ALNYLAM PHARMACEUTICALS, INC.
Form 10-K
February 15, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number 001-36407

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	77-0602661
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

300 Third Street, Cambridge, MA 02142

(Address of Principal Executive Offices) (Zip Code)

Registrant’s telephone number, including area code: (617) 551-8200

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.01 par value per share	The Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes No

The aggregate market value of the registrant's common stock, $0.01 par value per share ("Common Stock"), held by non-affiliates of the registrant, based on the last sale price of the Common Stock at the close of business on June 30, 2016, was $4,703,804,453. For the purpose of the foregoing calculation only, all directors and executive officers of the registrant are assumed to be affiliates of the registrant.

At January 31, 2017, the registrant had 86,013,785 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2017 annual meeting of stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2016, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

ALNYLAM PHARMACEUTICALS, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2016

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This annual report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve risks and uncertainties. All statements other than statements relating to historical matters should be considered forward-looking statements. When used in this report, the words “believe,” “expect,” “plan,” “anticipate,” “estimate,” “predict,” “may,” “could,” “should,” “intend,” “will,” “target,” “goal” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Our actual results could differ materially from those discussed in the forward-looking statements as a result of a number of important factors, including the factors discussed in this annual report on Form 10-K, including those discussed in Item 1A of this report under the heading “Risk Factors,” and the risks discussed in our other filings with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements, which reflect management’s analysis, judgment, belief or expectation only as of the date hereof. We explicitly disclaim any obligation to update these forward-looking statements to reflect events or circumstances that arise after the date hereof.

PART I

ITEM 1. BUSINESS

Overview

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 most advanced investigational RNAi therapeutic in development, patisiran, targets the transthyretin, or TTR, gene for the treatment of patients with polyneuropathy due to hereditary TTR-mediated amyloidosis, or hATTR amyloidosis. We expect to report top-line data from our ongoing APOLLO Phase 3 study of patisiran in mid-2017. Assuming that the APOLLO data are positive, we plan to submit our first new drug application, or NDA, and marketing authorization application, or MAA, for patisiran by the end of 2017. We expect to advance additional investigational RNAi therapeutics into Phase 3 development during 2017, including fitusiran, for the treatment of hemophilia and rare bleeding disorders, and givosiran (ALN-AS1), for the treatment of acute hepatic porphyrias. Given our plans for patisiran and the expected progress of our other late stage development programs, during 2016 we were focused on expanding our manufacturing, commercial and medical affairs capabilities to support our transition from a development-stage company toward a multi-product, commercial-stage biopharmaceutical company. For example, as a result of significant efforts in 2016, our manufacturing facility for patisiran formulated bulk drug product is now fully operational and ready for the potential launch of patisiran. In addition, we commenced construction of a manufacturing facility in Norton, Massachusetts for drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use. We also expanded our global footprint with the establishment of our European headquarters in Zug, Switzerland, as well as the opening of a new development and commercial hub in Maidenhead, United Kingdom. Lastly, we continued to build our commercial and medical affairs teams in preparation for the potential launch of patisiran in 2018, which we plan to market in the United States, Canada and Western Europe.

Finally, 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, and The Medicines Company, or MDCO.

RNAi Therapeutics – A Potential New Class of Innovative Medicines

RNAi is a natural biological pathway that occurs within cells to selectively silence the activity of specific genes. The discovery of RNAi first occurred in plants and worms in 1998, and two of the scientists who made this discovery, Dr. Andrew Fire and Dr. Craig Mello, received the 2006 Nobel Prize for Physiology or Medicine.

RNAi therapeutics harness the natural RNAi pathway to silence disease-associated genes and knock down production of disease-causing proteins, representing the opportunity to create a potential new class of innovative medicines. This potential new drug class is similar to the opportunity created with other major biological discoveries such as recombinant DNA and monoclonal antibodies. RNAi therapeutics also have a distinct mechanism of action, acting "upstream" of today's medicines. Specifically, RNAi therapeutics achieve their biological effects through a highly potent, catalytic mechanism. This unique mechanism of action confers a number of attributes that we believe have the potential to provide meaningful differentiation and distinct value for our investigational RNAi therapeutics relative to other drug classes.

Key Features of Alnylam Investigational RNAi Therapeutics Potential Attributes for Differentiation and Value
• Potential to silence any disease-associated gene, including so-called "undruggable" targets, where conventional therapeutic modalities (e.g., small molecule drugs and biologics) have not been successful
• Demonstrated potential in clinical trials to achieve robust clinical activity with up to 99 percent target gene knockdown in some cases
• Clamped pharmacodynamic effect that has potential to provide improved and consistent efficacy compared with intermittent and transient effects often achieved with other drug classes
• Demonstrated durability of effect in clinical trials that enables once-monthly, once-quarterly and, in some cases, possible bi-annual dose regimens
• Ability to achieve subcutaneous dose administration with our proprietary GalNAc-conjugate delivery platform
• Potential for room temperature stability, avoiding the inconveniences, costs and global challenges of a cold chain distribution

We believe that the combination of these attributes represents a very promising profile for our investigational therapeutics, even in competitive markets. We have reported on our advances in developing RNAi therapeutics as potential drugs in a large number of peer-reviewed publications and many scientific meetings, including publications by Alnylam scientists in the journals Nature, Nature Medicine, Nature Biotechnology, Cell, Proceedings of the National Academy of Sciences, the New England Journal of Medicine and The Lancet.

Our Product Platform

We are leading the translation of RNAi as a potential new class of innovative medicines, with a focus on development and commercialization of investigational RNAi therapeutics in three STArs: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases. With RNAi therapeutics, we believe that we have created a reproducible and modular platform for drug discovery, development and commercialization of innovative medicines.

Alnylam Reproducible and Modular Platform Strategic Framework for Innovative Medicines	
	• High unmet need population
1 Genetically validated, liver-expressed target gene	• Opportunity for highly competitive profile
	• Delivery with GalNAc-conjugate platform • Blood- or urine-based
2 Biomarker for human proof-of-concept in Phase 1	• Informative disease correlation
	• Establish dose/regimen for late stage development • Clinical development plans with established endpoints
3 Definable path to potential approval and market	• Demonstrable value for payors

Delivery of RNAi Therapeutics

In recent years, a tremendous amount of progress has been made in effectively delivering RNAi therapeutics to targeted organs and cells, and we believe Alnylam has been the leader of this advancement. This delivery success is now enabling execution on our product strategy and our Alnylam 2020 strategy.

Early efforts focused on delivery of RNAi therapeutics utilizing lipid nanoparticles, or LNPs, where siRNA molecules are encapsulated in specific lipid-based formulations. This technology enables systemic delivery with intravenous drug administration. Results with LNP-based investigational RNAi therapeutics demonstrate potent, rapid and durable target gene silencing in pre-clinical and clinical studies. Further, LNP-based investigational RNAi therapeutics have been found to be generally well tolerated in clinical studies conducted to date. Our lead product, patisiran, is formulated utilizing LNPs.

More recently, we began advancing proprietary technology that conjugates a sugar molecule called GalNAc to the siRNA molecule. This simpler delivery approach enables more convenient, subcutaneous administration of our drug candidates, a key aspect of our platform. Results from our Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform demonstrated a substantial increase in potency over our earlier “standard template chemistry” (STC)-GalNAc-conjugate approach in pre-clinical and clinical studies, and a durability of effect that we believe supports once-monthly, once-quarterly and in some cases, possibly even bi-annual subcutaneous dose regimens. Due to this increased potency and durability, as well as a wide therapeutic index, this conjugate platform has become our primary approach for development of investigational RNAi therapeutics.

We have extensive human safety experience with our investigational RNAi therapeutics, with over 1,000 patients or volunteers dosed for up to three years of treatment in over ten clinical programs. Our data demonstrates that to date,

RNAi therapeutics have been generally well tolerated with minimal platform-related safety findings. These findings, set forth below, occur at a low incidence and are monitorable. They are also generally asymptomatic and reversible even with continued dosing. Based on data as of December 2016, these findings include:

- Low incidence (2.2 percent) of generally mild, asymptomatic, reversible liver function test increases greater than three times the upper limit of normal, or ULN
- Low incidence (15.2 percent) of generally mild, transient injection site reactions, or ISRs

In our view, this is an acceptable tolerability profile in the high unmet need indications that we pursue.

In October 2016, we announced our decision to discontinue development of revusiran. Revusiran is an investigational therapeutic approach for the treatment of cardiomyopathy due to hATTR amyloidosis, which utilized our STC-GalNAc-conjugate delivery platform. 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 (N=17) as compared to those on placebo (N=2). This breakdown has been updated since October 2016 to reflect data available to us as of December 2016.

We are conducting a comprehensive evaluation of the revusiran data and expect this evaluation will take some time to complete, as uncertainty remains regarding the cause of the findings that led to the discontinuation of the revusiran program. Findings as of December 2016 showed that mortality events in the ENDEAVOUR trial were concentrated in the study patients with more advanced, end-stage heart failure.

Based on the ongoing evaluation there continues to be no evidence of any broader platform issue. The decision to discontinue development of revusiran did not affect patisiran or any of our other investigational RNAi therapeutic programs in development. The DMC for the APOLLO Phase 3 study of patisiran met at our request following our decision to discontinue development of revusiran, and recommended continuation of the APOLLO Phase 3 trial without modification.

We believe RNAi therapeutics represent a simplified and efficient new class of investigational medicines. We have achieved human proof of concept in multiple clinical trials of our investigational candidates, providing strong support for our approach to drug development. Moreover, we believe that our reproducible and modular platform will support our achievement of our 2020 strategy, such that by the end of 2020, we can grow into a multi-product commercial stage company with a deep and sustainable pipeline that can fuel continued growth for the future.

Our Product Pipeline

Our broad pipeline of investigational RNAi therapeutics is focused in three STArs: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases. The following is a summary of our product development programs as of January 31, 2017, that identifies those programs in which we have achieved human proof of concept, or POC, by demonstrating target gene knockdown and/or additional evidence of activity in clinical studies, the development stage of our programs and our commercial rights to such programs:

We have spent substantial funds over the past three years to develop our product pipeline and expect to continue to do so in the future. We incurred research and development costs of $382.4 million in 2016, $276.5 million in 2015 and $190.2 million in 2014.

The investigational therapeutics described below are in various stages of clinical development and the scientific information included about these therapeutics is preliminary and investigative. None of Alnylam's investigational therapeutics have been approved by the United States Food and Drug Administration, or FDA, European Medicines Agency, or EMA, or any other health authority and no conclusions can or should be drawn regarding the safety or efficacy of these therapeutics.

Late Stage Clinical Development Programs

Patisiran — Hereditary TTR-Mediated Amyloidosis

Patisiran, our most advanced investigational RNAi therapeutic in development, targets the TTR gene for the treatment of patients with polyneuropathy due to hATTR amyloidosis. hATTR amyloidosis is a progressively debilitating and often fatal disease caused by deposition of TTR in peripheral tissues. TTR protein is produced primarily in the liver and is normally a carrier of vitamin A. We believe TTR is a suitable target for an RNAi therapeutic formulated to maximize delivery to liver cells, which are the primary source of TTR synthesis. In hATTR amyloidosis, mutations in TTR result in the accumulation of damaging toxic deposits of the wild-type and mutant protein in several body organs and tissues, including the peripheral nervous system, heart and/or gastrointestinal tract. Our hATTR amyloidosis program targets wild-type and all known mutant forms of TTR, including the V30M and V122I mutations, which are the major mutations of hATTR amyloidosis, and therefore it represents a potential therapeutic approach for the treatment of all forms of hATTR amyloidosis.

hATTR amyloidosis represents a major unmet medical need with significant morbidity and mortality as an orphan, or rare, disease. Based on our analysis of the available patient and market data, we estimate that hATTR amyloidosis affects approximately 50,000 people worldwide. An estimated 10,000 people are typically classified as having predominant polyneuropathy symptoms and an estimated 40,000 people are classified as having predominant cardiomyopathy symptoms. We believe that our APOLLO and ENDEAVOUR Phase 3 studies, which targeted patients with polyneuropathy symptoms and cardiomyopathy symptoms, respectively, demonstrated that there is significant overlap between the two symptomatic presentations. Over 50 percent of patients in APOLLO had cardiac involvement at baseline and a significant percentage of ENDEAVOUR patients had polyneuropathy symptoms at baseline.

Patients with polyneuropathy due to hATTR amyloidosis have a mean life expectancy of five to 15 years from symptom onset, and the only approved treatment options for early stage disease are liver transplantation and TTR stabilizers such as tafamidis, a small molecule stabilizer of the TTR protein that has been approved for hATTR amyloidosis patients with early stage polyneuropathy in the European Union, or EU, certain countries in Latin America and Japan, where it is approved for all stages of disease. In some countries, patients may also be treated with diflunisal, a commercially available non-steroidal anti-inflammatory agent, which has been used off-label for the treatment of hATTR amyloidosis. The mean survival for patients with cardiomyopathy due to hATTR amyloidosis is approximately 2.5 to five years following diagnosis, and treatment is currently limited to supportive care. Although limited treatment options are available, there remains a significant need for novel therapeutics to treat patients with hATTR amyloidosis.

Our APOLLO Phase 3 clinical trial for patisiran is ongoing and we expect to report top-line data from APOLLO in mid-2017. Assuming that the APOLLO data are positive, we expect to submit an NDA and MAA for patisiran by the end of 2017.

- APOLLO Phase 3 Clinical Trial. In November 2013, we initiated our ongoing APOLLO Phase 3 clinical trial of patisiran. The APOLLO Phase 3 clinical trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in hATTR amyloidosis patients. The primary endpoint of the

study is the difference in the change in the modified composite Neuropathy Impairment Score (NIS), termed "mNIS+7," between patisiran and placebo at 18 months. The mNIS+7 score is an evaluation of muscle weakness, sensory and autonomic function, and nerve conductance across a 304-point scale, where neuropathy progression leads to an increased score over time. Secondary endpoints include: the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score; Neuropathy Impairment Score, or NIS-weakness; modified body mass index, or mBMI; timed ten-meter walk; and the COMPASS-31 autonomic symptom score. The trial was designed to enroll 200 hATTR amyloidosis patients with a baseline NIS in the range of five to 130, which represents patients with Stage 1 or Stage 2 familial amyloidotic polyneuropathy, or FAP. Patients were randomized two-to-one, patisiran-to-placebo, with patisiran administered at 0.30 mg/kg once every three weeks for 18 months by intravenous infusion. The study was designed with 90 percent power to conservatively detect as little as a 37.5 percent difference in change in mNIS+7 between treatment groups, with a two-sided alpha of 0.05. The placebo mNIS+7 progression rate was derived from an Alnylam analysis of natural history data from 283 hATTR amyloidosis patients. Patients completing the APOLLO Phase 3 clinical trial are eligible to enroll in a Phase 3 open-label extension, or OLE, study, called the APOLLO-OLE. In January 2016, we completed enrollment in our APOLLO study with a total of 225 hATTR amyloidosis patients with Stage 1 or Stage 2 disease, significantly exceeding the original anticipated enrollment of 200.

- Phase 2 OLE Clinical Trial. We have completed a Phase 2 clinical trial of patisiran. Patients participating in the Phase 2 study were eligible to participate in a Phase 2 OLE study with patisiran. The ongoing patisiran Phase 2 OLE study is an open-label, multi-center trial designed to evaluate the long-term safety and tolerability of patisiran administration. Patisiran is being administered once every three weeks at a dose of 0.30 mg/kg by intravenous infusion. The study is measuring a number of clinical endpoints every six months, including mNIS+7. In July 2016, we reported preliminary 24-month clinical data from this ongoing Phase 2 OLE study. The results for patients (N=24) who reached the 24-month endpoint as of a data cut off of May 12, 2016 showed a mean decrease of 6.7 points from baseline in mNIS+7 after 24 months of treatment. This compares favorably to an estimated mean increase (worsening) in mNIS+7 of 26 to 30 points at 24 months based upon analyses of historical data sets in untreated patients with polyneuropathy due to hATTR amyloidosis with similar baseline neurologic impairment. Similar results were seen in patients with or without concomitant use of TTR tetramer stabilizers. In a new analysis, over 70 percent of patients showed either improvement or no change in mNIS+7 at 24 months. In addition, patisiran administration was associated with statistically significant mean improvements in nerve fiber density from sweat gland biopsy samples from both the distal thigh and distal leg (p less than 0.01 for both), as read histologically in a blinded manner by a central lab. Over the 24-month period, hATTR amyloidosis patients with polyneuropathy with associated cardiac involvement (N=11) showed stability in their cardiac biomarkers, echocardiographic measures, and 10-meter walk test (i.e., gait speed). Serum TTR levels were also measured throughout the Phase 2 OLE study, and showed serum TTR reduction of up to 97 percent, a mean maximal reduction of 93 percent, and a mean reduction of 84 percent at 24 months.

In July 2016, we also presented the results of an exploratory analysis examining the relationship between the degree of serum TTR reduction with subsequent changes in mNIS+7. In the analysis, the degree of TTR reduction on Day 17 after the first dose of patisiran was compared to changes in mNIS+7 at 6, 12, 18 and 24 months. There was a positive correlation between the degree of serum TTR reduction and changes in mNIS+7. Specifically, greater degrees of TTR reduction resulted in greater levels of mNIS+7 improvement.

In the Phase 2 OLE study, patisiran administration was found to be generally well tolerated in patients with polyneuropathy due to hATTR amyloidosis out to 25 months, with no drug-related serious adverse events, or SAEs, reported through the data transfer date. The most common drug-related or possibly drug-related adverse events, or AEs, were flushing (22.2 percent) and infusion-related reactions (18.5 percent), all of which were mild in severity and did not result in any discontinuations. There were nine reports of SAEs in six patients, all of which were unrelated to study drug, including two deaths as previously reported. There were no clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelet counts.

We expect to report 36-month data from the patisiran Phase 2 OLE study in late 2017.

The Committee for Orphan Medicinal Products, or COMP, of the EMA has designated patisiran as an orphan medicinal product for the treatment of ATTR amyloidosis. In addition, the FDA provided Orphan Drug Designation to patisiran as a therapeutic approach for the treatment of ATTR amyloidosis. The FDA has also granted Fast Track designation to patisiran for the treatment of hATTR amyloidosis with polyneuropathy.

In January 2014, we entered into the 2014 Sanofi Genzyme collaboration, which is an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of Genetic Medicines, which includes our current and future Genetic Medicine programs that reach human proof-of-principal study completion, or Human POP, by the end of 2019, subject to extension to the end of 2021 in various circumstances. Under this collaboration, we are leading development and commercialization of patisiran in the United States, Canada and Western Europe while Sanofi Genzyme will develop and commercialize the product in the Sanofi Genzyme Territory. The 2014 Sanofi Genzyme collaboration is described below under the heading “Strategic Alliances.”

Fitusiran — Hemophilia and Rare Bleeding Disorders

Fitusiran is a subcutaneously administered, investigational RNAi therapeutic targeting antithrombin, or AT, for the treatment of hemophilia A and B and rare bleeding disorders, or RBD. Fitusiran is designed to lower levels of AT with the goal of promoting sufficient thrombin generation to prevent bleeding in patients with hemophilia and RBD. AT, also known as "antithrombin III" and "SERPINC1," is a liver expressed plasma protein and member of the “serpin” family of proteins that acts by inactivating thrombin and other coagulation factors. AT plays a key role in normal hemostasis by helping to limit the process of fibrin clot formation. However, in hemophilia, insufficient thrombin generation results in impaired fibrin clot formation. Lowering AT in the hemophilia setting may promote the generation of sufficient levels of thrombin needed to form an effective fibrin clot and prevent bleeding. This rationale is supported by human genetic data suggesting that co-inheritance of thrombophilic mutations, including AT deficiency, may ameliorate bleeding in hemophilia. We believe this approach is a unique and innovative strategy for preventing bleeding in people with hemophilia.

Hemophilia is an inherited bleeding disorder characterized by recurrent bleeding episodes, typically into the joints and muscles. Recurrent bleeding into joints results in arthritis and joint damage, reducing mobility and often requiring joint replacement surgeries. There are approximately 200,000 persons diagnosed with hemophilia worldwide. Hemophilia A, or HA, is defined by loss-of-function mutations in factor VIII and hemophilia B, or HB, is defined by a loss-of-function mutation in factor IX. In patients with hemophilia, a deficiency in plasma proteins factor VIII or factor IX prevents the generation of thrombin to levels that are sufficient to prevent or stop bleeding. Other RBD are defined by deficiencies of blood coagulation factors, including Factors II, V, VII, X and XI. Based on our analysis of the available patient and market data, we estimate that there are approximately 1,000 persons worldwide with a severe bleeding phenotype because of these conditions. The goal of treatment for persons living with hemophilia is to prevent bleeding, establish prompt management of bleeds, and manage the complications of bleeding and treatment. Current guidelines recommend management of hemophilia with regular intravenous infusions of recombinant or human-derived clotting factors. The most serious treatment-related complication is the development of antibodies, known as inhibitors, to replacement factor. Inhibitor development can occur in both HA and HB, impacting as many as one-third of people with severe HA, and persons in this inhibitor subset become refractory to standard replacement therapy. There exists a significant need for novel therapeutics to treat people living with hemophilia and RBD.

We believe fitusiran has the potential to prevent bleeding in severe HA and HB patients and in patients with other RBD. We are evaluating fitusiran in an ongoing Phase 1 study in HA and HB patients, with and without inhibitors, as well as in a Phase 2 OLE study. We plan to initiate our ATLAS Phase 3 program in early 2017. Subject to continued diligence and health authority feedback, the ATLAS program is expected to consist of three separate Phase 3 clinical trials: ATLAS-INH in severe HA and HB patients with inhibitors; ATLAS-A/B in severe HA and HB patients without inhibitors; and, ATLAS-PPX in severe HA and HB patients with or without inhibitors, switching from prophylactic factor or bypassing agent therapy to fitusiran prophylaxis.

- Phase 1/Phase 2 OLE Clinical Trials. The ongoing Phase 1 clinical trial of fitusiran is a single- and multi-dose, dose-escalation study comprised of four parts. Part A - which is complete - was a randomized, single-blind, placebo-controlled, single-dose, dose-escalation study (N=4 per cohort; 3:1 randomization of drug:placebo) in healthy volunteers. This part of the study was completed after the first dose cohort received a single subcutaneous dose of fitusiran at 30 micrograms per kilogram, or mcg/kg. Part B of the study - which is also complete - was an open-label, multi-dose, dose-escalation study that enrolled 12 patients with severe HA or HB. Patients in Part B received three weekly subcutaneous injections of fitusiran at doses of 15, 45, or 75 mcg/kg. Part C of the study - which has completed dosing - is an open-label, multi-dose, dose escalation study that enrolled 18 patients with moderate or severe hemophilia A or B without inhibitors. Twelve patients in Part C received three monthly subcutaneous doses of fitusiran at doses of 225, 450, 900, or 1800 mcg/kg. In addition, six patients in Part C received three fixed monthly subcutaneous doses of fitusiran at 80 mg. Part D of the study is designed to enroll up to 18 patients with inhibitors. Patients in Part D received three fixed monthly subcutaneous doses of fitusiran at 50 mg or 80 mg. The primary objective of Parts B, C, and D of the study is to evaluate the safety and tolerability of multiple doses of subcutaneously administered fitusiran in patients with hemophilia, with and without inhibitors. Secondary objectives include assessment of clinical activity as determined by lowering of plasma AT levels and increase in thrombin generation at pharmacologic doses of fitusiran. In addition, exploratory analyses of bleeding are being performed.

Patients with and without inhibitors who complete dosing in the Phase 1 trial are eligible to roll over into the fitusiran Phase 2 OLE study.

- Phase 1 Data – HA and HB Patients with Inhibitors. In December 2016, we reported interim results, as of the data cut-off date of October 6, 2016, from Part D of our ongoing fitusiran Phase 1 study in patients with HA or HB with inhibitors who were enrolled in two separate dose cohorts of 50 mg, once-monthly (N=6) or 80 mg, once-monthly (N=10). Treatment with fitusiran resulted in potent and dose-dependent lowering of AT and increases in thrombin generation. In an exploratory analysis of bleeding events, a median annualized bleeding rate, or ABR, of zero was

achieved for patients in combined dose cohorts in the observation period, compared to the pre-study median ABR of 31.

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