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 subst