CMOs, for our supply of synthetic siRNAs. For example, in July 2015, we amended our manufacturing agreement with Agilent, to provide for Agilent to supply, subject to any conflicting obligations under our third-party agreements, a specified percentage of the active pharmaceutical ingredients required for certain of our products in clinical development, as well as other products the parties may agree upon in the future. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our CMOs, including Agilent, to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are potential synthesis and purification failures and/or contamination during the manufacturing process, as well as other issues with the CMO s facility and ability to comply with the applicable manufacturing requirements, which could result in unusable product and cause delays in our manufacturing timelines and ultimately delay our clinical trials, as well as result in additional expense to us. To fulfill our siRNA requirements, we will likely need to secure alternative suppliers of synthetic siRNAs and such alternative suppliers are limited and may not be readily available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner. As noted above, in order to ensure long-term supply capabilities for our RNAi therapeutics, we are developing our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use.

In addition to the manufacture of the synthetic siRNAs, we may have additional manufacturing requirements related to the technology required to deliver the siRNA to the relevant cell or tissue type, such as lipid nanoparticles or conjugates. In some cases, the delivery technology we utilize is highly specialized or proprietary, and for technical and/or legal reasons, we may have access to only one or a limited number of potential manufacturers for such delivery technology. In addition, the scale-up of our delivery technologies could be very difficult and/or take significant time. We also have very limited experience in such scale-up and manufacturing, requiring us to depend on a limited number of third parties, who might not be able to deliver in a timely manner, or at all. Failure by manufacturers to properly manufacture our delivery technology and/or formulate our siRNAs for delivery could result in unusable product.

Furthermore, competition for supply from our manufacturers from other companies, a breach by such manufacturers of their contractual obligations or a dispute with such manufacturers would cause delays in our discovery and development efforts, as well as additional expense to us.

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Given the limited number of suppliers for our delivery technology and drug substance, we have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late stage clinical use and commercial supply. During 2015, we scaled our cGMP manufacturing capacity for patisiran and believe we should have adequate resources to supply our commercial needs. In addition, as noted above, we are developing our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use. In developing these manufacturing capabilities by building our own manufacturing facilities, we have incurred substantial expenditures, and expect to incur significant additional expenditures in the future. In addition, the construction and qualification of our drug substance facility is expected to take several years to complete and there are many risks inherent in the construction of a new facility that could result in delays and additional costs, including the need to obtain access to necessary equipment and third-party technology, if any. Also, we have had to, and will likely need to continue to, hire and train qualified employees to staff our facilities. We do not currently have a second source of supply for patisiran formulated bulk drug product. If we are unable to manufacture sufficient quantities of material or if we encounter problems with our facilities in the future, we may also need to secure alternative suppliers of patisiran formulated bulk drug product and drug substance, and such alternative suppliers may not be available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner.

The manufacturing process for any products that we may develop is subject to the FDA and foreign regulatory authority approval process and we will need to meet, and will need to contract with CMOs who can meet, all applicable FDA and foreign regulatory authority requirements on an ongoing basis. In addition, if we receive the necessary regulatory approval for any product candidate, we also expect to rely on third parties, including potentially our commercial collaborators, to produce materials required for commercial supply. We may experience difficulty in obtaining adequate manufacturing capacity for our needs and the needs of our collaborators, who we have, in some instances, the obligation to supply. If we are unable to obtain or maintain CMOs for these product candidates, or to do so on commercially reasonable terms, we may not be able to successfully develop and commercialize our products.

To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we depend, and will depend in the future, on these third parties, including Agilent, to perform their obligations in a timely manner and consistent with contractual and regulatory requirements, including those related to quality control and quality assurance. The failure of Agilent or any other CMO to perform its obligations as expected, or, to the extent we manufacture all or a portion of our product candidates ourselves, our failure to execute on our manufacturing requirements, could adversely affect our business in a number of ways, including:

- we or our current or future collaborators may not be able to initiate or continue clinical trials of product candidates that are under development;
- we or our current or future collaborators may be delayed in submitting regulatory applications, or receiving regulatory approvals, for our product candidates, including patisiran;
- we may lose the cooperation of our collaborators;
- our facilities and those of our CMOs, and our products could be the subject of inspections by regulatory authorities that could have a negative outcome and result in delays in supply;

we may be required to cease distribution or recall some or all batches of our products or take action to recover clinical trial material from clinical trial sites; and

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

If any CMO with whom we contract, including Agilent, fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different CMO, which we may not be able to do on reasonable terms, if at all. In either scenario, our clinical trials or commercial distribution could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills required to manufacture our products or product candidates

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may be unique or proprietary to the original CMO and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. In addition, if we are required to change CMOs for any reason, we will be required to verify that the new CMO maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce our product according to the specifications previously submitted to or approved by the FDA or another regulatory authority. The delays associated with the verification of a new CMO could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a CMO may possess technology related to the manufacture of our product candidate that such CMO owns independently. This would increase our reliance on such CMO or require us to obtain a license from such CMO in order to have another CMO manufacture our products or product candidates.

We have no sales or distribution experience and only early capabilities for marketing, sales and market access, and expect to invest significant financial and management resources to establish these capabilities and to establish infrastructure in the EU.

We have no sales or distribution experience and only early capabilities for marketing, sales and market access. We currently expect to rely heavily on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we intend to commercialize the majority of our products on our own in the United States, Canada and the EU, as well as globally in the case of givosiran. Accordingly, we will need to develop internal sales, distribution and marketing capabilities as part of our core product strategy initially in the United States, Canada and the EU, and longer-term on a global basis, which will require significant financial and management resources. For the majority of our Genetic Medicine programs where we will perform sales, marketing and distribution functions ourselves in the United States, Canada and Western Europe, including patisiran, if approved, and for future Cardio-Metabolic and Hepatic Infectious Disease products we successfully develop where we may retain certain product development and commercialization rights, we could face a number of additional risks, including:

- we may not be able to attract and build a significant marketing or sales force;
- we may not be able to establish our capabilities and infrastructure in the EU or in other territories in a timely manner;
- the cost of establishing a marketing or sales force may not be justifiable in light of the revenues generated by any particular product; and
- our direct sales and marketing efforts may not be successful.

If we are unable to develop our own sales, marketing and distribution capabilities in the United States, Canada and the EU for patisiran and other products, as well as globally for certain products, we will not be able to successfully commercialize our products in our sales territories without reliance on third parties.

Credit and financial market conditions may exacerbate certain risks affecting our business from time to time.

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

Our ability to secure additional financing in addition to our term loan agreements and to satisfy our financial obligations under indebtedness outstanding from time to time will depend upon our future operating performance, which is subject to then prevailing general economic and credit market conditions, including interest rate levels and the availability of credit generally, and financial, business and other factors, many of

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which are beyond our control. In light of periodic uncertainty in the capital and credit markets, there can be no assurance that sufficient financing will be available on desirable or even any terms to fund investments, acquisitions, stock repurchases, dividends, debt refinancing or extraordinary actions.

Risks Related to Managing Our Operations

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

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

We have grown our workforce significantly over the past several years and anticipate continuing to add a significant number of additional employees as we focus on achieving our *Alnylam 2020* strategy. We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to reward qualified individuals than we do. In addition, due to the risks associated with developing a new class of medicine, we may experience disappointing results in a clinical program and our stock price may decline as a result, as was the case following our decision in October 2016 to discontinue our revusiran program, and, to less of an extent, following our temporary suspension of dosing in our fitusiran program in September 2017. As a result, we may face additional challenges in attracting and retaining employees. Accordingly, we may be unable to attract and retain suitably qualified individuals in order to support our growing research, development and commercialization efforts and initiatives, and our failure to do so could have an adverse effect on our ability to implement our future business plan.

We may have difficulty expanding our operations successfully as we evolve from a U.S.-based company primarily involved in discovery, pre-clinical testing and clinical development into a global company that develops and commercializes multiple drugs.

We expect that as we increase the number of product candidates we are developing we will also need to expand our operations in the United States and continue to build operations in the EU and eventually other geographies. Based on the positive data recently reported from our APOLLO Phase 3 study of patisiran, we plan to file an NDA by the end of 2017 and an MAA shortly thereafter. Assuming regulatory approvals, we are preparing to commercialize patisiran in 2018. As noted above, we grew our workforce significantly during 2016 and during 2017 and anticipate continuing to hire additional employees, including employees in the EU, as we focus on the potential commercial launch of patisiran and achieving our *Alnylam 2020* strategy. This expected growth is placing a strain on our administrative and operational infrastructure, and we will need to develop additional and/or new infrastructure and capabilities to support our growth and obtain additional space to conduct our operations in the United States, the EU and other geographies. If we are unable to develop such additional infrastructure or obtain sufficient space to accommodate our growth in a timely manner and on commercially reasonable terms, our business could be negatively impacted. As product candidates we develop enter and advance through clinical trials, we will need to expand our development, regulatory, manufacturing, quality, compliance, and marketing and sales capabilities in the United States and the EU, as well as other geographies, or contract with other organizations to provide these capabilities for us. In addition, as our operations expand due to our development progress, we expect that we will need to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls and systems, reporting

systems and infrastructure, and policies and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

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The increasing use of social media platforms presents new risks and challenges.

Social media is increasingly being used to communicate about our clinical development programs and the diseases our investigational RNAi therapeutics are being developed to treat. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business. For example, patients may use social media channels to comment on their experience in an ongoing blinded clinical study or to report an alleged adverse event. When such disclosures occur, there is a risk that we fail to monitor and comply with applicable adverse event reporting obligations or we may not be able to defend our business or the public s legitimate interests in the face of the political and market pressures generated by social media due to restrictions on what we may say about our investigational products. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any social networking website. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face regulatory actions or incur other harm to our business.

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

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

The results of the United Kingdom s referendum on withdrawal from the EU may have a negative effect on global economic conditions, financial markets and our business.

In June 2016, the United Kingdom, or UK, held a referendum in which voters approved an exit from the EU, commonly referred to as Brexit. This referendum has created political and economic uncertainty, particularly in the UK and the EU, and this uncertainty may persist for years. A withdrawal could, among other outcomes, disrupt the free movement of goods, services and people between the UK and the EU, and result in increased legal and regulatory complexities, as well as potential higher costs of conducting business in Europe. The UK s vote to exit the EU could also result in similar referendums or votes in other European countries in which we do business. Given the lack of comparable precedent, it is unclear what financial, trade and legal implications the withdrawal of the UK from the EU would have and how such withdrawal would affect us.

For example, Brexit could result in the UK or the EU significantly altering its regulations affecting the clearance or approval of our product candidates that are developed in the UK. Any new regulations could add time and expense to the conduct of our business, as well as the process by which our products receive regulatory approval in the UK, the EU and elsewhere. In addition, the announcement of Brexit and the withdrawal of the UK from the EU have had and may continue to have a material adverse effect on global economic conditions and the stability of global financial markets, and may significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Any of these effects of Brexit, among others, could adversely affect our business, our results of operations, liquidity and financial condition.

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Risks Related to Our Industry

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

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

Before obtaining regulatory approval for the commercial distribution of our product candidates, we must conduct, at our own expense, extensive nonclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Nonclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome, and the historical failure rate for product candidates is high. In October 2016, we discontinued development of one of our product candidates, which included a Phase 3 clinical trial. We currently have multiple other programs in clinical development, including several internal programs and one partnered program currently in Phase 3 development, as well as several earlier stage clinical programs. We recently reported positive complete results from our APOLLO Phase 3 clinical trial for our lead product candidate, patisiran, and expect to file an NDA by the end of 2017 and an MAA shortly thereafter. However, we may not be able to further advance these or any other product candidate through clinical trials and regulatory approval.

If we enter into clinical trials, the results from nonclinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in subsequent subjects or in subsequent human clinical trials of that product candidate or any other product candidate. For example, in June 2017, we announced updated results from our Phase 1 clinical trial of givosiran. Although the clinical data from this trial are encouraging, the data are preliminary in nature, based on a limited number of patients with acute intermittent porphyria, or AIP. These data, or other positive data, may not continue for patients with AIP, and may not be repeated or observed in our ENVISION Phase 3 study. There can be no assurance that our studies with givosiran will ultimately be successful or support further clinical advancement or regulatory approval of this product candidate. There is a high failure rate for drugs proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies, and any such setbacks in our clinical development could have a material adverse effect on our business and operating results. Moreover, patisiran, fitusiran, givosiran and our other product candidates each employ novel delivery technologies that have yet to be extensively evaluated in human clinical trials and proven safe and effective.

In addition, we, the FDA or other applicable regulatory authorities, or an institutional review board, or IRB, or similar foreign review board or committee, may delay initiation of or suspend clinical trials of a product candidate at any time for various reasons, including if we or they believe the healthy volunteer subjects or patients participating in such trials are being exposed to unacceptable health risks. Among other reasons, adverse side effects of a product candidate or related product on healthy volunteer subjects or patients in a clinical trial could result in our decision, or a decision by the FDA or foreign regulatory authorities, to suspend or terminate the trial, or, in the case of regulatory agencies, a refusal to approve a particular product candidate for any or all indications of use. For example, in October 2016, we announced our decision to discontinue development of revusiran, an investigational RNAi therapeutic that was being developed for the treatment of patients with cardiomyopathy due to hATTR amyloidosis. Our decision followed the recommendation of the revusiran ENDEAVOUR Phase 3 study Data Monitoring Committee, or DMC, to suspend dosing and the observation of an imbalance in mortality in revusiran-treated patients as compared to those on placebo. Separately, the patisiran APOLLO DMC met at our request following our decision to discontinue development of revusiran, and recommended continuation of the APOLLO Phase 3 trial of patisiran, without modification. We conducted a comprehensive evaluation of the revusiran data and reported the results of our evaluation on August 9, 2017. Following our evaluation, we continue to believe that the decision to discontinue development of revusiran does not affect patisiran, which is in development for the treatment of hATTR amyloidosis, or any of our other

investigational RNAi therapeutic programs in development. In September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE

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and agreement with regulatory authorities on a risk mitigation strategy. We have reached alignment with study investigators and the FDA on safety measures and a risk mitigation strategy to enable resumption of dosing in clinical studies with fitusiran, including our Phase 2 OLE study and the ATLAS Phase 3 program. Following regulatory and institutional review and approval of amended study protocols and other clinical materials implementing these measures, we intend to resume our fitusiran studies as soon as possible.

Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the age and condition of the patients, the stage and severity of disease, the availability of clinical trials for other investigational drugs for the same disease or condition, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, and the eligibility criteria for the clinical trial. For example, we may experience difficulty enrolling our clinical trials, including, but not limited to, our clinical trials for fitusiran, due to the availability of existing approved treatments, as well as other investigational treatments in development. Moreover, given the recent temporary suspension of dosing in our fitusiran studies due to a fatal thrombotic SAE, people with hemophilia may be more reluctant to enroll in our ATLAS Phase 3 program when it is resumed. Delays or difficulties in patient enrollment or difficulties retaining trial participants, including as a result of the availability of existing or other investigational treatments or safety concerns, can result in increased costs, longer development times or termination of a clinical trial.

Although our investigational RNAi therapeutics have been generally well tolerated in our clinical trials to date, new safety findings may emerge. For example, as noted above, in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE that occurred in a patient with hemophilia A without inhibitors who was receiving fitusiran in our Phase 2 OLE study. In addition, in October 2016, we made the decision to discontinue our revusiran program. Following reports in the revusiran Phase 2 OLE study of new onset or worsening peripheral neuropathy, the revusiran ENDEAVOUR Phase 3 study DMC assembled in early October 2016 at our request to review these reports and ENDEAVOUR safety data on an unblinded basis. The DMC did not find conclusive evidence for a drug-related neuropathy signal in the ENDEAVOUR trial, but informed us that the benefit-risk profile for revusiran no longer supported continued dosing. We subsequently reviewed unblinded ENDEAVOUR data which revealed an imbalance of mortality in the revusiran arm as compared to placebo. Further, a review by us in 2017 of the ENDEAVOUR results subsequent to the completion of follow-up of the patients post-dosing discontinuation revealed an imbalance in new onset or worsening peripheral neuropathy in the revusiran arm as compared to placebo. We had previously reported, in July 2016, preliminary data from our revusiran Phase 2 OLE study for 12 patients who had reached the 12-month endpoint as of the data transfer date of May 26, 2016. SAEs were observed in 14 patients, one of which, a case of lactic acidosis, was deemed possibly related to the study drug and the patient discontinued treatment. There were a total of seven deaths reported at that time in the revusiran OLE study, all of which were unrelated to the study drug. The majority of the adverse events, or AEs, were mild or moderate in severity; injection site reactions, or ISRs, were reported in 12 patients. In August 2015, we reported that three patients had discontinued from the revusiran Phase 2 OLE study due to recurrent localized reactions at the injection site or a diffuse rash; no further discontinuations due to ISRs had occurred as of May 26, 2016.

In our patisiran APOLLO Phase 3 study in patients with polyneuropathy due to hATTR amyloidosis, the most commonly reported AEs that occurred more frequently in patisiran patients were peripheral edema and infusion-related reactions, or IRRs. These were generally mild to moderate in severity and only one patient discontinued from the APOLLO study due to an IRR. Compared to placebo, patisiran treatment was associated with fewer treatment discontinuations and fewer study withdrawals due to AEs. The incidence of SAEs across the patisiran and placebo groups was similar and the SAEs reported in two or more patients in the patisiran group included:

diarrhea, cardiac failure, congestive cardiac failure, orthostatic hypotension, pneumonia and atrioventricular block complete. These were all considered unrelated to patisiran, except for one SAE of diarrhea. SAEs occurred with similar frequency in the placebo group, except for diarrhea. Deaths were recorded with a similar incidence across the patisiran and placebo treatment groups and no deaths were considered related to the study drug.

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In addition, in our ALN-VSP clinical trial, one patient with advanced pancreatic neuroendocrine cancer with extensive involvement of the liver developed hepatic failure five days following the second dose of ALN-VSP and subsequently died; this was deemed possibly related to the study drug. As demonstrated by the discontinuation of our revusiran program in October 2016 and the temporary suspension of dosing in September 2017 in our fitusiran studies, the occurrence of SAEs and/or AEs can result in the suspension or termination of clinical trials of a product candidate by us or the FDA or a foreign regulatory authority, or refusal to approve a particular product candidate for any or all indications of use.

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

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

A failure of one or more of our clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, nonclinical testing and the clinical trial process that could delay or prevent regulatory approval or our ability to commercialize our product candidates, including:

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

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

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

- problems in engaging IRBs or ethics committees to oversee clinical trials or problems in obtaining or maintaining IRB or ethics committee approval of trials;

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

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

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

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

greater than anticipated clinical trial costs;

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

poor or disappointing effectiveness of our product candidates during clinical trials;

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

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

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

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

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

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

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

We have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA. The time required to obtain FDA and other regulatory approvals is unpredictable but typically takes many years following the commencement of clinical trials, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when regulating us are not always applied predictably or uniformly and can change. Any analysis we perform of data from nonclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

Because the drugs we are developing may represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any regulatory filings that we may submit. Moreover, the FDA may respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the clinical development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek approval, in order to receive regulatory approval, we may need to demonstrate through clinical trials that the product candidates we develop to treat

these diseases, if any, are not only safe and effective, but safer or more effective than existing products. Furthermore, in recent years, there has been increased public and political pressure on the FDA with respect to the approval process for new drugs, and the FDA s standards, especially regarding drug safety, appear to have become more stringent.

Based on the positive complete results from our APOLLO Phase 3 clinical trial that we recently reported, we expect to file our first NDA for patisiran at the end of 2017 and an MAA shortly thereafter. Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from

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patisiran or any product candidate for which we may seek approval in the future. Furthermore, any regulatory approval to market patisiran or any other product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions. In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, plan as part of an NDA, or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. In the EU, we could be required to adopt a similar plan, known as a risk management plan, and our products could be subject to specific risk minimization measures, such as restrictions on prescription and supply, the conduct of post-marketing safety or efficacy studies, or the distribution of patient and/or prescriber educational materials. In either instance, these limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

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

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

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

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

The CMO and manufacturing facilities we use to make our product candidates, including our Cambridge facility, our future Norton facility, and Agilent and other CMOs, will also be subject to periodic review and inspection by the FDA and other regulatory agencies. To date, our Cambridge manufacturing facility has not been subject to an inspection by any regulatory authority. The discovery of any new or previously unknown problems with us or our CMOs, or our or their manufacturing processes or facilities, may result in restrictions on the drug or CMO or facility, including withdrawal of the drug from the market. We have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for Phase 3 clinical and commercial use. In addition, in April 2016, we

completed our purchase of a parcel of land in Norton, Massachusetts, where we have commenced construction of a cGMP manufacturing facility for drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use. We may not have the ability or capacity to manufacture material at a

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broader commercial scale in the future. We may manufacture clinical trial materials or we may contract a third party to manufacture these materials for us. Reliance on CMOs entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the CMO for regulatory compliance. Our product promotion and advertising will also be subject to regulatory requirements and continuing regulatory review.

If we or our collaborators, CMOs or service providers fail to comply with applicable continuing regulatory requirements in the United States or foreign jurisdictions in which we may seek to market our products, we or they may be subject to, among other things, fines, warning letters, holds on clinical trials, refusal by the FDA or foreign regulatory authorities to approve pending applications or supplements to approved applications, suspension or withdrawal of regulatory approval, product recalls and seizures, refusal to permit the import or export of products, operating restrictions, injunction, civil penalties and criminal prosecution.

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

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

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

- the timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained;
- the safety and efficacy of our product candidates, as demonstrated in clinical trials and as compared with alternative treatments, if any;
- relative convenience and ease of administration of our product candidates;
- the willingness of patients to accept potentially new routes of administration or new or different therapeutic approaches and mechanisms of action;
- the success of our physician education programs;
- the availability of adequate government and third-party payor reimbursement;
- the pricing of our products, particularly as compared to alternative treatments; and

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

For example, patisiran utilizes an intravenous mode of administration that physicians and/or patients may not readily adopt or which may not compete with other potentially available options. In addition, fitusiran represents a new approach to treating hemophilia which may not be readily accepted by patients and their caregivers.

In addition, our estimates regarding the potential market size for patisiran or our other product candidates may be materially different from what we currently expect at the time we commence commercialization, which could result in significant changes in our business plan and may have a material adverse effect on our results of operations and financial condition.

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

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

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

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

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

- the U.S. federal Open Payments requirements were implemented by The Centers for Medicare and Medicaid Services, or CMS, pursuant to the Patient Protection and Affordable Care Act, also referred to as the Affordable Care Act or PPACA. Under the Open Payments Program, manufacturers of medical devices, medical supplies, biological products and drugs covered by Medicare, Medicaid and the Children s Health Insurance Programs report all transfers of value, including consulting fees, travel reimbursements, research grants, and other payments or gifts with values over $10 made to physicians and teaching hospitals; and

- state and foreign laws comparable to each of the above federal laws, including in the EU laws prohibiting giving healthcare professionals any gift or benefit in kind as an inducement to prescribe our products, national transparency laws requiring the public disclosure of payments made to healthcare professionals and institutions, and data privacy laws, in addition to anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to government reimbursement programs, patient data privacy and security.

If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, criminal prosecution, monetary damages, the curtailment or restructuring of our operations, loss of eligibility to obtain approvals from the FDA, or exclusion from participation in government contracting, healthcare reimbursement or other government programs, including Medicare and Medicaid, or the imposition of a corporate integrity agreement with the Office of Inspector General of the Department of Health and Human Services, any of which could adversely affect our financial results. Although effective compliance programs can mitigate the risk of

investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management s attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

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

adverse regulatory inspection findings;

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warning letters;

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

restrictions on, or prohibitions against, marketing our products;

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

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

exclusion from participation in government-funded healthcare programs;

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

suspension or withdrawal of product approvals;

product seizures;

injunctions; and

civil and criminal penalties, up to and including criminal prosecution resulting in fines, exclusion from healthcare reimbursement programs and imprisonment.

Moreover, federal, state or foreign laws or regulations are subject to change, and while we, our collaborators, CMOs and/or service providers currently may be compliant, that could change due to changes in interpretation, prevailing industry standards or the legal structure.

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

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. We are actively monitoring these regulations as we prepare to file for regulatory approval for patisiran in the U.S. and the EU and several of our other programs move into late stages of development, however, a number of our programs are currently in the earlier stages of development and we will not be able to assess the impact of price regulations for such programs for a number of years. As a result, we might obtain regulatory approval for a product in

a particular country, but then be subject to price regulations that delay our commercial launch of the product and negatively impact the revenues we are able to generate from the sale of the product in that country and potentially in other countries due to reference pricing.

Our ability to commercialize patisiran or any other products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Even if we succeed in bringing one or more products to the market, patisiran and our other products may not be considered cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for drug products. If the price we are able to charge for patisiran or any other products we develop, or the reimbursement provided for such products, is inadequate in light of our development and other costs, or if reimbursement is denied, our return on investment could be adversely affected.

We currently expect that some of the drugs we develop may need to be administered under the supervision of a physician or other healthcare professional on an outpatient basis, including patisiran. Under currently applicable U.S. law, certain drugs that are not usually self-administered (including injectable drugs) may be eligible for coverage under the Medicare Part B program if:

they are incident to a physician s services;

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they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice; and

they have been approved by the FDA and meet other requirements of the statute.

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

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory changes in the healthcare system in the United States and other major healthcare markets have been proposed in recent years, and such efforts have expanded substantially in recent years. These developments have included prescription drug benefit legislation that was enacted in 2003 and took effect in January 2006, healthcare reform legislation enacted by certain states, and major healthcare reform legislation that was passed by Congress and enacted into law in the United States in 2010. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

In particular, in March 2010, the PPACA was signed into law. This legislation changed the system of healthcare insurance and benefits intended to broaden coverage and control costs. The law also contains provisions that affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Provisions affecting pharmaceutical companies include the following:

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

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

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

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

The law provides that approval of an application for a follow-on biologic product may not become effective until 12 years after the date on which the reference innovator biologic product was first

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licensed by the FDA, with a possible six-month extension for pediatric products. After this exclusivity ends, it will be easier for generic manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect our profitability.

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

As a result of the 2016 election in the United States, there is great political uncertainty concerning the fate of the PPACA and other healthcare laws. Members of the United States Congress and the Trump Administration have expressed an intent to pass legislation or adopt executive orders to fundamentally change or repeal parts of the PPACA, but it is uncertain whether such legislation will be enacted, what the scope of any replacement law (if any) would encompass or what the ultimate impact of any executive orders might be**.**

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

Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending.

Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least $1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts included aggregate reductions to Medicare payments to providers of up to 2 percent per fiscal year, starting in 2013. Certain of these automatic cuts have been implemented resulting in reductions in Medicare payments to physicians, hospitals, and other healthcare providers, among other things. The full impact on our business of these automatic cuts is uncertain.

If other federal spending is reduced, any budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or National Institutes of Health to continue to function. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop.

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

Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. Following the decision to discontinue clinical development of revusiran, we conducted a comprehensive evaluation of available revusiran data. We reported the results of this evaluation on August 9, 2017, however, our investigation did not result in a conclusive explanation regarding the cause of the mortality imbalance observed in the ENDEAVOUR Phase 3 study. In addition, in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal

thrombotic SAE and agreement with regulatory authorities on a risk mitigation strategy. Notwithstanding the risks undertaken by all persons who participate in clinical trials, and the information on risks provided to study investigators and patients participating in revusiran and fitusiran studies, it is possible that product liability claims

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

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

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

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

Risks Related to Patents, Licenses and Trade Secrets

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

Our success depends, in part, on our ability to protect proprietary methods and technologies that we develop under the patent and other intellectual property laws of the United States and other countries, so that we can prevent others from unlawfully using our inventions and proprietary information. However, we may not hold proprietary rights to some patents required for us to manufacture and commercialize our proposed products. Because certain U.S. patent applications are confidential until the patents issue, such as applications filed prior to November 29, 2000, or

applications filed after such date which will not be filed in foreign countries, third parties may have filed patent applications for technology covered by our pending patent applications without our being aware of those applications, and our patent applications may not have priority over those applications. For this

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and other reasons, we may be unable to secure desired patent rights, thereby losing desired exclusivity. Further, we may be required to obtain licenses under third-party patents to market our proposed products or conduct our research and development or other activities. If licenses are not available to us on acceptable terms, we may not be able to market the affected products or conduct the desired activities.

Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we may rely on third-party collaborators to file patent applications relating to proprietary technology that we develop jointly during certain collaborations. The process of obtaining patent protection is expensive and time-consuming. If our present or future collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business may be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may be able to obtain and use information that we regard as proprietary. While issued patents are presumed valid, this does not guarantee that the patent will survive a validity challenge or be held enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable or circumvented by parties attempting to design around our intellectual property. Moreover, third parties or the United States Patent and Trademark Office, or USPTO, may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management and could have a material adverse effect on our business.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the United States and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts and lawmakers. Moreover, there are periodic discussions in the Congress of the United States and in international jurisdictions about modifying various aspects of patent law. For example, the America Invents Act included a number of changes to the patent laws of the United States. If any of the enacted changes do not provide adequate protection for discoveries, including our ability to pursue infringers of our patents for substantial damages, our business could be adversely affected. One major provision of the America Invents Act, which took effect in March 2013, changed United States patent practice from a first-to-invent to a first-to-file system. If we fail to file an invention before a competitor files on the same invention, we no longer have the ability to provide proof that we were in possession of the invention prior to the competitor s filing date, and thus would not be able to obtain patent protection for our invention. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or biotechnology patents.

Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others. We also rely to a certain extent on trade secrets, know-how and technology, which are not protected by patents, to maintain our competitive position. If any trade secret, know-how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business and financial condition could be materially adversely affected.

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

We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from, among others, Cancer Research Technology Limited, Ionis Pharmaceuticals, Inc., or Ionis (formerly Isis Pharmaceuticals, Inc.), the Massachusetts Institute of Technology,

or MIT, the Whitehead Institute for Biomedical Research, or Whitehead, Max Planck Innovation and Arbutus. We also intend to enter into additional licenses to third-party intellectual property in the future.

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

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

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

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

As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference, reexamination and opposition proceedings, as well as *inter partes* and post-grant review proceedings introduced by provisions of the America Invents Act, which became available to third party challengers on September 16, 2012, in various patent offices relating to patent rights in the RNAi field. For example, various third parties have initiated oppositions to patents in our McSwiggen, Kreutzer-Limmer and Tuschl II series in the EPO and in other jurisdictions. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business if we are not successful in defending the patentability and scope of our pending and issued patent claims. In addition, third parties may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business and our ability to successfully compete in the field of RNAi.

There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need for our siRNA therapeutic candidates. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for siRNA drugs we wish to develop. In addition, there may be issued and

pending patent applications that may be asserted against us in a court proceeding or otherwise based upon the asserting party s belief that we may need such patents for our siRNA therapeutic candidates. Thus, it is possible that one or more organizations will hold patent rights to which we may need a license, or hold patent

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rights which could be asserted against us. If those organizations refuse to grant us a license to such patent rights on reasonable terms and/or a court rules that we need such patent rights that have been asserted against us and we are not able to obtain a license on reasonable terms, we may be unable to market products or perform research and development or other activities covered by such patents. For example, Silence Therapeutics plc, or Silence, issued and has now served, a claim in the High Court of England and Wales, naming us, our wholly owned subsidiary Alnylam UK Ltd., and The Medicines Company UK Ltd as co-defendants. The claim seeks a declaration that Silence is entitled to supplementary protection certificates, or SPCs, based on a European patent held by Silence, that Silence alleges covers certain of our product candidates. An SPC is an intellectual property right that could extend the life of the Silence patent in relation to a specified product for a period of up to five additional years bringing the potential expiration date to 2028. While we have not yet filed in court our formal response to the claim issued by Silence, we have stated that we do not believe that any of our products infringe any valid patent held by Silence, and that we will vigorously defend any claim brought against us by Silence. On October 27, 2017, we, through our affiliate Alnylam UK Ltd., and The Medicines Company UK Ltd filed and served a claim against Silence Therapeutics GmbH and Silence in the High Court of England and Wales seeking revocation of Silence s patent, as well as a declaration of non-infringement by each of the products of such patent, and costs and interest among other potential remedies.

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

Third parties may sue us for infringing their patent rights. Likewise, we may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of proprietary rights of others or protect our proprietary information and trade secrets. For example, during the second quarter of 2015, we filed a trade secret misappropriation lawsuit against Dicerna Pharmaceuticals, Inc., or Dicerna, to protect our rights in the RNAi assets we purchased from Merck. A third party may also claim that we have improperly obtained or used its confidential or proprietary information. For example, in March 2011, Arbutus (formerly Tekmira) filed a civil complaint against us alleging, among other things, misappropriation of its confidential and proprietary information and trade secrets. In November 2012, we settled this litigation and restructured our contractual relationship with Arbutus. In connection with this restructuring, we incurred a $65.0 million charge to operating expenses during the quarter ended December 31, 2012.

Furthermore, third parties may challenge the inventorship of our patents or licensed patents. For example, in March 2011, The University of Utah, or Utah, filed a complaint against us, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and the University of Massachusetts, claiming that a professor of Utah was the sole inventor, or in the alternative, a joint inventor of certain of our in-licensed patents. Utah was seeking correction of inventorship of the Tuschl patents, unspecified damages and other relief. After several years of court proceedings and discovery, the court granted our motions for summary judgment, and dismissed Utah s state law damages claims as well. During the pendency of this litigation, as well as the Arbutus litigation described above, we incurred significant costs, and in each case, the litigation diverted the attention of our management and other resources that would otherwise have been engaged in other activities.

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

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

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

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, milestone, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and other obligations on us. If we breach any of these obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license or render the license non-exclusive, which could result in us being unable to develop, manufacture, market and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. For example, in 2013, Arbutus (formerly Tekmira) notified us that it believed it had achieved a $5.0 million milestone payment under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. We notified Arbutus that we did not believe that the milestone has been achieved under the terms of the cross-license agreement. In August 2013, we initiated binding arbitration proceedings seeking a declaratory judgment that Arbutus had not yet met the conditions of the milestone and was not entitled to payment at the time. The Arbutus arbitration hearing was held in May 2015. On March 9, 2016, the arbitration panel ruled in our favor and as a result, no milestone payment is due to Arbutus at this time. Arbutus did not appeal this ruling.

Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor s rights. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

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

In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, outside scientific collaborators and sponsored researchers, and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently

discover trade secrets and proprietary information, and in such cases we could not assert any trade secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

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Risks Related to Competition

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

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

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;
- more extensive experience in pre-clinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing and selling drug products;
- product candidates that are based on previously tested or accepted technologies;
- products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

We will face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. We also expect to face competition from new drugs that enter the market. We believe a number of drugs are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop drugs. These drugs may be more effective, safer, less expensive, or marketed and sold more effectively, than any products we develop. For example, we are developing patisiran for the treatment of hATTR amyloidosis. In November 2017, we reported positive complete results from our APOLLO Phase 3 clinical trial and generally encouraging safety data, and we expect to submit our first NDA for patisiran by the end of 2017 and an MAA shortly thereafter. We are aware of other approved products used to treat this disease, including tafamidis, marketed by Pfizer in Europe and certain countries outside the United States, as well as product candidates in various stages of clinical development, including an investigational drug being developed by Ionis. In October and November 2017, Ionis reported positive efficacy data as well as safety data from its Phase 3 clinical trial in hATTR amyloidosis, including thrombocytopenia and renal insufficiency SAEs. In November 2017, Ionis reported that it has filed its NDA and MAA for this investigational drug. While we believe that patisiran will have a competitive product profile, it is possible it will not compete favorably with these products and product candidates, or others, and even if approved, it may not achieve commercial success.

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

the safety and effectiveness of our products relative to alternative therapies, if any;

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

the timing and scope of regulatory approvals for these products;

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

price;

reimbursement coverage; and

patent position.

Our competitors may develop or commercialize products with significant advantages over any products we develop based on any of the factors listed above or on other factors. Our competitors may therefore be more

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successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and the ability to execute on our business plan. Furthermore, we also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we are targeting could make our product candidates noncompetitive, obsolete or uneconomical.

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

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of several other companies that are working to develop RNAi therapeutic products. Some of these companies are seeking, as we are, to develop chemically synthesized siRNAs as drugs. Others are following a gene therapy approach, with the goal of treating patients not with synthetic siRNAs but with synthetic, exogenously-introduced genes designed to produce siRNA-like molecules within cells. Companies working on chemically synthesized siRNAs include Takeda Pharmaceutical Company Limited, or Takeda, Marina Biotech, Inc., Arrowhead Research Corporation, or Arrowhead, and its subsidiary, Calando Pharmaceuticals, Inc., or Calando, Quark Pharmaceuticals, Inc., or Quark, Silence, Arbutus, Sylentis S.A.U., or Sylentis, Dicerna, WAVE Life Sciences Ltd. and Arcturus Therapeutics, Inc. In addition, we granted licenses or options for licenses to Ionis, Benitec Ltd., Arrowhead, and its subsidiary, Calando, Arbutus, Quark, Sylentis and others under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any one of these companies may develop its RNAi technology more rapidly and more effectively than us.

In addition, as a result of agreements that we have entered into, Arrowhead, as the assignee of F. Hoffmann-La Roche Ltd, and Takeda have obtained non-exclusive licenses, and Arrowhead, as the assignee of Novartis Pharma AG, has obtained specific exclusive licenses for 30 gene targets, to certain aspects of our technology that give them the right to compete with us in certain circumstances. We also compete with companies working to develop antisense-based drugs. Like RNAi therapeutics, antisense drugs target messenger RNAs, or mRNAs, in order to suppress the activity of specific genes. Ionis is currently marketing an antisense drug and has several antisense product candidates in clinical trials, including one for the treatment of hATTR amyloidosis. Ionis is also developing antisense drugs using ligand-conjugated GalNAc technology licensed from us, and these drugs have been shown to have increased potency at lower doses in clinical and pre-clinical studies, compared with antisense drugs that do not use such licensed GalNAc technology. The development of antisense drugs is more advanced than that of RNAi therapeutics, and antisense technology may become the preferred technology for drugs that target mRNAs to silence specific genes.

In addition to competition with respect to RNAi and with respect to specific products, we face substantial competition to discover and develop safe and effective means to deliver siRNAs to the relevant cell and tissue types. Safe and effective means to deliver siRNAs to the relevant cell and tissue types may be developed by our competitors, and our ability to successfully commercialize a competitive product would be adversely affected. In addition, substantial resources are being expended by third parties in the effort to discover and develop a safe and effective means of delivering siRNAs into the relevant cell and tissue types, both in academic laboratories and in the corporate sector. Some of our competitors have substantially greater resources than we do, and if our competitors are able to negotiate exclusive access to those delivery solutions developed by third parties, we may be unable to successfully

commercialize our product candidates.

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Risks Related to this Offering and Our Common Stock

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

If you purchase common stock in this offering, you will incur an immediate and substantial dilution of $122.32 per share after giving effect to the assumed sale by us of 4,822,117 shares of common stock offered in this offering at the assumed public offering price of $139.98 per share (the last reported sale price of our common stock on The Nasdaq Global Select Market on November 10, 2017), and after deducting estimated underwriting discounts and commissions for shares sold in the public offering and estimated offering expenses payable by us. See Dilution. In the past, we have issued options to acquire common stock at prices significantly below this offering price. To the extent these outstanding options are ultimately exercised, you will incur additional dilution. Furthermore, if the underwriters exercise their option to purchase additional shares, you will also incur additional dilution.

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

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

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

The market price of our common stock has fluctuated significantly and may continue to fluctuate significantly in response to factors that are beyond our control. The stock market in general has from time to time experienced extreme price and volume fluctuations, and the biotechnology in particular has experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the clinical development progress or operating performance of these companies, including as a result of adverse development events. These broad market and sector fluctuations have resulted and could in the future result in extreme fluctuations in the price of our common stock, which could cause purchasers of our common stock to incur substantial losses.

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

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development efforts or the development efforts of our collaborators and/or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. For example, in October 2016, we announced that we were discontinuing the development of revusiran and our stock price declined significantly as a result and in September 2017, following our temporary suspension of dosing in our fitusiran program, our stock also declined, although to a lesser extent. When the market price of a stock has been volatile as our stock price has been, holders of that stock have occasionally brought securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. The lawsuit could also divert the time and attention of our management.

Sales of additional shares of our common stock, including by us or our directors and officers following expiration or early release of the 60-day lock-up, could cause the price of our common stock to decline.

Sales of substantial amounts of our common stock in the public market, or the availability of such shares for sale, by us or others, including the issuance of common stock upon exercise of outstanding options, could adversely affect the price of our common stock. In connection with this offering, we, our directors and officers and Sanofi

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Genzyme have entered into lock-up agreements for a period of 60 days following this offering (which period may be extended under certain circumstances). We, our directors, officers or Sanofi Genzyme may be released from lock-up prior to the expiration of the lock-up period at the discretion of Goldman Sachs & Co. LLC and J.P. Morgan Securities LLC. See Underwriting. Upon expiration or earlier release of the lock-up, we, our directors, officers or Sanofi Genzyme may sell shares into the market, which could adversely affect the market price of shares of our common stock. In addition, during the lock-up period and thereafter, sales of shares held by our directors and officers are permitted under trading plans, as in effect as of the date of the applicable lock-up agreement, established pursuant to Rule 10b5-1 of the Exchange Act. Sales of a substantial number of such shares upon expiration of the lock-up agreements, the perception that such sales may occur, or early release of these agreements, could cause our market price to fall or make it more difficult for you to sell your common stock at a time and price that you deem appropriate.

Sanofi Genzyme s ownership of our common stock could delay or prevent a change in corporate control.

Sanofi Genzyme currently holds approximately 11 percent of our outstanding common stock and has the right to increase its ownership up to 30 percent, as well as the right to maintain its ownership percentage through the term of our collaboration, subject to certain limitations. This concentration of ownership may harm the market price of our common stock by:

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

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in our management. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

- a classified board of directors;
- a prohibition on actions by our stockholders by written consent;
- limitations on the removal of directors; and

advance notice requirements for election to our board of directors and for proposing matters that can be acted upon at stockholder meetings.

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

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Use of proceeds

We estimate that the net proceeds from the assumed sale of 4,822,117 shares of our common stock in this offering will be approximately $657.7 million, based on an assumed public offering price of $139.98 per share (the last reported sale price of our common stock on The Nasdaq Global Select Market on November 10, 2017), after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us and assuming the underwriters do not exercise their option to purchase additional shares of common stock. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds to us from the public offering will be approximately $756.4 million.

We intend to use the net proceeds of this offering for general corporate purposes, ultimately focused on advancing and potentially accelerating our clinical pipeline and continuing to build capabilities and expand geographically, as required for commercialization of investigational RNAi therapeutics in our pipeline that may obtain regulatory approval. Programs in Phase 3 or expected to enter Phase 3 during 2018 that we intend to advance include givosiran, for the treatment of acute hepatic porphyrias, fitusiran, for the treatment of hemophilia, and ALN-TTRsc02, for the treatment of ATTR amyloidosis, one or more of which may be accelerated as development progresses. Although we have not yet identified specific uses for these proceeds, we currently anticipate using the proceeds for some or all of the following purposes:

- research and development expenses, including for the advancement of our *Alnylam 2020* strategy for the development and commercialization of RNAi therapeutics as a potential new class of innovative medicines, with the goal of achieving, by the end of 2020, a company profile with three marketed products and ten RNAI therapeutic clinical programs, including four in late stages of development, across our three STArs;

- continued growth of our manufacturing, quality, commercial and medical affairs capabilities to support our transition from a development-stage company toward a multi-product, commercial-stage biopharmaceutical company, including the anticipated commercial launches of patisiran, givosiran and fitusiran across several continents, assuming favorable regulatory reviews, the expected commercial expansion beyond the United States, Canada and Western Europe for givosiran and other potential future products, and the potential expansion of patisiran commercialization efforts in mixed phenotype populations, assuming consistent product labelling;

- potential repayment of $150.0 million (plus accrued interest) in term loans related to the build out of our new drug substance manufacturing facility that mature in April 2021 and have a floating interest rate of LIBOR plus 0.45 percent;

- acquisitions, investments or licenses in businesses, products or technologies that are complementary to our own, although we have no present commitments for any such acquisitions or investments;

- working capital;

capital expenditures; and

general and administrative expenses.

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

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Price range of common stock

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

	High	Low
2015		
First Quarter	$ 121.93	$ 82.06
Second Quarter	140.00	98.63
Third Quarter	137.89	76.46
Fourth Quarter	110.75	71.14
2016		
First Quarter	$ 98.00	$ 51.51
Second Quarter	75.08	49.96
Third Quarter	80.11	53.56
Fourth Quarter	71.67	31.38
2017		
First Quarter	$ 60.41	$ 35.98
Second Quarter	86.92	46.90
Third Quarter	119.02	70.76
Fourth Quarter (through November 10, 2017)	147.63	111.25

On November 10, 2017, the last reported sale price of our common stock was $139.98 per share.

Dividend policy

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

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Dilution

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

Our net tangible book value at September 30, 2017 was $1.06 billion, or $11.46 per share, based on approximately 92.4 million shares of our common stock then outstanding. After giving effect to the assumed sale by us of 4,822,117 shares of common stock in this offering at an assumed public offering price of $139.98 per share (the last reported sale price of our common stock on The Nasdaq Global Select Market on November 10, 2017), less the estimated underwriting discounts and commissions for shares sold in the public offering and estimated offering expenses payable by us, our net tangible book value at September 30, 2017 would be approximately $1.72 billion, or $17.66 per share. This represents an immediate increase in net tangible book value of $6.20 per share to existing stockholders and an immediate dilution of $122.32 per share to investors in this offering. The following table illustrates this per share dilution:

Assumed public offering price per share		$ 139.98
Net tangible book value per share as of September 30, 2017	$ 11.46	
Increase per share attributable to new investors purchasing shares in this offering	6.20	
Net tangible book value per share after this offering		17.66
Dilution per share to new investors		$ 122.32

Each $1.00 increase (decrease) in the assumed public offering price of $139.98 per share, which was the last reported sale price of our common stock on The Nasdaq Global Select Market on November 10, 2017, would (decrease) increase the number of shares of common stock to be issued by us in this offering by (34,204) and 34,696, respectively, assuming the aggregate dollar amount of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same. We may also increase or decrease the aggregate dollar amount of shares we are offering. The as adjusted information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

In the discussion and table above, we assume no exercise of outstanding options after September 30, 2017. As of September 30, 2017, there were 11,905,223 shares of common stock issuable upon exercise of outstanding options with a weighted-average exercise price of $59.35 per share. To the extent that any of these outstanding options are exercised, there will be further dilution to new investors. In addition, in the discussion and table above, we assume no exercise by the underwriters of their option to purchase additional shares. If the underwriters exercise their option to purchase additional shares, there will be further dilution to new investors.

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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 one hundred twenty-five million (125,000,000) shares of common stock and five million (5,000,000) shares of preferred stock. As of October 31, 2017, 92,730,812 shares of common stock were outstanding and no shares of preferred stock were outstanding.

Common Stock

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, except on any amendment to our certificate of incorporation that relates solely to the terms of one or more outstanding series of preferred stock if the holders of such affected series are entitled to vote thereon.

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

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.

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

Preferred Stock

We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the rights, preferences and privileges of the shares of each wholly unissued series, and any qualifications, limitations or restrictions thereon, including dividend rights, conversion rights, preemptive rights, terms of redemption

or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at the holder s option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the rights, preferences and privileges of the preferred stock of such series, as well as any qualifications, limitations or restrictions thereon, in the certificate of

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designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

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 Select 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.

Registration Rights

In February 2014, we entered into an investor agreement with Sanofi Genzyme in connection with our strategic collaboration. The investor agreement provides that, following the expiration of the lock-up period described in the investor agreement (which period will expire no earlier than December 31, 2019, unless the collaboration earlier terminates), Sanofi Genzyme will have three demand rights to require us to conduct a registered underwritten public offering with respect to the 8,766,338 shares of our common stock purchased by Sanofi Genzyme in February 2014. In addition, following the expiration of such lock-up period and until the tenth anniversary of such expiration or the date Sanofi Genzyme no longer owns at least 5 percent of our common stock, Sanofi Genzyme will be entitled to register such shares in our registered underwritten public offerings if other selling stockholders are included in the registration. These registration rights are subject to conditions and limitations, including the right, in certain circumstances, of the underwriters of an offering to limit the number of shares included in such registration, our right not to effect a demand registration more than once in any twelve-month period, and minimum thresholds for the number of shares that may comprise a demand registration.

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. Under our bylaws, members of our board of directors may only be removed for cause by the affirmative vote of the holders of at least 75 percent 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

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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 percent stockholder. A 15 percent stockholder is generally considered by Section 203 to be a person owning 15 percent or more of the corporation s outstanding voting stock. Section 203 refers to a 15 percent stockholder as an interested stockholder. Section 203 restricts these transactions for a period of three years from the date the stockholder acquires 15 percent 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 percent or more of our outstanding voting stock, or
- the interested stockholder owns at least 85 percent of our outstanding voting stock as a result of a transaction in which such stockholder acquired 15 percent or more of our outstanding voting stock. Shares held by persons who are both directors and officers or by some types of employee stock plans are not counted as outstanding when making this calculation.

Directors Liability

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

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

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

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

for transactions where the director derived an improper personal benefit.

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

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proceeding to the fullest extent permitted by Delaware law. We have also entered into indemnification agreements with our directors, in addition to the indemnification provided for in our certificate of incorporation, and intend to enter into indemnification agreements with any new directors in the future. We have purchased and intend to maintain insurance on behalf of any person who is or was a director against any loss arising from any claim asserted against him or her and incurred by him or her in any such capacity, subject to certain exclusions.

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Underwriting

We have entered into an underwriting agreement with Goldman Sachs & Co. LLC and J.P. Morgan Securities LLC, as representatives of the several underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the estimated underwriting discounts and commissions set forth on the cover page of this prospectus, the number of shares of common stock listed next to its name on the following table:

Name	Number of Shares
Goldman Sachs & Co. LLC	
J.P. Morgan Securities LLC	
Barclays Capital Inc.	
Credit Suisse Securities (USA) LLC	
Total	

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters are committed to purchase all the shares of common stock offered by us in the public offering if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters right to reject any order in whole or in part.

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

The underwriters have an option to buy up to $101,250,000 of additional shares of common stock from us. The underwriters have 30 days from the date of this prospectus supplement to exercise this option. If any shares are purchased with this option to purchase additional shares, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

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

	Without exercise of option to purchase additional shares	With full exercise of option to purchase additional shares

Per Share	$	$
Total		

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately $400,000.

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A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We have agreed that we will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise transfer or dispose of, directly or indirectly, or file with the SEC a registration statement under the Securities Act relating to, any shares of our common stock or securities convertible into or exercisable or exchangeable for our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing; (ii) enter into any swap or other arrangement that transfers, in whole or in part, any of the economic consequences associated with the ownership of any shares of common stock or any such other securities (whether any such transaction described in clause (i) or (ii) above is to be settled by delivery of common stock or such other securities, in cash or otherwise); or (iii) file any registration statement (other than a registration statement on Form S-8 or a registration statement filed in connection with a demand for registration pursuant to an existing agreement) with the SEC relating to the offering by us of any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock without the prior written consent of Goldman Sachs & Co. LLC and J.P. Morgan Securities LLC for a period of 60 days after the date of this prospectus supplement.

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

- the sale of shares of common stock pursuant to the underwriting agreement;
- the issuance by us of shares of common stock upon the exercise of an option or the conversion of a security outstanding as of the date of this prospectus supplement;
- the issuance or distribution by us of shares of common stock in accordance with the terms of our employee stock purchase plan and 401(k) plan in existence as of the date of this prospectus;
- the grant of options, restricted stock or other equity-based awards under equity incentive plans established and currently maintained by us or as inducement material to employees entering employment with us pursuant to NASDAQ Listing Rule 5635(c)(4); or
- the issuance by us of common stock representing up to 10 percent of our outstanding shares of common stock in connection with any strategic alliance, license, collaboration, acquisition or loan agreement entered into during the lock-up period.

Each of our directors and executive officers and Sanofi Genzyme have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant to which each of these persons or entities, with limited exceptions described below, for a period of 60 days after the date of this prospectus, may not, without the prior written consent of Goldman Sachs & Co. LLC and J.P. Morgan Securities LLC, (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to

purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock (including without limitation, common stock or such other securities which may be deemed to be beneficially owned by the undersigned in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant), or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

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

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

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

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

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The underwriters have advised us that, pursuant to Regulation M of the Securities Act, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

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

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

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

Selling Restrictions

Notice to Prospective Investors in the United Kingdom

This prospectus supplement and the accompanying prospectus are only being distributed to and are only directed at (i) persons who are outside the United Kingdom or (ii) to investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order) or (iii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as relevant persons). The shares are only available to, and any invitation, offer or agreement to subscribe, purchase or otherwise acquire such shares will be engaged in only with, relevant persons. Any person who is not a relevant person should not act or rely on this document or any of its contents.

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a Relevant Member State) an offer to the public of shares of our common stock may not be made in that

Relevant Member State, except that an offer to the public in that Relevant Member State of our common shares may be made at any time under the following exemptions under the Prospectus Directive:

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

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(b) to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive,

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

This European Economic Area selling restriction is in addition to any other selling restrictions set out herein.

Notice to Prospective Investors in Canada

The shares of our common stock may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares of our common stock must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser s province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser s province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in Hong Kong

The shares may not be offered or sold by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), or (ii) to professional investors within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a prospectus within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong)

and any rules made thereunder.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or

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purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries rights and interest in that trust shall not be transferable for 6 months after that corporation or that trust has acquired the shares under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

Notice to Prospective Investors in Japan

The shares have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (the Financial Instruments and Exchange Law) and each underwriter has agreed that it will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

Other Relationships

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include sales and trading, commercial and investment banking, advisory, investment management, investment research, principal investment, hedging, market making, brokerage and other financial and non-financial activities and services. The underwriters and their respective affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking, investment research and other financial and non-financial activities and services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, the underwriters and their respective affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

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Legal matters

The validity of the shares of common stock offered hereby will be passed upon for us by Goodwin Procter LLP. The underwriters are being represented in connection with this offering by Davis Polk & Wardwell LLP.

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Experts

The consolidated financial statements 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) incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2016 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

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Where you can find more information

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

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

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Incorporation of certain information by reference

The SEC allows us to incorporate into this prospectus supplement information that we file with the SEC in other documents. This means that we can disclose important information to you by referring to other documents that contain that information. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus. Information that we file with the SEC in the future and incorporate by reference in this prospectus supplement and the accompanying prospectus automatically updates and supersedes previously filed information as applicable. The following documents filed with the SEC pursuant to the Exchange Act are incorporated herein by reference (other than, in each case, documents or information deemed to have been furnished and not filed in accordance with SEC rules):

- our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on February 15, 2017, including portions of our definitive Proxy Statement on Schedule 14A, as filed with the SEC on March 17, 2017 in connection with our 2017 annual meeting of stockholders, to the extent specifically incorporated by reference therein;

- our Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2017, June 30, 2017 and September 30, 2017 as filed with the SEC on May 5, 2017, August 9, 2017 and November 7, 2017, respectively;

- our Current Reports on Form 8-K filed with the SEC on January 3, 2017, May 5, 2017 (solely with respect to Item 5.07 therein), May 9, 2017 (solely with respect to Item 5.02 therein), May 25, 2017 and September 7, 2017; and

- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on May 5, 2004, as amended by Amendment No. 1 to Form 8-A on Form 8-A/A filed with the SEC on June 3, 2004, Amendment No. 2 to Form 8-A on Form 8-A/A filed with the SEC on July 14, 2005 and our Registration Statement on Form 8-A filed with the SEC on April 8, 2014.

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

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

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PROSPECTUS

Alnylam Pharmaceuticals, Inc.

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 Select 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 May 5, 2017

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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.

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.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information others may give you. 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 r collectively, to Alnylam Pharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiaries.

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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 *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.

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INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. 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. 001-36407) 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) 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, 2016, including the information specifically incorporated by reference into the Annual Report on Form 10-K from our definitive proxy statement for the 2017 Annual Meeting of Stockholders;

- Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2017;

- Current Reports on Form 8-K filed on January 3, 2017 and May 5, 2017 (solely with respect to Item 5.07 therein); and

- The description of our common stock contained in our Registration Statement on Form 8-A filed on April 8, 2014, 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

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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, int anticipates, believes, estimates, predicts, potential, continue, target, goal and similar expressions are int 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.

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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 innovative medicines, and that this potential new drug class is similar to the opportunity created with other major biological discoveries such as recombinant DNA and monoclonal antibodies. Using our intellectual property and expertise, we are developing what we believe to be a reproducible and modular platform to develop RNAi therapeutics for a variety of human diseases.

Our research and development strategy is focused primarily on the use of our proprietary N-acetylgalactosamine, or GalNAc-conjugate platform for delivery of small interfering RNAs, or siRNAs the molecules that mediate RNAi toward genetically validated, liver-expressed target genes involved in the cause or pathway of human diseases. We are also focused on clinical indications where there are high unmet needs, early biomarkers for the assessment of clinical activity in Phase 1 clinical studies, and a definable path for drug development, regulatory approval, patient access and commercialization.

Specifically, our broad pipeline of investigational RNAi therapeutics is focused in three Strategic Therapeutic Areas, or STArs: Genetic Medicines, with multiple product candidates for the treatment of rare diseases; Cardio-Metabolic Diseases, with product candidates directed toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases; and Hepatic Infectious Diseases, with product candidates designed to address the major global health challenges of hepatic infectious diseases, beginning with hepatitis B and hepatitis D viral infections. We are focused on advancement of our *Alnylam 2020* strategy for the development and commercialization of RNAi therapeutics as a potential new class of innovative medicines. Specifically, our goal is to achieve, by the end of 2020, a company profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArs.

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

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CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES

The following table sets forth our consolidated ratios 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	Fiscal Year Ended				
	March 31, 2017	December 31, 2016	December 31, 2015	December 31, 2014	December 31, 2013	December 31, 2012
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, 2017 or for any of the years ended December 31, 2016, 2015, 2014, 2013 and 2012. 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, 2017 and the years ended December 31, 2016, 2015, 2014, 2013 and 2012, the ratio coverage was less than 1:1. We would have needed to generate additional earnings of $107,290,000, $410,108,000, $290,073,000, $400,604,000, $91,920,000 and $112,064,000, respectively, to achieve a coverage ratio of 1:1 in those periods.

Our consolidated ratios of earnings to combined fixed charges and preferred stock dividends for the periods indicated above are the same as our consolidated 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 and supporting our growth and the build out of our manufacturing and commercial infrastructure, 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, manufacturing expenses, commercial infrastructure expenses, general and administrative expenses, and 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.

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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 One Hundred Twenty-Five Million (125,000,000) shares of common stock and Five Million (5,000,000) shares of preferred stock. As of April 28, 2017, 86,190,192 shares of common stock were outstanding and no shares of preferred stock were outstanding.

Common Stock

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, except on any amendment to our certificate of incorporation that relates solely to the terms of one or more outstanding series of preferred stock if the holders of such affected series are entitled to vote thereon.

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

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.

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

Preferred Stock

We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the rights, preferences and privileges of the shares of each wholly unissued series, and any qualifications, limitations or restrictions thereon, including dividend rights, conversion rights, preemptive rights, terms of redemption

or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at the holder s option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the rights, preferences and privileges of the preferred stock of such series, as well as any qualifications, limitations or restrictions thereon, in the

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certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of that series of preferred stock. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

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 Select Market. We may utilize these additional shares for a variety of corporate purposes, including for future public offerings to raise additional capital or facilitate corporate acquisitions or for payment as a dividend on our capital stock. The existence of unissued and unreserved common stock and preferred stock may enable our board of directors to issue shares to persons friendly to current management or to issue preferred stock with terms that could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a controlling interest in our company by means of a merger, tender offer, proxy contest or otherwise. In addition, if we issue preferred stock, the issuance could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation.

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

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

Removal of Directors by Stockholders. Under our bylaws, members of our board of directors may only be removed for cause by the affirmative vote of the holders of at least 75% 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

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for a period of three years from the date the stockholder acquires 15% or more of our outstanding voting stock. With some exceptions, unless the transaction is approved by the board of directors and the holders of at least two-thirds of our outstanding voting stock, Section 203 prohibits significant business transactions such as:

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

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

The prohibition against these transactions does not apply if:

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

Directors Liability

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

- for any breach of the director s legal duty to act in the best interests of us and our stockholders;
- for acts or omissions by the director with dishonest intentions or which involve intentional misconduct or an intentional violation of the law;
- for declaring dividends or authorizing the purchase or redemption of shares in violation of Delaware law; or
- for transactions where the director derived an improper personal benefit.

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. We have also entered into indemnification agreements with our directors, in addition to the indemnification provided for in our certificate of incorporation, and intend to enter into indemnification agreements with any new directors in the future. We have purchased and intend to maintain insurance on behalf of any person who is or was a director against any loss arising from any claim asserted against him or her and incurred by him or her in any such capacity, subject to certain exclusions.

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DESCRIPTION OF DEBT SECURITIES

We may issue debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. We urge you to read the applicable prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the particular series of debt securities being offered, as well as the complete indenture that contains the terms of the debt securities. We will file as exhibits to the registration statement of which this prospectus is a part, the form of indenture and any supplemental agreements that describe the terms of the series of debt securities we are offering before the issuance of the related series of debt securities.

We may evidence each series of debt securities we will issue by an indenture that we enter into with a trustee. We will indicate the name and address of the trustee, if applicable, in the prospectus supplement relating to the particular series of debt securities being offered.

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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.

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DESCRIPTION OF WARRANTS

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

- the specific designation and aggregate number of, and the offering price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- 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.

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FORMS OF SECURITIES

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

Registered Global Securities

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

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agreement. We understand that under existing industry practices, if we request any action of holders or if an owner of a beneficial interest in a registered global security desires to give or take any action that a holder is entitled to give or take under the applicable indenture, purchase contract, purchase unit agreement or warrant agreement, the depositary for the registered global security would authorize the participants holding the relevant beneficial interests to give or take that action, and the participants would authorize beneficial owners owning through them to give or take that action or would otherwise act upon the instructions of beneficial owners holding through them.

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

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

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

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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.

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.

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

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

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and

- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

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

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

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.

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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 Goodwin Procter LLP.

EXPERTS

The consolidated financial statements 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) incorporated in this Prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2016 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

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$675,000,000

Common Stock

Prospectus Supplement

November , 2017

Goldman Sachs & Co. LLC

J.P. Morgan

Barclays

Credit Suisse

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

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