UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 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, 2015

Commission file number 0-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	33-0336973
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

2855 Gazelle Court, Carlsbad, CA 92010
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

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

Securities registered pursuant to Section 12(g) of the Act: **Common Stock, $.001 Par Value**

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

Indicate by check mark whether 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 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 definition 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 approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The NASDAQ Global Select Market was $5,760,508,916 as of June 30, 2015.*

The number of shares of voting common stock outstanding as of February 19, 2016 was 120,658,638.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 15, 2016 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 3, 2016 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 68 to 73 incorporates several documents by reference as indicated therein.

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* Excludes 19,785,891 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10 percent of the common stock outstanding at June 30, 2015. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference includes forward-looking statements regarding our business, the business of Akcea Therapeutics, Inc., a subsidiary of Ionis Pharmaceuticals, and the therapeutic and commercial potential of our technologies and products in development, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

In this report, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals, Inc. and its subsidiaries.

TRADEMARKS

Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc.

Akcea Therapeutics™ is a trademark of Ionis Pharmaceuticals, Inc.

Regulus Therapeutics® is a registered trademark of Regulus Therapeutics Inc.

KYNAMRO® is a registered trademark of Genzyme Corporation

Glybera® is a registered trademark of uniQure NV

CORPORATE INFORMATION

We incorporated in California in 1989 and in January 1991 we changed our state of incorporation to Delaware. In December 2015, we changed our name to Ionis Pharmaceuticals, Inc. from Isis Pharmaceuticals, Inc. Our principal offices are in Carlsbad, California. We make available, free of charge, on our website, *www.ionispharma.com*, our reports on Forms 10-K, 10-Q, 8-K and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that we include on or link to our website is not a part of this report or any registration statement that incorporates this report by reference. You may also read and copy our filings at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-732-0330. The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is *www.sec.gov*.

In December 2014, we formed our wholly owned subsidiary, Akcea Therapeutics, Inc., as a Delaware corporation, with its principal office in Cambridge, Massachusetts, to develop and commercialize drugs for people with serious cardiometabolic disorders.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2015
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PART I

Item 1. Business

Overview

We are leaders in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform. Using this platform, we have developed a large, diverse and advanced pipeline of potentially first-in-class and/or best-in-class drugs that we believe can provide high value for patients with significant unmet medical needs. In this way, we believe that we are fundamentally changing medicine with the goal to improve the quality of and save lives.

We have discovered and are developing three potentially transformational drugs, nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, which we believe are close to commercialization. We designed each of these three drugs to treat patients with orphan diseases who have limited or no therapeutic options. In total, we are developing these three drugs for six different patient populations. In 2015, we completed target enrollment in the first pivotal Phase 3 study for each of these three drugs, and we anticipate reporting data from these studies in the first half of 2017. We designed nusinersen to treat patients with spinal muscular atrophy, or SMA, a severe motor-neuron disease that is the leading genetic cause of infant mortality. We designed IONIS-TTR$_{Rx}$ to treat patients with transthyretin amyloidosis, or TTR amyloidosis, a fatal disease in which patients experience progressive buildup of amyloid plaque deposits in tissues throughout the body, including peripheral nerves, heart, intestinal tract, kidney and bladder. We designed volanesorsen to treat patients with diseases associated with extremely high levels of triglycerides, including patients with two severe and rare genetic conditions called familial chylomicronemia syndrome, or FCS, and patients with familial partial lipodystrophy, or FPL. We anticipate that the data from our pivotal Phase 3 studies of these drugs, if positive, will support global regulatory filings for each drug. We believe that the significant unmet medical need and the severity of these diseases could warrant a rapid path to market. Already our partners for these programs, Biogen for nusinersen and GSK for IONIS-TTR$_{Rx}$, are preparing to commercialize these drugs. Our wholly owned subsidiary, Akcea Therapeutics Inc., or Akcea, is preparing to commercialize volanesorsen. All three companies are engaging in pre-commercialization activities to understand the patient journey, build disease awareness with physicians and patients and develop their launch plans.

Nusinersen has the potential to be a transformational drug for infants and children with SMA. We are evaluating nusinersen in a broad development program designed to support marketing authorization for infants and children with this devastating disease. In our open-label studies, we have observed increases in the median event-free age in infants and increases in muscle function scores in infants and children with SMA. Although the studies are open-label with small numbers of patients, the totality of the data across these studies and multiple measures of activity suggest nusinersen could provide significant therapeutic benefit. Together with Biogen, we are conducting a broad development plan that supports a potentially rapid path to market for nusinersen.

IONIS-TTR$_{Rx}$ is potentially a first-in-class and best-in-class drug for the treatment of all forms of TTR amyloidosis. It is one drug, given as one subcutaneous injection, once a week. We and GSK are evaluating IONIS-TTR$_{Rx}$ in a broad development program designed to support marketing authorization of IONIS-TTR$_{Rx}$ for all forms of TTR amyloidosis: familial amyloid polyneuropathy, or FAP, and the cardiomyopathy form of TTR amyloidosis, which includes both familial amyloid cardiomyopathy, or FAC, and wild-type TTR, or wt-TTR. Together, these forms of TTR amyloidosis represent a large potential market for IONIS-TTR$_{Rx}$. In our open-label extension study we have observed substantial TTR reductions in patients with FAP. In a Phase 2 open-label, investigator-initiated study, Dr. Merrill Benson, professor of pathology and lab medicine and molecular genetics at Indiana University School of Medicine, observed sustained reductions in TTR and evidence of disease stabilization in patients with the cardiomyopathy form of TTR amyloidosis.

Volanesorsen has the potential to significantly improve the lives of patients who, because of their severely elevated triglycerides, are at constant risk of pancreatitis, which can require hospitalization and can be life-threatening. In our Phase 2 clinical program, patients with elevated triglycerides treated with volanesorsen showed significantly improved lipid profiles with substantial reductions of triglycerides and other risk factors of cardiovascular disease. To maximize the value of volanesorsen and other earlier-stage drugs for serious cardiometabolic disorders, we formed Akcea Therapeutics to focus on developing and commercializing these drugs. Akcea's pipeline includes volanesorsen, IONIS-APOCIII-L$_{Rx}$, IONIS-APO(a)-L$_{Rx}$ and IONIS-ANGPTL3-L$_{Rx}$. Moving these drugs into a company that we own and control allows us to retain substantial value from them and ensures Ionis' core focus remains on innovation. Akcea is building development and commercialization expertise in lipid and cardiometabolic diseases, including highly trained, specialized medical, marketing and sales teams, to successfully commercialize volanesorsen and the other lipid drugs in its pipeline.

In addition to our Phase 3 programs, we have a pipeline of drugs with the potential to be first-in-class and/or best-in-class drugs to treat patients with inadequately treated diseases. Our pipeline has over a dozen drugs in Phase 2 development, many of which we believe have the potential to be significant commercial opportunities. In particular, IONIS-FXI$_{Rx}$ and IONIS-APO(a)-L$_{Rx}$ are representative of the value we have created. IONIS-FXI$_{Rx}$ is the first antithrombotic in development that has shown it can decrease the risk of blood vessel obstruction caused by a blood clot without increasing bleeding risk. Given the unique profile of IONIS-FXI$_{Rx}$, we believe that IONIS-FXI$_{Rx}$ has the potential to be an important therapy for the many patients who need an antithrombotic but cannot take currently available therapies due to the high risk of bleeding. Because of the significant commercial opportunities for this drug, we licensed it to Bayer HealthCare, a leader in developing and commercializing antithrombotics. Bayer plans to conduct a robust development program to maximize the commercial value of IONIS-FXI$_{Rx}$. We are eligible to participate in this value through significant milestone payments and substantial royalties in the low-to-high 20 percent range on gross margins. IONIS-APO(a)-L$_{Rx}$ is the first and only drug in clinical development designed to selectively and robustly lower Lp(a), a key driver of cardiovascular disease. We believe that addressing Lp(a) is the next important horizon in lipid-focused cardiovascular disease treatment. In our clinical studies, we observed significant and sustained reductions in Lp(a) after only a single dose of IONIS-APO(a)-L$_{Rx}$. With our support, Akcea has designed a broad development program to evaluate IONIS-APO(a)-L$_{Rx}$ in patients who are at significant cardiovascular risk due to their high Lp(a) levels. In addition to these two examples, our Phase 2 pipeline includes drugs to treat patients with diseases spanning numerous therapeutic areas, including severe and rare diseases, viral infections, ocular diseases, metabolic disorders and cardiovascular diseases. We plan to expand the therapeutic reach of our technology by adding three to five new drugs to our pipeline every year.

We believe that our technology is the most versatile and most efficient drug discovery technology today. We can develop drugs to act upon disease targets in many different tissues, including the liver, muscle, kidney, brain, lung, eye, tumors and others. Many of these disease targets are inaccessible with other types of drugs. Our drugs also work through numerous different cellular mechanisms, allowing us to develop drugs that can decrease or increase the production of a target protein involved in disease and remove disease-causing RNAs. In our clinical studies, we have demonstrated that we can administer our drugs by numerous different routes of administration, including oral, local, intrathecal and subcutaneous administration. The recent advances we have made in our technology have already translated into significant value in many of our newer drugs, which patients tolerate better and which are more potent than our earlier Generation 2 drugs. We continue to advance our RNA technology to create even better medicines and to expand the reach of our technology. We actively patent the advances we have made across all areas of our technology and the drugs we are developing. In this way, we have amassed a substantial intellectual property position that provides us with extensive protection for our drugs and our technology.

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our products. Our partners bring resources and expertise that augment and build upon our internal capabilities. The depth of our knowledge and expertise with antisense technology provides us the flexibility to partner our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. We have distinct partnering strategies that we employ based on the specific program, therapeutic area and the expertise and resources our potential partners may bring to the collaboration. We have strategic partnerships with Biogen and AstraZeneca through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas that are outside of our expertise or in which our partners can provide tools and resources to complement our drug discovery efforts. We also form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas. For example, we established a collaboration with Janssen, which brings together our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation to discover and develop antisense drugs to treat autoimmune disorders in the gastrointestinal, or GI, tract. Additionally, we form development and commercialization partnerships that enable us to leverage our partner's global expertise and resources needed to support large commercial opportunities. For example, we licensed IONIS-FXI$_{Rx}$ to Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As a leader in the antithrombotic market, Bayer has the expertise, resources and commitment to broadly develop IONIS-FXI$_{Rx}$. Lastly, we also work with a consortium of companies that can exploit our drugs and technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Through our partnerships, we have created a broad and sustaining base of potential license fees, upfront payments, milestone payments, royalties, and earn out payments while controlling our drug development expenses. We have the potential to earn significant revenue from all of our partnerships. Since 2007, we have received more than $1.7 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn nearly $12 billion in future milestone payments and licensing fees from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out or royalty arrangements.

Corporate Highlights in 2015 and early 2016

- We formed a wholly owned subsidiary, Akcea Therapeutics, to develop and commercialize our lipid drugs, volanesorsen, IONIS-APOCIII-L$_{Rx}$, IONIS-APO(a)-L$_{Rx}$ and IONIS-ANGPTL3-L$_{Rx}$.
- We licensed IONIS-FXI$_{Rx}$ to Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis.
- We and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases, primarily focused on targets in the kidney, and renal diseases.
- We formed an alliance with Janssen to discover and develop antisense drugs to treat autoimmune disorders of the gastrointestinal tract.
- We received more than $320 million in payments from our partners in 2015.
- We changed our name to Ionis Pharmaceuticals, Inc. in December 2015 and our stock now trades under the ticker symbol "IONS".

Drug Development Highlights in 2015 and early 2016

- We continued to make significant advances in our pipeline and completed target enrollment for three pivotal phase 3 studies, including:
    - CHERISH, a Phase 3 study evaluating nusinersen in children with SMA.
    - NEURO-TTR, a Phase 3 study evaluating IONIS-TTR$_{Rx}$ in patients with FAP.
    - APROACH, a Phase 3 study evaluating volanesorsen in patients with FCS.
- We and our partners reported positive data from 13 clinical studies. These data exemplify the broad applicability and potential for antisense drugs to provide therapeutic benefit for many different diseases. These data include:
    - Phase 2 data from two ongoing open-label studies in which infants and children with SMA treated with nusinersen experienced increases in muscle function scores. Additionally, there were no events of death or permanent ventilation reported in 2015 in nusinersen-treated infants in the ongoing Phase 2 clinical study.
    - Data from the ongoing open-label extension study of NEURO-TTR in which patients with FAP treated with IONIS-TTR$_{Rx}$ for at least three months experienced reductions in TTR protein of up to 92 percent with a mean maximum (nadir) reduction of 76 percent compared to baseline.
    - Phase 2 data from an ongoing open-label, investigator-initiated study in patients with FAC and patients with wt-TTR treated with IONIS-TTR$_{Rx}$ for 12 months preliminarily evidencing disease stabilization and sustained TTR reductions.
    - Phase 2 data in which patients with high lipoprotein(a), or Lp(a), treated with IONIS-APO(a)$_{Rx}$ experienced reductions in Lp(a) of up to 94 percent.

- Phase 1/2 data in which patients with high Lp(a) treated with IONIS-APO(a)-L_{Rx} experienced a greater than 30-fold increase in potency over IONIS-APO(a)$_{Rx}$, the non-LICA Lp(a) drug. Patients also experienced dose-dependent reductions in Lp(a) of up to 97 percent and 99 percent after a single dose and multiple doses of IONIS-APO(a)-L_{Rx}, respectively.
- Clinical and preclinical data in patients with cancer, including advanced/metastatic hepatocellular carcinoma and diffuse large B cell lymphoma, treated with IONIS-STAT3-2.5$_{Rx}$ evidencing antitumor activity.
- Phase 2 data in which patients with type 2 diabetes treated with IONIS-PTP1B$_{Rx}$ experienced statistically significant mean reductions in body weight and HbA1c (0.7 percentage point).
- Phase 1 results in which healthy volunteers dosed with IONIS-ANGPTL3$_{Rx}$ experienced significant reductions of up to 93 percent in angiopoietin-like 3 protein, up to 63 percent in triglycerides and up to 46 percent in total cholesterol.
- Phase 1 results in which healthy volunteers dosed with IONIS-PKK$_{Rx}$ experienced significant, dose-dependent reductions of prekallikrein of up to 95 percent.
- Phase 3 data from the FOCUS FH study evaluating Kynamro in patients with severe heterozygous familial hypercholesterolemia. This study met its primary endpoint with a statistically significant reduction of LDL-Cholesterol, or LDL-C.

- We published clinical data from our novel lipid drugs, volanesorsen and IONIS-APO(a)$_{Rx}$, in the New England Journal of Medicine and The Lancet, respectively.
- The U.S. Food and Drug Administration, or FDA, granted volanesorsen orphan drug designation for the treatment of patients with FCS.
- The European Medicines Agency, or EMA, granted IONIS-HTT$_{Rx}$ orphan drug designation for the treatment of patients with Huntington's Disease.
- We, together with our partners, continued to advance our pipeline of drugs, initiating 11 clinical studies, including one Phase 3 study and six Phase 2 studies.

Drug Discovery and Development

Introduction to Drug Discovery

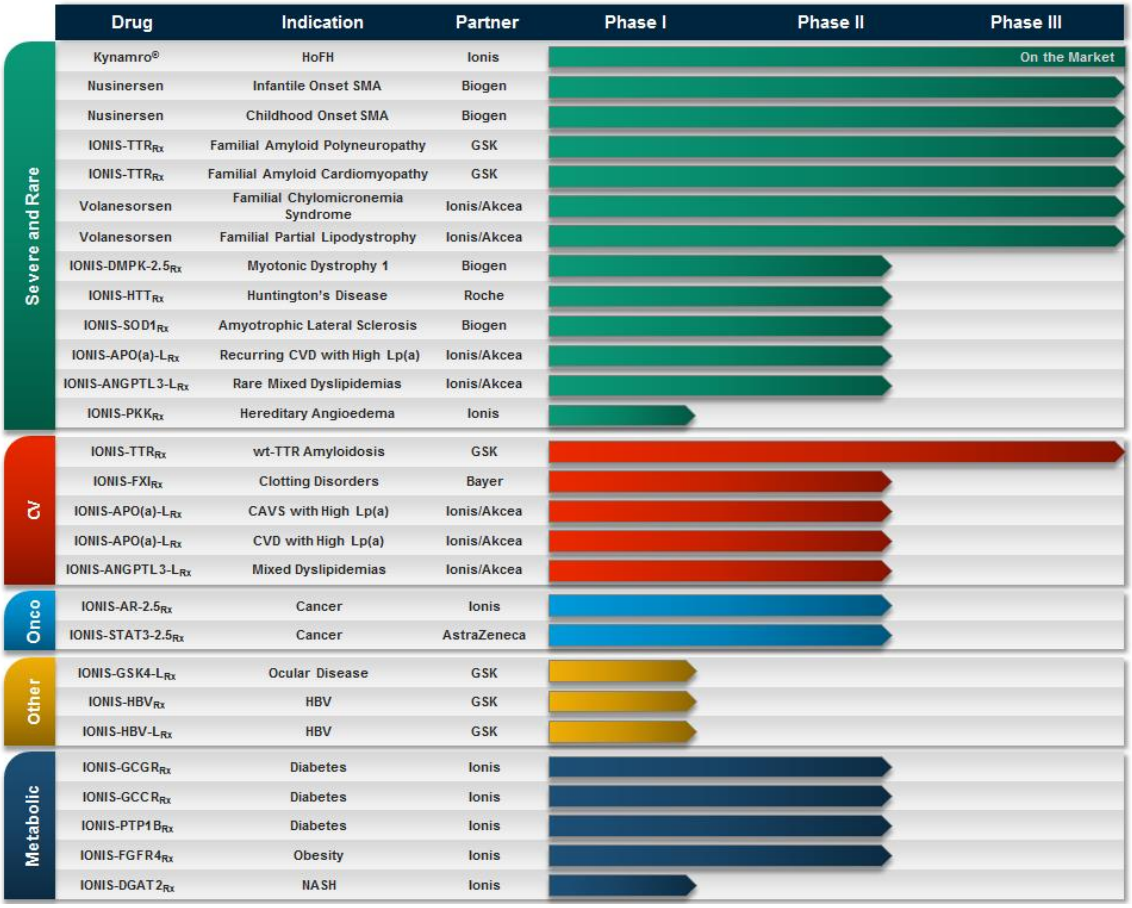
Proteins are essential working molecules in a cell. Almost all human diseases result from inappropriate protein production, improper protein activity or loss of a protein. Scientists use traditional drug discovery methods to design drugs to interact with the proteins in the body that are supporting or causing a disease. Antisense drugs are different from traditional small molecule drugs because antisense drugs can modify the production of proteins by targeting RNAs. In this way, antisense drugs can reduce the production of a disease-causing protein or increase the production of a protein that, when absent, causes disease. Antisense drugs also can treat disease by targeting and reducing RNAs that may be causing disease. RNAs are naturally occurring molecules in the body that primarily provide the information the cell needs to produce proteins. When our antisense drugs bind to the specific RNAs of a particular gene, they will ultimately alter the production of the protein encoded in the target gene or, in the case of disease-causing RNAs, degrade the RNA.

Our Development Projects

We are the leader in the discovery and development of an exciting class of RNA-targeted drugs called antisense drugs. With our proprietary drug discovery platform, we can rapidly identify drugs from a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. By combining this efficiency with our rational approach to selecting disease targets, we have built a large and diverse portfolio of drugs we designed to treat a variety of health conditions, with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological diseases, and cancer. We are developing antisense drugs for systemic, intrathecal and local delivery. We expect to continue to add new drugs to our pipeline, building a broad proprietary portfolio of drugs to treat many diseases and creating opportunities to generate substantial revenue. We also continue to improve our scientific understanding of our drugs, including how our drugs impact the biological processes of the diseases we target.

With our expertise in discovering and characterizing novel antisense drugs, our scientists can optimize the properties of our antisense drugs for use with particular targets. Our scientists have made significant advances in chemistries. Our Generation 2.0+ antisense drugs have increased potency and an improved side effect profile over our earlier generation drugs. Our scientists have further improved upon our second-generation chemistry with our Generation 2.5 chemistry, an advancement that further increases the potency of our drugs and broadens the tissues in which our drugs can work. We currently have four Generation 2.5 drugs in development, and we expect that some of our future drugs will also incorporate our Generation 2.5 chemistry. In addition to improving the chemical foundation of our drugs, we have also created LIgand-Conjugated Antisense, or LICA, technology, which we designed to enhance the delivery of our drugs to particular tissues. We believe that our LICA technology could further enhance the potency of our drugs. For example, our LICA technology directed toward liver targets produced a ten-fold increase in potency in preclinical studies in both our second-generation and our Generation 2.5 drugs. Our first clinical data from a LICA drug demonstrated an increase in potency that was more than 30-fold greater than what we observed with our non-LICA drug to the same target. We currently have eight second-generation LICA drugs in our pipeline, all of which we designed to inhibit targets in the liver. We expect we can also enhance some of our future drugs, including our Generation 2.5 drugs, with our LICA technology.

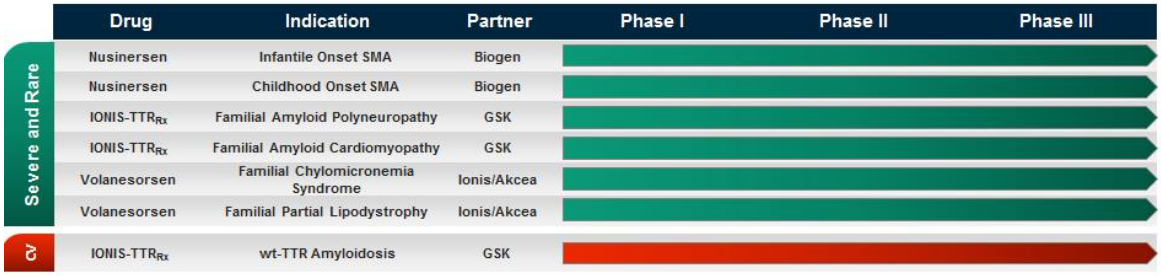
We have utilized our chemistry advancements to expand the therapeutic and commercial opportunities of our pipeline. These advancements, along with the manufacturing and analytical processes that are the same for all of our drugs, shorten our timeline from initial concept to the first human dose when compared to small molecule drugs.



The above table lists our pipeline, including the disease indications, our development partner if the drug is partnered, and the development status of each drug. Typically, the names of our drugs incorporate the target of the drug, such as IONIS-TTR$_{Rx}$. In this case, TTR is the target of the drug. Unless indicated otherwise, the majority of the drugs in our pipeline are Generation 2.0+ antisense drugs. We differentiate our Generation 2.5 drugs by adding a 2.5 notation at the end of the drug name, such as IONIS-DMPK-2.5$_{Rx}$. We differentiate our LICA drugs by adding an L at the end of the drug name, such as IONIS-APO(a)-L$_{Rx}$. We also plan to add Generation 2.5 drugs that incorporate our LICA technology. We will identify these drugs by the addition of both the 2.5 and L into the drug name. As the drugs in our pipeline advance in clinical development, we will adopt nonproprietary names given to each drug from the United States Adopted Names Council. For example, nusinersen is a nonproprietary name that we obtained for ISIS-SMN$_{Rx}$. Once we or our partners establish a brand name, we will adopt the brand name.

With a pipeline as large and advanced as ours, we have a number of clinical events each year as we initiate new clinical studies, complete and report data from clinical studies and add new drugs to our pipeline. In 2016, we plan to initiate multiple clinical studies, report data on multiple drugs and add three to five new drugs into development.

Our Phase 3 Drugs



We have three drugs for which we are conducting pivotal Phase 3 studies: nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen. Each of these drugs has the potential to transform the treatment of patients with an orphan disease, and we believe all three of these drugs are close to commercialization. In 2015,we completed target enrollment in a Phase 3 study for each of these drugs. We expect to have Phase 3 data for all three drugs in the first half of 2017 and potentially file for marketing authorization in the 2017/2018 timeframe if the data are positive.

Nusinersen – Nusinersen is an antisense drug we and Biogen are developing to treat patients with spinal muscular atrophy, or SMA. SMA is a severe motor-neuron disease that is the leading genetic cause of infant mortality. SMA occurs from a deletion or mutation of a gene responsible for producing a protein critical for normal cellular function. We designed nusinersen to compensate for this underlying genetic defect by increasing the production of the protein from a closely related gene. In January 2012, we and Biogen entered into an alliance that provides Biogen with an option to develop and commercialize nusinersen. We discovered nusinersen in collaboration with Dr. Adrian R. Krainer at Cold Spring Harbor Laboratory.

SMA affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. One in 50 people, approximately six million people in the United States, carry the gene mutation that causes SMA. Carriers experience no symptoms and do not develop the disease. When both parents are carriers, however, there is a one in four chance their child will have SMA. SMA is caused by a loss of, or defect in, the survival motor neuron 1, or SMN1, gene leading to a decrease in the survival motor neuron, or SMN protein. SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular growth and function. The severity of SMA correlates with the amount of SMN protein produced in motor neurons. Infants with Type I SMA, the most severe life-threatening form, produce very little SMN protein and have a significantly shortened life expectancy of less than two years according to natural history studies that researchers have conducted in patients with SMA. In a 2009 paper by Rudnik-Schöneborn, the median age for event-free survival in infants with Type I SMA was 6.2 months. In a contemporaneous study published in 2014 by the Pediatric Neuromuscular Clinical Research group, or PNCR, the median age for event-free survival in infants with two copies of SMN2 was 10.5 months. Children with Type II SMA generally have more copies of the SMN2 gene and have greater amounts of SMN protein than Type 1 infants but still have a shortened lifespan. Type II SMA patients are never able to walk. Children with Type III SMA have a normal lifespan but incur additional life-long physical disabilities as they grow.

We are evaluating nusinersen in a broad Phase 3 program. We have completed target enrollment in the Phase 3 study, CHERISH, in children with SMA and expect to complete enrollment in the Phase 3 study, ENDEAR, in infants with SMA in the second quarter of 2016. CHERISH is a randomized, international, double-blind, sham-procedure controlled fifteen month study in approximately 120 children with SMA who are non-ambulatory. We designed this study to support an application for marketing authorization of nusinersen in children with SMA. CHERISH is evaluating the efficacy and safety of a 12 mg dose of nusinersen with a primary endpoint of a change in the Hammersmith Functional Motor Scale-Expanded, or HFMSE, a validated method to measure changes in muscle function in children with SMA. We also included additional efficacy endpoints in the study. ENDEAR is a randomized, international, double-blind, sham-procedure controlled, thirteen month study in approximately 110 infants diagnosed with SMA. We designed this study to support an application for marketing authorization of nusinersen in infants with SMA. ENDEAR is evaluating the efficacy and safety of a 12 mg dose of nusinersen with a primary endpoint of survival or time to permanent ventilation. We also included additional efficacy endpoints in the study. We plan to report data from both ENDEAR and CHERISH in 2017.

The FDA has granted Orphan Drug Designation and Fast Track Status to nusinersen for the treatment of patients with SMA. The EMA has granted Orphan Drug Designation to nusinersen for the treatment of patients with SMA.

IONIS-TTR$_{Rx}$ – IONIS-TTR$_{Rx}$ is an antisense drug we and GSK are developing to treat patients with all forms of TTR amyloidosis. TTR amyloidosis is a severe, progressive and fatal disease. In all forms of TTR amyloidosis TTR protein forms amyloid deposits in various tissues and organs, including peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to organ failure and eventually death. Together with GSK, we are developing IONIS-TTR$_{Rx}$ as one drug with one product presentation, in one broad development plan for the treatment of patients with all forms of TTR amyloidosis. We designed IONIS-TTR$_{Rx}$ to be administered as one subcutaneous injection, once a week for all TTR amyloidosis patients.

TTR amyloidosis is a single disease that clinicians characterize into three forms that can have multiple overlapping clinical manifestations: FAP, FAC and wt-TTR. FAP affects approximately 10,000 patients worldwide. FAP patients primarily have TTR build up in the peripheral nervous system, but can also have significant TTR build up in multiple organs. FAP is a painful, fatal disease that ultimately leads to multi-organ failure and death within five to 15 years after symptom onset and diagnosis. FAC affects approximately 40,000 patients worldwide and wt-TTR amyloidosis affects approximately 200,000 patients worldwide. While both FAC and wt-TTR differ in the genetic cause of TTR amyloidosis, both diseases progress in similar ways. Patients with FAC and wt-TTR amyloidosis have TTR build up in the heart muscle and succumb to heart failure within three to five years after symptom onset and diagnosis. TTR amyloidosis is fatal and there are limited therapeutic options to treat patients with this disease.

We are evaluating IONIS-TTR$_{Rx}$ in a broad Phase 3 development program. We have completed target enrollment in the NEURO-TTR study which is a randomized, double-blind, placebo-controlled, international, Phase 3 study of IONIS-TTR$_{Rx}$ in FAP patients. We plan to report data from this study in 2017. We designed this study to support an application for marketing authorization of IONIS-TTR$_{Rx}$ in patients with FAP. Our study is measuring the effects of IONIS-TTR$_{Rx}$ on neurological dysfunction and on quality-of-life. In 2016, our partner, GSK, plans to initiate a Phase 3 outcome study, CARDIO-TTR, in all forms of TTR amyloid cardiomyopathy, including both FAC and wt-TTR amyloidosis. In 2016, GSK is also planning to initiate a small Phase 3 study in Japan in patients with FAP to support Japanese regulatory filings.

The FDA has granted Orphan Drug Designation and Fast Track Status to IONIS-TTR$_{Rx}$ for the treatment of patients with FAP. The EMA has granted Orphan Drug Designation to IONIS-TTR$_{Rx}$ for the treatment of patients with all types of TTR amyloidosis.

Volanesorsen – Volanesorsen is an antisense drug we and Akcea are developing to treat patients with FCS and patients with FPL. We designed volanesorsen to reduce ApoC-III, a protein the liver produces that regulates triglyceride metabolism in the blood. Physicians associate higher levels of ApoC-III with a higher risk of cardiovascular disease. Akcea is responsible for developing and commercializing volanesorsen.

Both FCS and FPL are ultra-orphan diseases, each affecting an estimated 3,000 to 5,000 patients worldwide. FCS is often associated with triglyceride levels higher than 2,000 mg/dL. Because of their extremely high triglyceride levels, FCS patients are at significant risk of many serious health conditions, including frequent episodes of pancreatitis, which can require hospitalization and can be life-threatening. FPL is associated with the inability of a patient to store fat, resulting in high triglyceride levels that are often above 1,000 mg/dL and increased risk for pancreatitis. In addition, most patients with FPL have diabetes and other metabolic abnormalities. Current treatment options do not reduce triglyceride levels enough to reduce the risk of serious illness in patients with FCS or FPL. We believe that the robust triglyceride reduction and the improvements in glucose control we observed in our Phase 2 program support our evaluation of volanesorsen in both of these patient populations.

We are evaluating volanesorsen in a broad Phase 3 development program. We have completed target enrollment in the APPROACH study, which is a randomized, double-blind, placebo-controlled, international Phase 3 study in patients with FCS. We are also evaluating volanesorsen in a Phase 3 study, BROADEN, in patients with FPL. BROADEN is a randomized, double-blind, placebo-controlled, international study in patients with FPL. The primary endpoint of both APPROACH and BROADEN is percent change in fasting triglycerides from baseline after three months of dosing with volanesorsen.

The FDA and EMA have granted Orphan Drug Designation to volanesorsen for the treatment of patients with FCS.

Akcea Therapeutics: Our Wholly Owned Subsidiary to Develop and Commercialize Drugs for Cardiometabolic Disorders

Akcea Therapeutics, our wholly owned subsidiary, is a company focused on developing and commercializing potentially transformative medicines for people with serious cardiometabolic diseases caused by lipid disorders. This report includes financial information for this separate business segment in Note 7, *Segment Information and Concentration of Business Risk,* in the Notes to the Consolidated Financial Statements. Since its formation in late 2014, Akcea has advanced its portfolio of development-stage drugs covering multiple targets and diseases. We believe each drug in the Akcea portfolio has the potential to treat several diseases with substantial overlap in the treating physician community, particularly among lipid disease thought leaders. Akcea is building expertise in lipids and cardiometabolic diseases which it can leverage across its entire portfolio.

Akcea plans to develop and successfully commercialize globally a portfolio of our cardiometabolic drugs. These drugs include volanesorsen, IONIS-APOCIII-L_{Rx}, IONIS-APO(a)-L_{Rx} and IONIS-ANGPTL3-L_{Rx}. In 2015, Akcea enhanced its development and commercial capabilities by hiring several seasoned professionals whose collective experience includes multiple rare disease launches over two decades and deep clinical and commercial experience focused primarily on lipid disorders, cardiovascular disease and endocrinology.

Also in 2015, Akcea advanced the commercial development activities for volanesorsen in patients with FCS. These activities include:

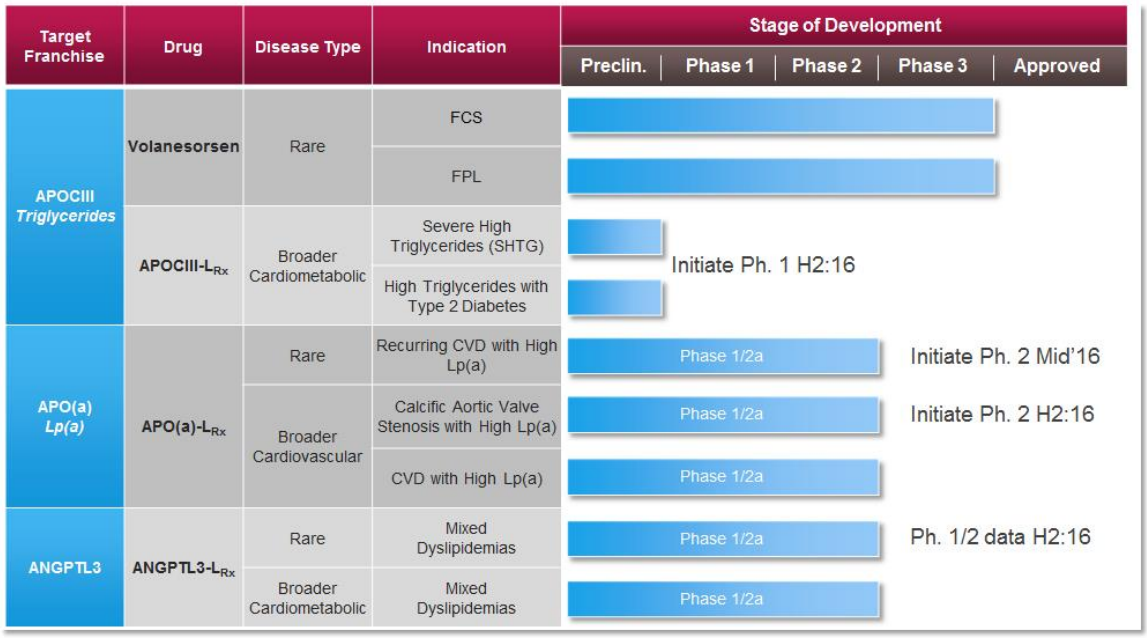
- Increasing the understanding of the patients and treating physicians who take care of these patients;
- Increasing awareness of FCS;
- Enhancing the speed and quality of diagnosis; and
- Understanding the burden of disease.

Akcea plans to leverage these same commercialization activities across its portfolio to commercialize its drugs for rare populations. Akcea may establish relationships with large pharmaceutical companies to co-commercialize select Akcea drugs for large patient populations that require a substantial sales force.

In 2016, Akcea plans to prepare the regulatory filings for volanesorsen so it can file for marketing authorization as quickly as possible after reporting Phase 3 FCS data in 2017, assuming the data are positive. Akcea also plans to continue to build the development, regulatory, and commercial infrastructure required to commercialize volanesorsen, including a specialized clinical field force and physician and patient support teams. Akcea intends to build these functions in the United States and Europe first.

We granted Akcea exclusive rights to develop and commercialize volanesorsen, IONIS-APOCIII-L_{Rx}, IONIS-APO(a)-L_{Rx}, and IONIS-ANGPTL3-L_{Rx} as part of its formation. Akcea is responsible for globally developing and commercializing these drugs. Ionis will provide business support services to Akcea and Akcea will compensate Ionis for providing such services. Below is Akcea's product pipeline that includes the disease type, disease indication and the stage of development for each drug.

Akcea's Cardiometabolic Disease Pipeline



Volanesorsen – Volanesorsen is an antisense drug we and Akcea are developing to treat patients with FCS and FPL. For more information on the development plan for volanesorsen see the drug description under Our Phase 3 Drugs.

IONIS-APO(a)-L_{Rx} – IONIS-APO(a)-L_{Rx} is a LICA drug we designed to reduce apolipoprotein(a) in the liver to offer a direct approach for reducing lipoprotein(a), or Lp(a). Lp(a) is an independent risk factor for cardiovascular disease. Physicians associate high levels of Lp(a) with an increased risk of atherosclerosis, coronary heart disease, heart attack and stroke. IONIS-APO(a)-L_{Rx} is the first and only clinical program to selectively reduce Lp(a) in patients by inhibiting apo(a).

Unlike other cardiovascular risk factors, Lp(a) levels are genetically determined and remain constant throughout the life of the individual. This means that patients who have high Lp(a) levels have been exposed to high levels of Lp(a) for their entire life. The European Atherosclerosis Society recommends that Lp(a) be less than or equal to 50 mg/dL. Diet and lifestyle changes have little impact on Lp(a) levels and current therapies do not adequately reduce Lp(a) to acceptable levels in patients with elevated Lp(a). Even patients who can control their LDL-C remain at high-risk of cardiovascular events if they have high levels of Lp(a). As a result, there is a significant need for a highly specific drug that can lower Lp(a).

Physicians characterize calcific aortic valve stenosis, or CAVS, as the progressive restriction of a patient's supply of oxygenated blood to the rest of the patient's body due to calcium deposits on the aortic valve. Aortic valve replacement, or AVR, is the only option once CAVS progresses to a severe stage and/or the patient is symptomatic with fainting, shortness of breath, or congestive heart failure. Patients with elevated Lp(a) levels experience a faster progression of CAVS leading to the need for AVR. Therefore, an effective medical therapy to reduce the progression of CAVS and delay the need for AVR could potentially improve symptoms, enhance heart function and reduce mortality in patients with CAVS.

We completed a Phase 1/2 study for IONIS-APO(a)-L_{Rx} in subjects with high Lp(a). We and Akcea plan to develop IONIS-APO(a)-L_{Rx} in a broad program that addresses near, mid and long-term commercial opportunities that include patients with recurrent cardiovascular events and high Lp(a); patients with CAVS and high Lp(a); and patients with cardiovascular disease and high Lp(a).

IONIS-ANGPTL3-L_{Rx} – IONIS-ANGPTL3-L_{Rx} is a LICA drug we designed to reduce angiopoietin-like 3 protein, or ANGPTL3, an independent risk factor for cardiovascular disease. ANGPTL3 is a glycoprotein that is principally expressed in the liver and regulates lipid, glucose and energy metabolism. People with elevated levels of ANGPTL3 have high LDL-C and triglyceride levels, which physicians associate with an increased risk of premature heart attacks, increased arterial wall thickness and multiple metabolic abnormalities, such as insulin resistance. In contrast, people with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels. We designed IONIS-ANGPTL3-L_{Rx} to treat multiple dyslipidemias from rare lipid disorders to broader cardiometabolic disease, including mixed dyslipidemia. Akcea is responsible for developing and commercializing IONIS-ANGPTL3-L_{Rx}.

Patients with mixed dyslipidemia often have elevated LDL-C, and triglyceride levels. These patients frequently also have low levels of HDL. A growing body of clinical data demonstrates an association between elevated cholesterol and triglycerides and increased cardiovascular risk. Further, the increasing obesity rates throughout the world have fueled the development of metabolic syndrome, a disorder characterized by dyslipidemia, loss in insulin sensitivity and increased fat accumulation in the liver.

Genome-wide association studies have confirmed the association of mutations in ANGPTL3 with improvements in lipid levels. Patients with dyslipidemia often have multiple cardiovascular and metabolic risk factors that remain challenging to treat. Despite existing therapies, there remains an unmet need for a therapy that could significantly decrease multiple cardiovascular risk factors, such as LDL-C and triglycerides. Our preclinical data suggests that reducing ANGPTL3 could improve lipid parameters, including LDL-C, triglycerides, and total cholesterol, as well as metabolic parameters, such as insulin sensitivity.

Akcea is evaluating IONIS-ANGPTL3-L_{Rx} in a randomized, placebo-controlled, dose-escalation Phase 1/2 study in healthy volunteers with elevated triglycerides and in patients with familial hypercholesterolemia.

Cardiovascular Franchise

Cardiovascular disease is an area of focus for us. Our cardiovascular franchise includes the drugs Akcea is developing that we describe above and other drugs. The drugs in our cardiovascular franchise target all the key components of cardiovascular disease, including various atherogenic lipids, inflammation and thrombosis. Volanesorsen is our most advanced drug in this franchise.

IONIS' Cardiovascular Disease Pipeline

IONIS-TTR_{Rx} – IONIS-TTR_{Rx} is an antisense drug we designed to reduce the production of TTR to treat patients with all forms of TTR amyloidosis, including the cardiomyopathy forms in which TTR protein accumulates in heart muscle leading to heart failure. For more information on the development plan for IONIS-TTR_{Rx} see the drug description under Our Phase 3 Drugs.

IONIS-FXI$_{Rx}$ – IONIS-FXI$_{Rx}$ is an antisense drug we designed to reduce the production of Factor XI. Factor XI is important in the growth of blood clots. High levels of Factor XI increase the risk of thrombosis, which is the formation of a blood clot inside blood vessels. Thrombosis can cause heart attacks and strokes. People who are deficient in Factor XI have a lower incidence of these events with minimal increase in bleeding risk. Although currently available anticoagulants reduce the risk of thrombosis, physicians associate these anticoagulants with increased bleeding, which can be fatal. Given the mechanism of Factor XI inhibition, IONIS-FXI$_{Rx}$ has the potential for physicians to use it broadly as an antithrombotic in many different therapeutic settings for which there is a need for additional safe and well tolerated antithrombotic drugs.

In May 2015, we exclusively licensed IONIS-FXI$_{Rx}$ to Bayer. Bayer plans to evaluate the therapeutic profile of IONIS-FXI$_{Rx}$ in patients for whom currently available antithrombotics may not be used, such as in patients with a high risk of bleeding due to multiple co-morbidities. After successful completion of ongoing activities at Ionis, Bayer will assume all global development, regulatory and commercialization responsibilities for IONIS-FXI$_{Rx}$.

We completed a Phase 2 open-label, comparator-controlled global study evaluating IONIS-FXI$_{Rx}$ in patients undergoing total knee replacement surgery. The study compared the safety and activity of IONIS-FXI$_{Rx}$ to enoxaparin. In this study patients treated with 300 mg of IONIS-FXI$_{Rx}$ experienced a seven-fold lower rate of venous thromboembolic events, such as blood clots in a deep vein or in a lung, compared to those patients treated with enoxaparin. The data from this study was published in the New England Journal of Medicine in December 2014.

We are currently evaluating IONIS-FXI$_{Rx}$ in a Phase 2 study in patients with end-stage renal disease on hemodialysis. We designed this study to further characterize the profile of IONIS-FXI$_{Rx}$ and to provide essential data for Bayer's future clinical development program for IONIS-FXI$_{Rx}$.

IONIS-APO(a)-L$_{Rx}$ – IONIS-APO(a)-L$_{Rx}$ is a LICA drug we designed to reduce apolipoprotein(a) in the liver to offer a direct approach for reducing Lp(a). We and Akcea are developing IONIS-APO(a)-L$_{Rx}$ for patients with high Lp(a). For more information on the development plan for IONIS-APO(a)-L$_{Rx}$, see the drug description under Akcea Therapeutics.

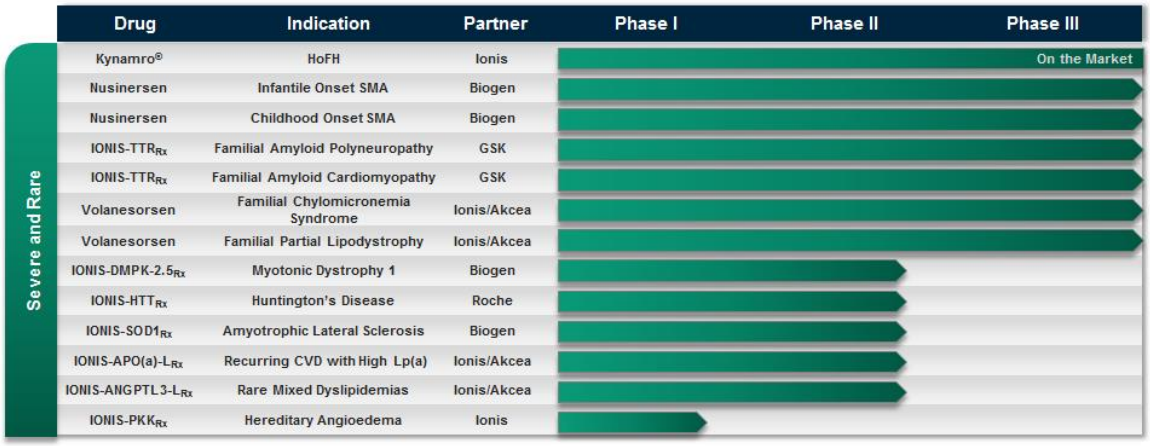
IONIS-ANGPTL3-L$_{Rx}$ – IONIS-ANGPTL3-L$_{Rx}$ is a LICA drug we designed to reduce ANGPTL3, an independent risk factor for cardiovascular disease. We and Akcea are developing IONIS-ANGPTL3-L$_{Rx}$ for patients with mixed dyslipidemias. For more information on the development plan for IONIS-ANGPTL3-L$_{Rx}$, see the drug description under Akcea Therapeutics.

Severe and Rare Disease Franchise

Our severe and rare disease franchise is the largest franchise in our pipeline. We are discovering and developing antisense drugs to treat patients with severe and rare and neurological diseases who need new treatment options. We believe our antisense technology could offer effective therapies for these patients. According to the National Institutes of Health, or NIH, there are approximately 5,000 to 8,000 rare diseases and more than 600 neurological diseases, many life-threatening or fatal. Unfortunately, patients with many of these severe and rare diseases have few effective therapies available. Since most of these diseases are genetic or have a genetic component, parents often pass the disease to their children, creating a legacy of the disease and resulting in profound effects on the family. We are evaluating nusinersen, the most advanced neurological drug in our pipeline, in two Phase 3 studies to treat infants and children with SMA.

Due to the severe nature of these diseases and the lack of available treatments, there is an opportunity for more flexible and efficient development paths to the market. This means that, in some cases, the studies necessary for us to demonstrate proof-of-concept with a particular drug may also be the studies that complete our marketing registration package, thereby providing us with a relatively rapid path to market for potential new treatments for these devastating and often fatal diseases.

IONIS' Severe and Rare Disease Pipeline



Kynamro – Kynamro (mipomersen sodium) injection is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet, to reduce low density lipoprotein-cholesterol, or LDL-C, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with HoFH. Kynamro is approved for use in patients with HoFH in the United States and several other countries.

Nusinersen – Nusinersen is an antisense drug we designed to treat patients with SMA. SMA is a severe motor-neuron disease that is the leading genetic cause of infant mortality. Together with Biogen, we are developing nusinersen to treat all forms of SMA. For more information on the development plan for nusinersen, see the drug description under Our Phase 3 Drugs.

IONIS-TTR$_{Rx}$ – IONIS-TTR$_{Rx}$ is an antisense drug we designed to treat all forms of TTR amyloidosis. TTR amyloidosis is a severe, progressive and fatal disease. For more information on the development plan for IONIS-TTR$_{Rx}$ see the drug description under Our Phase 3 Drugs.

Volanesorsen – Volanesorsen is an antisense drug we and Akcea are developing to treat patients with FCS and FPL. For more information on the development plan for volanesorsen see the drug description under Our Phase 3 Drugs.

IONIS-DMPK-2.5$_{Rx}$ – IONIS-DMPK-2.5$_{Rx}$ is an antisense drug we designed to reduce the toxic dystrophia myotonica-protein kinase, or DMPK, RNA to treat patients with myotonic dystrophy type 1, or DM1. Together with Biogen, we are developing IONIS-DMPK-2.5$_{Rx}$ to treat patients with DM1.

DM1 is a genetic neuromuscular disease caused by a defect in the DMPK gene which causes the accumulation of toxic DMPK RNA. Physicians characterize DM1 by progressive muscle atrophy, weakness, disabling muscle spasms and prolonged muscle contractions. DM1 also affects many other organs within the body and patients can also experience insulin insensitivity, cataracts and infertility. Currently, there are no disease-modifying therapies for patients with DM1 and currently available treatments are intended only to manage symptoms.

We are evaluating IONIS-DMPK-2.5$_{Rx}$ in a randomized, placebo-controlled, dose-escalation Phase 1/2 clinical study in patients with DM1.

The FDA has granted Orphan Drug Designation for IONIS-DMPK-2.5$_{Rx}$ for the treatment of patients with DM1.

IONIS-HTT$_{Rx}$ – IONIS-HTT$_{Rx}$ is an antisense drug we designed to reduce the production of the huntingtin, or HTT, protein, which is the genetic cause of Huntington's disease, or HD. We are collaborating with Roche to develop IONIS-HTT$_{Rx}$ to treat patients with HD.

HD is a rare, genetic, progressive neurological disease resulting in deterioration in mental abilities and physical control. HD is a triplet repeat disorder and is one of a large family of genetic diseases in which the body mistakenly repeats certain gene sequences. The resulting HTT protein gradually damages neurons in the brain. Symptoms of HD usually appear between the ages of 30 to 50 years and continually worsen over a 10 to 25 year period. Ultimately, the weakened individual succumbs to pneumonia, heart failure or other complications. Presently, there is no effective disease-modifying treatment, and current approaches only focus on managing the severity of some disease symptoms.

We are evaluating IONIS-HTT$_{Rx}$ in a randomized, placebo-controlled, dose escalation, Phase 1/2 clinical study in patients with early stage HD.

The FDA and EMA have granted Orphan Drug Designation for IONIS-HTT$_{Rx}$ to treat patients with HD.

IONIS-SOD1$_{Rx}$ – IONIS-SOD1$_{Rx}$ is an antisense drug we designed to reduce the production of superoxide dismutase 1, or SOD1, which is the best understood genetic cause of familial amyotrophic lateral sclerosis, or ALS. We are collaborating with Biogen to develop IONIS-SOD1$_{Rx}$ to treat patients with an inherited form of ALS, SOD1-ALS.

ALS is a rare, fatal neurodegenerative disorder. Patients with ALS suffer progressive degeneration of the motor neurons, which results in a declining quality of life and ultimately death. The second most common familial form of ALS is SOD1-ALS, in which patients have a mutation in the SOD1 gene that causes a progressive loss of motor neurons. As a result, patients with SOD1-ALS experience muscle weakness, loss of movement, difficulty in breathing and swallowing and eventually succumb to their disease. Currently, treatment options for patients with ALS are extremely limited with no drugs that significantly slow disease progression.

We are evaluating IONIS-SOD1$_{Rx}$ in a randomized, placebo-controlled, dose escalation, Phase 1/2 clinical study in patients with ALS, including patients with SOD1-ALS.

IONIS-APO(a)-L$_{Rx}$ – IONIS-APO(a)-L$_{Rx}$ is a LICA drug we designed to reduce apolipoprotein(a) in the liver to offer a direct approach for reducing Lp(a). We and Akcea are developing IONIS-APO(a)-L$_{Rx}$ for patients with recurrent cardiovascular disease and high Lp(a). For more information on the development plan for IONIS-APO(a)-L$_{Rx}$, see the drug description under Akcea Therapeutics.

IONIS-ANGPTL3-L$_{Rx}$ – IONIS-ANGPTL3-L$_{Rx}$ is a LICA drug designed to reduce ANGPTL3, an independent risk factor for cardiovascular disease. We and Akcea are developing IONIS-ANGPTL3-L$_{Rx}$ for patients with mixed dyslipidemias. For more information on the development plan for IONIS-ANGPTL3-L$_{Rx}$, see the drug description under Akcea Therapeutics.

IONIS-PKK$_{Rx}$ – IONIS-PKK$_{Rx}$ is an antisense drug we designed to reduce the production of prekallikrein, or PKK, to treat patients with hereditary angioedema, or HAE. HAE is a rare genetic disease that is characterized by rapid and painful attacks of inflammation in the hands, feet, limbs, face, abdomen, larynx and trachea and can be fatal if swelling occurs in the larynx. PKK plays an important role in acute attacks of HAE. By inhibiting the production of PKK, IONIS-PKK$_{Rx}$ could be an effective prophylactic approach to preventing HAE attacks. In patients with frequent or severe attacks, doctors may use prophylactic treatment approaches to prevent and reduce the severity of HAE attacks. However, current prophylactic treatment approaches are very limited and have significant tolerability issues leaving patients with few therapeutic options.

We have completed a Phase 1 study evaluating IONIS-PKK$_{Rx}$ in healthy volunteers.

Cancer Franchise

Cancer is an area of significant unmet medical need. Cancer is an extremely complex disease that involves a large number of targets. With our technology, we can evaluate a very broad and diverse range of targets and identify their involvement in different types of cancers. Using the information we gain early in research on each of these targets, we can quickly identify promising targets for anti-cancer drugs. We preferentially select anti-cancer targets that provide a multi-faceted approach to treating cancer.

Our cancer franchise consists of anti-cancer antisense drugs that act upon biological targets associated with cancer progression and/or treatment resistance. We have a strategic alliance with AstraZeneca, which includes an anti-cancer collaboration that expands our anti-cancer efforts and supports an aggressive and broad clinical development plan for IONIS-STAT3-2.5$_{Rx}$. AstraZeneca brings significant experience that enables the identification of novel genetic and epigenetic targets for cancer. Combining AstraZeneca's expertise with our drug discovery technology, we plan to expand our cancer franchise with a number of promising new anti-cancer targets.

Our Generation 2.5 chemistry enhances the potency and effectiveness of our antisense drugs, and potentially allows us to extend the applicability of our technology to cancers that are difficult to treat. For instance, data from a Phase 1/2 clinical study of IONIS-STAT3-2.5$_{Rx}$ showed evidence of antitumor activity in patients with cancer, including advanced/metastatic hepatocellular carcinoma.

IONIS' Oncology Pipeline

IONIS-AR-2.5$_{Rx}$ – IONIS-AR-2.5$_{Rx}$ is an antisense drug we designed to treat patients with prostate cancer by reducing the production of all known forms of androgen receptor, or AR, including variants of the AR gene. Prostate cancer is the second leading cause of cancer deaths in American men. Prostate cancer growth, proliferation and progression are all androgen-dependent, and AR function is involved in disease progression at all stages of prostate cancer. For patients diagnosed with metastatic prostate cancer, current treatments largely involve opposing the action of androgens by blocking the AR or removing circulating androgens. Although androgen deprivation therapy approaches are initially effective in delaying disease progression, patients with metastatic prostate cancer will progress in their disease. Resistance to current therapies is frequent and can occur through a variety of mechanisms, including the activation of AR signaling in tumor cells through the amplification, over expression and mutation of the AR gene. Because IONIS-AR-2.5$_{Rx}$ can inhibit the production of all known forms of AR, we believe that this drug has the potential to be useful in treating patients with all stages of prostate cancer, including those who are resistant to current therapies.

AstraZeneca completed an open-label, dose-escalation, Phase 1/2 clinical study of IONIS-AR-2.5$_{Rx}$ in patients with advanced tumors for which the androgen receptor pathway is potentially a contributing factor. We plan to continue developing IONIS-AR-2.5$_{Rx}$, independent of AstraZeneca.

IONIS-STAT3-2.5$_{Rx}$ – IONIS-STAT3-2.5$_{Rx}$, also referred to as AZD9150, is an antisense drug we designed to reduce the production of signal transducer and activator of transcription 3, or STAT3, to treat patients with cancer. IONIS-STAT3-2.5$_{Rx}$ is a part of our collaboration with AstraZeneca to discover and develop anti-cancer drugs. We believe the significant potency we observed in our preclinical studies with IONIS-STAT3-2.5$_{Rx}$ broadens the therapeutic opportunities for IONIS-STAT3-2.5$_{Rx}$ into many different types of cancer where STAT3 is implicated.

STAT3 is a protein involved in the translation of key factors critical for tumor cell growth and survival. STAT3 is over-active in a variety of cancers, including brain, lung, breast, bone, liver and multiple myeloma. Physicians believe that overactivity in STAT3 prevents cancer cell death and promotes tumor cell growth.

We and AstraZeneca have evaluated IONIS-STAT3-2.5$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma and advanced lymphoma. AstraZeneca is evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with MEDI4736, AstraZeneca's investigational anti-PD-L1 drug, in patients with head and neck cancer. AstraZeneca also plans to start an additional clinical study evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with MEDI4736 in patients with diffuse large B cell lymphoma.

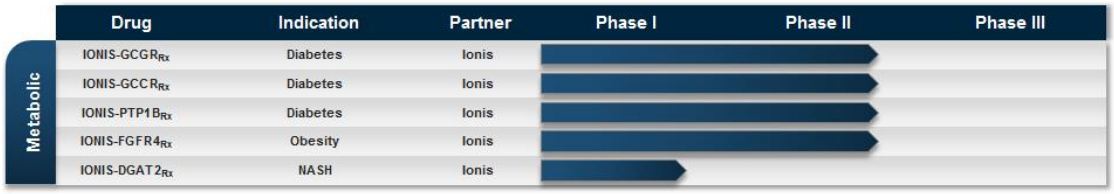
Metabolic Franchise

Metabolic disorders are chronic diseases that affect millions of people. There is a significant need for new therapies for these patients. According to the Centers for Disease Control and Prevention, diabetes affects more than 29 million people in the United States, or nine percent of the population, with type 2 diabetes constituting 90 to 95 percent of those cases.

We designed the majority of our drugs in our metabolic disease franchise to be effective alone or when added to existing therapies to treat metabolic diseases, such as diabetes. One hurdle for traditional drug development is that most traditional drugs cannot selectively target a disease-causing protein without also affecting closely related proteins, which often results in unwanted side effects. We design our antisense drugs to target the gene responsible for producing the disease-causing protein while avoiding unwanted effects on closely related proteins, thereby reducing the risk of side effects.

We have reported positive Phase 2 data from IONIS-GCGR$_{Rx}$ and IONIS-PTP1B$_{Rx}$, the most advanced drugs in our metabolic franchise. We designed these two drugs and our third drug, IONIS-GCCR$_{Rx}$, to act upon targets in the liver or fat tissue through a distinct mechanism to improve insulin sensitivity, reduce glucose production, or affect other metabolic aspects of this complex disease. In addition to our work in diabetes, we are also evaluating other metabolic syndromes, including obesity and nonalcoholic steatohepatitis, or NASH. Obesity has reached global epidemic proportions in both adults and children. According to the World Health Organization, in 2014, there were more than 600 million adults over the age of 18 who were obese and in 2013, there were 42 million children under the age of five who were overweight or obese. Obesity is a major risk factor for a number of chronic diseases, including type 2 diabetes, dyslipidemia, hypertension and cardiovascular diseases. Despite the growing epidemic, there are very few weight loss drugs that have been approved to treat patients with obesity. Although many anti-obesity drugs have entered development, most of them have not been approved due to their adverse effects in the CNS and/or heart. There is an unmet medical need for drugs that can cause weight loss by acting on peripheral tissues without causing cardiac or CNS related side effects. In 2015, we initiated a Phase 2 clinical study evaluating IONIS-FGFR4$_{Rx}$ in patients who are obese. Currently, it is estimated that two to three percent of the general population have NASH. However, with the growing obesity epidemic, the number of patients with NASH should also continue to rise. About 20 percent of NASH patients are reported to develop cirrhosis, and 30 to 40 percent of patients with NASH cirrhosis experience liver-related death. IONIS-DGAT2$_{Rx}$ is an antisense drug we designed to treat patients with NASH.

IONIS' Metabolic Disease Pipeline



IONIS-GCGR$_{Rx}$ – IONIS-GCGR$_{Rx}$ is an antisense drug we designed to reduce the production of glucagon receptors, or GCGR, to treat patients with type 2 diabetes. GCGR is a receptor for the hormone glucagon. Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose, particularly in type 2 diabetes. We are developing IONIS-GCGR$_{Rx}$ to provide better glucose control for patients with type 2 diabetes. Given the unique mechanism of action, we believe that physicians could use IONIS-GCGR$_{Rx}$ in diabetic patients with severe hyperglycemia who are not controlled with current treatments and who could benefit from a drug that significantly decreases glucose levels and preserves pancreatic function.

Although glucose is an important source of energy for people's bodies and is vital to people's health, uncontrolled increases in glucose can lead to serious health problems, such as diabetes. In patients with advanced diabetes, uncontrolled glucagon action can lead to a significant increase in blood glucose level. In addition, reducing GCGR produces more active glucagon-like peptide, or GLP-1, a hormone that preserves pancreatic function and enhances insulin secretion.

We completed a double-blind, randomized, placebo-controlled, Phase 2 study of IONIS-GCGR$_{Rx}$ in patients with type 2 diabetes who were poorly controlled on stable metformin therapy. We have initiated a second Phase 2 study of IONIS-GCGR$_{Rx}$ in patients with type 2 diabetes to identify the optimal dose and schedule to achieve glucose control with manageable glucagon receptor-related liver enzyme elevations.

IONIS-GCCR$_{Rx}$- IONIS-GCCR$_{Rx}$ is an antisense drug we designed to reduce the production of glucocorticoid receptor, or GCCR, to treat patients with type 2 diabetes. Glucocorticoid hormones affect a variety of processes throughout the body, including the production of liver glucose and fat storage. Excessive GCCR activity in the liver and fat is associated with obesity, insulin resistance and glucose intolerance.

Physicians recognize that inhibiting GCCR is an attractive strategy for improving glycemic and lipid control in patients with type 2 diabetes. However, the side effects associated with systemic GCCR inhibition have challenged traditional drug developers. Targeted reduction of GCCR in the liver and fat tissues with antisense drugs is an attractive therapeutic approach because it can lower glucose and lipids without causing potential side effects associated with systemic GCCR inhibition.

We completed a Phase 2 study of IONIS-GCCR$_{Rx}$ in patients with type 2 diabetes.

IONIS-PTP1B$_{Rx}$ – IONIS-PTP1B$_{Rx}$ is an antisense drug we designed to reduce the production of protein tyrosine phosphatase-1B, or PTP-1B, to treat patients with type 2 diabetes. PTP-1B is a phosphatase that negatively regulates insulin receptor signaling and is responsible for turning off the activated insulin receptor. Reducing PTP-1B enhances insulin activity. We designed IONIS-PTP1B$_{Rx}$ to increase the body's sensitivity to the natural hormone, insulin, resulting in better glucose control for patients with type 2 diabetes. Because of its unique mechanism, IONIS-PTP1B$_{Rx}$ may help treat patients with type 2 diabetes without causing weight gain or hypoglycemia, also known as low blood sugar.

Scientists have long recognized PTP-1B as an attractive target for treating diabetes. However, efforts to develop drugs that target PTP-1B have been challenging due to the structural similarities among closely related protein phosphatases. Targeted reduction of PTP-1B with an antisense drug represents an ideal therapeutic approach because we design our drugs to specifically reduce the PTP-1B mRNA, without affecting mRNAs of other protein phosphatases. This approach eliminates the off-target side effects observed with traditional small-molecule drugs.

We believe that physicians may use IONIS-PTP1B$_{Rx}$ in combination with most of the other commonly used diabetes drugs, including insulin, GLP-1 agonists, and more traditional drugs like metformin, to treat patients with diabetes. The clinical development plan for IONIS-PTP1B$_{Rx}$ focuses on two types of diabetic patients. The first type are those who are inadequately controlled on insulin, helping them utilize insulin more efficiently and the second type are those who are beginning to fail oral therapies, extending the time they have before becoming dependent on insulin.

We have completed a randomized, double-blind, placebo-controlled, Phase 2 study of IONIS-PTP1B$_{Rx}$ study in obese patients with type 2 diabetes taking metformin or metformin plus sulfonylurea.

IONIS-FGFR4$_{Rx}$ – IONIS-FGFR4$_{Rx}$ is an antisense drug we designed to reduce the production of fibroblast growth factor receptor 4, or FGFR4, to treat obese patients. FGFR4 is expressed in the liver and fat tissues, and plays an important role regulating fat burning and body weight. Reducing FGFR4 decreases the body's ability to store fat while it simultaneously increases fat burning and energy expenditure. Many anti-obesity drugs act in the brain to suppress appetite, commonly resulting in central nervous system, or CNS, side effects. However, IONIS-FGFR4$_{Rx}$ does not distribute to the brain or CNS and therefore should not produce any CNS side effects. IONIS-FGFR4$_{Rx}$ is the first drug in our metabolic franchise to treat obesity and utilizes technology we in-licensed from Verva Pharmaceuticals Ltd.

We completed a Phase 1 study of IONIS-FGFR4$_{Rx}$ in healthy volunteers. We initiated a double blind, placebo-controlled, Phase 2 study of IONIS-FGFR4$_{Rx}$ in obese patients in July 2015.

IONIS-DGAT2$_{Rx}$ – IONIS-DGAT2$_{Rx}$ is an antisense drug we designed to reduce the production of DGAT2, or diacylglycerol acyltransferase 2, to treat patients with NASH. NASH is a common liver disease characterized by excessive triglycerides in the liver with concurrent inflammation and cellular damage. As NASH progresses, scarring, or fibrosis, begins to accumulate in the liver. Ultimately, cirrhosis of the liver develops and the liver can no longer function normally. Currently, liver transplantation is the only treatment for advanced cirrhosis and liver failure. Because of the high prevalence of NASH, it has recently become the third most common indication for liver transplantation in the United States.

DGAT2 is an enzyme that catalyzes the final step in triglyceride synthesis in the liver. Reducing the production of DGAT2 should therefore decrease triglyceride synthesis in the liver. In animal models of obesity and fatty liver disease, antisense inhibition of DGAT2 significantly improved liver damage, lowered blood lipid levels and reversed diet-induced insulin resistance.

We are evaluating IONIS-DGAT2$_{Rx}$ in a randomized, placebo-controlled, dose-escalation, Phase 1 study in healthy, overweight volunteers. We designed this study to give us valuable insights on the effects of IONIS-DGAT2$_{Rx}$ in a patient population that is closely matched to patients with NASH.

Other Drugs in Development

Together with our partners, we continue to advance drugs in clinical development that are outside of our core therapeutic areas, such as the antiviral drugs we and GSK are developing.

IONIS' Pipeline of Drugs in Development for Viral Infection or Ocular Disease

IONIS-GSK4-L$_{Rx}$ – IONIS-GSK4-L$_{Rx}$ is a LICA drug we designed to reduce an undisclosed ocular target. Together with GSK, we are developing IONIS-GSK4-L$_{Rx}$ to treat patients with an undisclosed ocular disease.

IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ – IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ are antisense drugs we designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV. These include proteins associated with infection and replication, including the hepatitis B surface antigen, which is present in both acute and chronic infections and is associated with a poor prognosis in patients with chronic HBV infection. IONIS-HBV-L$_{Rx}$ is the first anti-infective drug in development that incorporates our LICA technology, which we designed to increase drug potency by enhancing drug delivery to target tissue. Together with GSK, we are evaluating IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ to treat HBV infection.

HBV infection is a serious health problem that can lead to significant and potentially fatal health conditions. Chronic HBV infection is one of the most common persistent viral infections in the world. Currently available therapies, including oral antiviral agents or injectable interferons, do not clear HBV and do not effectively clear HBV antigens from these patients. As a result, patients cannot fully control their HBV infection and therefore, achieve sustained disease remission. Many of these patients are at elevated risk for severe liver complications such as cirrhosis and primary liver cancer.

We have completed a randomized, placebo-controlled, dose-escalation, Phase 1 study of IONIS-HBV$_{Rx}$ in healthy volunteers. In January 2016, GSK initiated a Phase 1 study evaluating IONIS-HBV-L$_{Rx}$ in healthy volunteers. The Phase 1 study of IONIS-HBV-L$_{Rx}$ is a randomized, placebo-controlled, dose-escalation study in healthy volunteers. We have designed this study to evaluate the safety, tolerability, and pharmacokinetics of single and multiple doses of IONIS-HBV-L$_{Rx}$.

Preclinical Drugs in Development

The efficiency and broad applicability of our technology provides us with nearly unlimited targets against which to develop drugs. Our goal is to add three to five new drugs into the pipeline every year. In 2015, we far exceeded this goal and added nine new drugs into development. Already in 2016, we have added two new drugs into development. On average, it takes 12 to 18 months to complete the preclinical studies necessary to support clinical development.

IONIS' Preclinical Pipeline

Severe and Rare

Drug	Indication	Partner
IONIS-BIIB4$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-BIIB5$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-BIIB6$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-GHR-L$_{Rx}$	Acromegaly	Ionis
IONIS-RHO-2.5$_{Rx}$	Autosomal Dominant Retinitis Pigmentosa	GSK
IONIS-TMPRSS6-L$_{Rx}$	β-Thalassemia	Ionis

Cardiovascular

Drug	Indication	Partner
IONIS-AGT-L$_{Rx}$	Treatment-Resistant Hypertension	Ionis
IONIS-APOCIII-L$_{Rx}$	Severely High TGs	Ionis/Akcea

Satellite Company Drugs in Development

We have successfully developed novel drugs we designed to treat many different diseases. In therapeutic areas that are outside of our core areas of development, we have licensed our drugs to highly focused satellite companies that have the specific expertise and resources to continue developing the drugs. For our satellite company drugs, we refer to the drug by the partner's own compound number, such as ATL1103 or RG-101. We have listed these drugs below in the Satellite Company pipeline.

IONIS' Satellite Company Pipeline

Drug	Indication	Satellite Company	Phase I	Phase II	Phase III
Severe and Rare					
Alicaforsen	*Pouchitis	Atlantic			
ATL1103	Acromegaly	Antisense Therapeutics			
RG-012	Alport Syndrome	Regulus			
Oncology					
Custirsen (OGX-011)	Prostate / Lung Cancer	OncoGenex			
Apatorsen (OGX-427)	Cancer	OncoGenex			
Other					
Plazomicin	Severe Bacterial Infection	Achaogen			
ATL1102	Multiple Sclerosis	Antisense Therapeutics			
RG-101	HCV	Regulus			
Metabolic					
RG-125	NASH with Diabetes	Regulus			

* Named Patient Supply (see below).

Alicaforsen – Alicaforsen is an antisense drug we designed to reduce the production of intercellular adhesion molecule 1, or ICAM-1. Ulcerative colitis, or UC, is an inflammatory bowel disease of the colon, a part of the large intestine, and pouchitis is an inflammation of the surgically constructed internal pouch created in UC patients who have had their diseased colons removed. In 2007, we licensed alicaforsen to Atlantic Pharmaceuticals for pouchitis, UC and other inflammatory diseases. Atlantic Pharmaceuticals is developing alicaforsen for the treatment of UC and currently supplies alicaforsen in response to physicians' requests under international Named Patient Supply regulations for patients with inflammatory bowel disease.

ATL1103 – ATL1103 is an antisense drug we designed to reduce the production of the growth hormone receptor, or GHr, to treat patients with acromegaly. Acromegaly is a serious chronic life threatening disease triggered by excess secretion of GHr by benign pituitary tumors. In 2001, we licensed ATL1103 to Antisense Therapeutics Limited, or ATL. In May 2015, ATL entered into an exclusive license agreement that provides Strongbridge Biopharma with development and commercialization rights to ATL1103 for endocrinology applications outside Australia and New Zealand.

RG-012 – RG-012 is an anti-miR, or an antisense oligonucleotide inhibitor of microRNA, targeting microRNA-21, or miR-21, to treat patients with Alport syndrome. Alport syndrome is a life-threatening genetic kidney disease with no approved therapy. While there is little known information on the progression of this disease, scientists believe that miR-21 plays a critical role because they have observed increased miR-21 levels in animal models of Alport syndrome and in patients with chronic kidney disease. Regulus is developing RG-012 in a strategic alliance with Genzyme, a Sanofi company, to treat Alport syndrome. In June 2015, Regulus initiated a randomized, double-blind, placebo-controlled, single ascending dose Phase 1 study in healthy volunteers to evaluate the safety, tolerability and pharmacokinetics of RG-012.

Custirsen – Custirsen is an antisense drug we designed to improve survival in patients with advanced cancer. We and OncoGenex jointly discovered and conducted the initial development of custirsen. In July 2008, we and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely responsible for the costs, development and commercialization of custirsen as an adjunct therapy to enhance the effectiveness of chemotherapy. OncoGenex is evaluating custirsen in two Phase 3 studies, AFFINITY and ENSPIRIT. The AFFINITY study is evaluating custirsen in combination with cabazitaxel/prednisone as a second-line chemotherapy in men with CRPC. The ENSPIRIT study is evaluating custirsen as a second-line treatment in patients with NSCLC.

Apatorsen – Apatorsen is an antisense drug we designed to reduce the production of heat shock protein 27, or Hsp27, to treat patients with cancer. In January 2005, we entered into an agreement with OncoGenex to develop apatorsen. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities. OncoGenex and collaborators are evaluating apatorsen in multiple Phase 2 studies in patients with cancer.

Plazomicin – Plazomicin is an aminoglycoside drug that Achaogen, Inc. is developing for the treatment of multi-drug resistant gram-negative bacterial infections. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis that physicians can use to treat serious bacterial infections. In 2006, we licensed our proprietary aminoglycoside program to Achaogen. Achaogen discovered plazomicin based on technology licensed from us. Achaogen is currently evaluating plazomicin in a Phase 3 study in patients with serious multi-drug resistant infection due to carbapenem-resistant Enterobacteriaceae, or CRE. In September 2014, Achaogen initiated a Phase 3 study, CARE, to evaluate the efficacy of plazomicin in patients with infections caused by CRE. Achaogen announced that it has a special protocol assessment, or SPA, with the FDA for this Phase 3 study. Achaogen plans to initiate a second Phase 3 study of plazomicin for the treatment of patients with complicated urinary tract infections.

ATL1102 – ATL1102 is an antisense drug we designed to reduce the production of CD49d, a subunit of Very Late Antigen-4, or VLA-4, for the treatment of patients with multiple sclerosis, or MS. Results from preclinical studies demonstrate that inhibition of VLA-4 could positively affect a number of inflammatory diseases, including MS. In 2001, we licensed ATL1102 to ATL. ATL is currently undertaking a chronic toxicology study in primates to support a potential Phase 2b trial of ATL1102 in patients with MS.

RG-101 – RG-101 is an anti-miR targeting microRNA-122, or miR-122, to treat patients with hepatitis C virus, or HCV. RG-101 is wholly owned by Regulus, but Regulus has entered into a clinical trial collaboration with GSK. Regulus is evaluating RG-101 as part of an HCV combination regimen with GSK’s investigational HCV compound. Regulus completed a Phase 1/2 study in patients with HCV and is evaluating RG-101 in a Phase 2 study in combination with direct acting antivirals in patients with HCV. Regulus is also evaluating RG-101 in a Phase 1 study in patients with severe renal insufficiency or end-stage renal disease.

RG-125 – RG-125, also referred to as AZD4076, is an anti-miR targeting microRNA-103/107, or miR-103/107, for the treatment of NASH in patients with type 2 diabetes/pre-diabetes. Regulus reported that inhibition of miR-103/107 with anti-miRs led to a sustained reduction in fasting glucose and fasting insulin levels in mouse models. RG-125 is part of the strategic alliance between Regulus and AstraZeneca to discover and develop microRNA therapeutics for cardiovascular diseases, metabolic diseases and oncology.

Regulus and AstraZeneca are evaluating RG-125 in a Phase 1 study for the treatment of NASH in patients with type 2 diabetes or pre-diabetes.

Antisense Technology

Our antisense technology is an innovative platform for discovering first-in-class or best-in-class drugs for treating disease. We believe this technology represents an important advance in the way we treat disease because, unlike most other drug technologies that target existing proteins in the body, antisense technology is an RNA-targeted drug technology. The unique properties of antisense drugs provide several advantages over traditional drug discovery technologies. These advantages include:

- Direct application to diseases at the genetic level by targeting RNA: antisense technology represents a direct route from gene to drug. The explosion in genomic information has led to the discovery of many new disease-causing proteins and RNAs, and has created new opportunities accessible to antisense technology.

- Precise specificity: we design antisense drugs to target a single RNA, which minimizes or eliminates the possibility our drugs will bind to unintended targets which can cause unwanted side effects.
- Good drug properties: antisense drugs distribute well throughout the body without the need for special formulations or vehicles. They also have a relatively long half-life of approximately two to four weeks, which means patients and/or healthcare providers can dose our drugs once a week. Antisense drugs using our more advanced technology also have the potential for patients and/or their healthcare providers to dose our drugs once a month, once a quarter or even less frequently.
- Ability to combine with other drugs: because antisense drugs do not interact with the enzymes that metabolize or break down other drugs, physicians can use our drugs in combination with other drugs.
- Broad applications to multiple disease targets, multiple tissues and multiple mechanisms: there are virtually no "undruggable" targets with antisense technology.
- Efficient discovery and early development: because of the efficiency of our antisense technology, our drug discovery and early development costs and success rates compare favorably to small molecule or antibody drug discovery and development.

We identify antisense drugs to treat diseases for which there is a large unmet medical need, including severe and rare diseases for which there are limited or no current treatments or in diseases for which we believe our drugs have a competitive advantage over existing therapies.

Technology Overview

We use our core technology platform to discover and develop drugs that affect targets in the body at the genetic level. Genes contain the information necessary to produce proteins. A gene is made up of nucleotides containing the nucleoside bases: adenine, thymine, guanine, and cytosine, commonly known as A, T, G and C, which are linked together to form a two-stranded structure that resembles a twisted ladder, known as deoxyribonucleic acid, or DNA. The nucleotides on one side of the ladder bind weakly to complementary nucleotides on the other strand according to specific rules; for example, A pairs with T and G pairs with C, creating the ladder's rungs (figure 1). Scientists call this highly specific nucleotide pairing hybridization. The sequence or order of these nucleotides establishes the cell's recipes for making proteins. Each protein's instructions reside in a corresponding segment of DNA known as a gene.

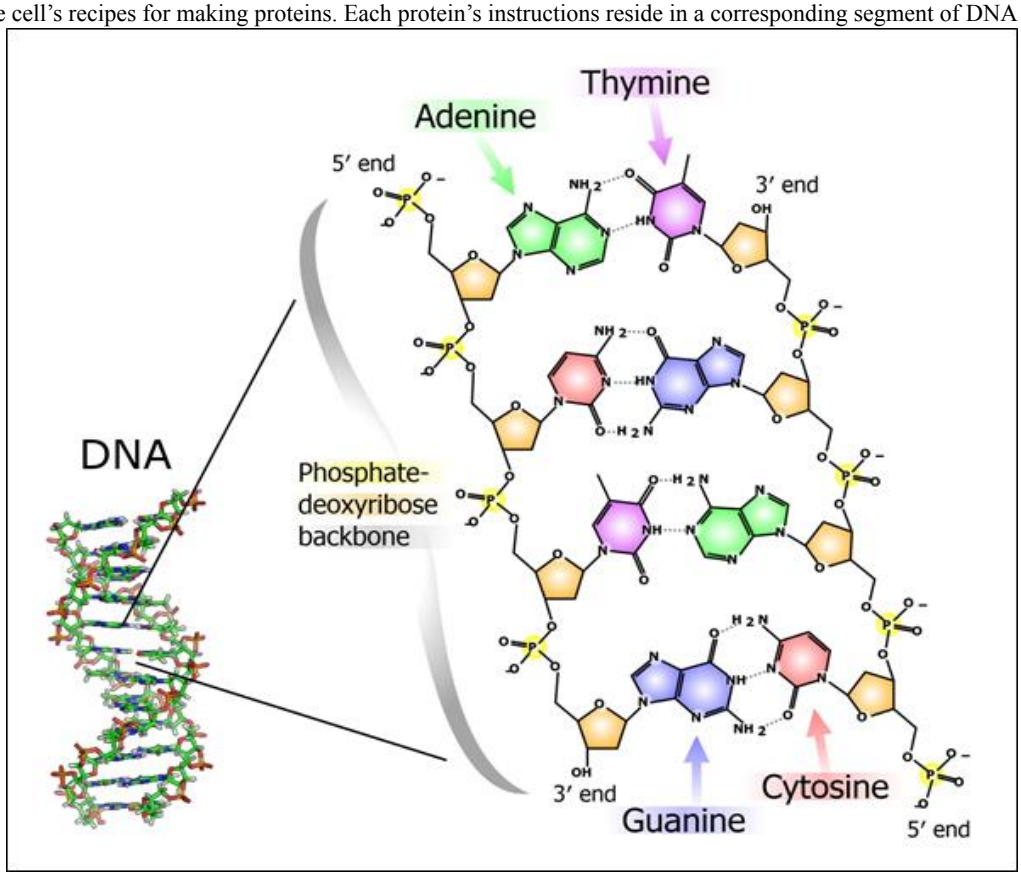


Figure 1: Illustration of DNA.

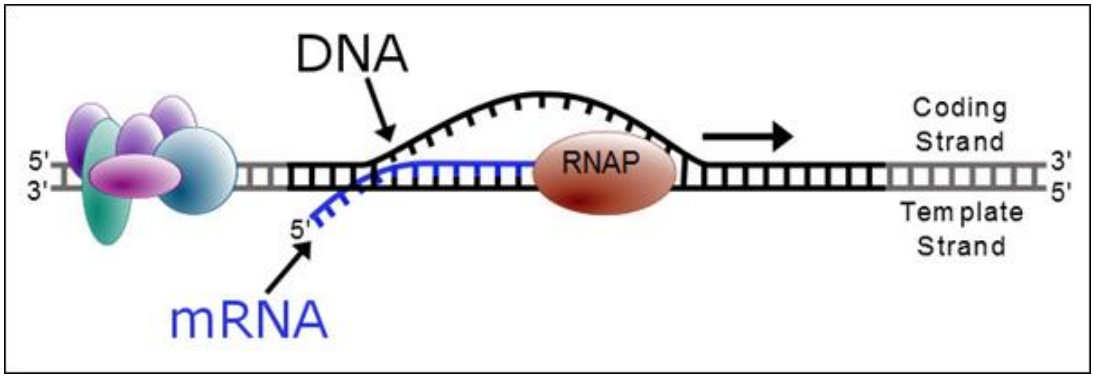


Figure 2: Transcription of information contained in a gene, or DNA, to mRNA.

The instructions for making a protein are transcribed from a gene, or DNA, into a different genetic molecule called messenger RNA. This process starts with the partial uncoiling of the two complementary strands of the DNA. One strand acts as a template and information stored in the DNA template strand is copied into a complementary RNA (figure 2). Messenger RNA, or mRNA, are mature, fully processed RNA that code for proteins. Ribosomes, the cell's factories for manufacturing proteins, translate mRNA into proteins. The ribosome reads the encoded information, the mRNA's nucleotide sequence, and in doing so, strings together amino acids to form a specific protein (figure 3).

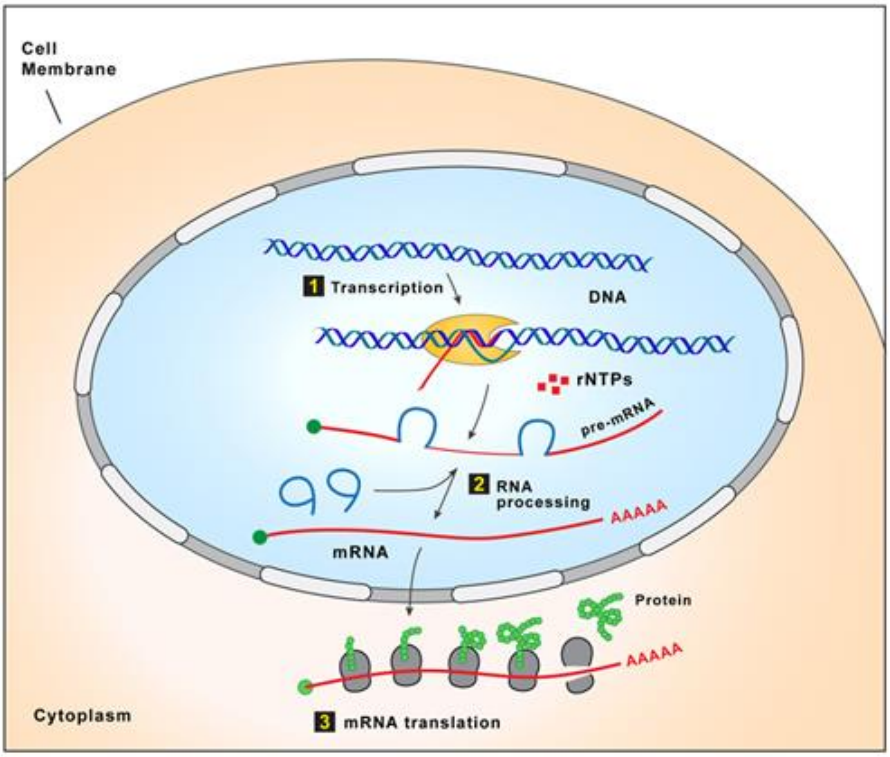


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

We primarily use our antisense technology to interrupt the cell's protein production process by preventing the mRNA instructions from reaching the ribosome, thus inhibiting the production of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the 'sense' strand. Scientists call the complementary nucleotide chain that binds specifically to the sense strand is called the "antisense" strand. We use the information contained in mRNA to design chemical structures, that we call antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of RNA. Our antisense drugs can selectively bind to an mRNA that codes for a specific protein and will not bind to closely related RNAs, providing a level of specificity that is better than traditional drugs. As a result, we can design antisense drugs that selectively inhibit the disease-causing member of the protein group without interfering with those members of the protein group necessary for normal bodily functions. This unique specificity means that antisense drugs may be less toxic than traditional drugs because we can design them to minimize the impact on unintended targets. We can also design antisense drugs to increase the production of beneficial proteins.

We have developed the majority of the drugs in our pipeline using our advanced screens to produce drugs with what we believe are the best possible safety and tolerability profiles. We refer to our drugs that have passed these advanced screens as Generation 2.0+ drugs. We continue to advance our antisense technology to create even more potent drugs that we can use in more tissues and against more targets. These advances allow us to expand the mechanisms through which we can use our drugs. These advancements provide us with greater opportunities to use our antisense drugs to treat a greater number of diseases and reach more patient populations. Today several of our early stage drugs and those entering our pipeline use our most advanced antisense technology, including our next generation chemistry, Generation 2.5, and our LICA technology.

Generation 2.5 chemistry is an advancement that we believe increases the potency of our drugs by up to 10-fold over our Generation 2+ drugs. This increase in potency enables our drugs to engage targets in a broader array of tissues. We have published data demonstrating that our Generation 2.5 drugs generally have enhanced potency over our Generation 2.0+ drugs and are broadly distributed throughout the body to multiple tissues including liver, kidney, lung, muscle, adipose, adrenal gland, peripheral nerves and tumor tissues. Our Generation 2.5 drugs constitute some of our recently added new drugs.

In addition to improving the chemical foundation of our drugs, we design our LICA technology to enhance the delivery of our drugs to particular tissues. This technology adds specific chemical structures or molecules, such as conjugates, onto antisense drugs to increase the efficiency of drug uptake in a particular tissue. We have demonstrated that our LICA technology can further enhance the potency of our drugs. For example, our LICA technology directed toward liver targets has produced a greater than thirty fold increase in potency in a Phase 1 study of IONIS-APO(a)-L_{Rx}. We can combine our LICA technology with both our Generation 2.0+ and our Generation 2.5 drugs to increase the potency of these drugs. We designed these first LICA drugs to inhibit targets in the liver. We are also developing LICA conjugation technology that we can use to target other tissues. We expect that we can enhance some of our future drugs, including our Generation 2.5 drugs with our LICA technology.

Antisense Targets and Mechanisms

There are more than a dozen different antisense mechanisms that we can exploit with our antisense technology. The majority of the drugs in our pipeline bind to mRNAs and inhibit the production of disease-causing proteins. Our antisense technology is broadly applicable to many different antisense mechanisms, including RNA splicing, exon skipping, RNA interference, or RNAi, and enhancing protein translation to increase protein production. We have also recently published research showing that we can use our antisense technology with CRISPR/Cas9, a gene editing system. Our work in this area provides an important step toward development of a potential therapeutic application for CRISPR technology.

The antisense drugs we design to inhibit the production of disease-causing proteins or reduce harmful RNAs bind to the target RNA via highly specific nucleotide pairing, or hybridizing, and recruiting a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target RNA. The drug itself remains intact during this process, so it can remain active against additional target RNA molecules and repeatedly trigger their degradation (figure 4). Examples of our clinical development stage antisense drugs that use the RNase H1 mechanism to reduce disease protein production include, IONIS-TTR$_{Rx}$, volanesorsen, IONIS-FXI$_{Rx}$, IONIS-APO(a)-L$_{Rx}$ and others.

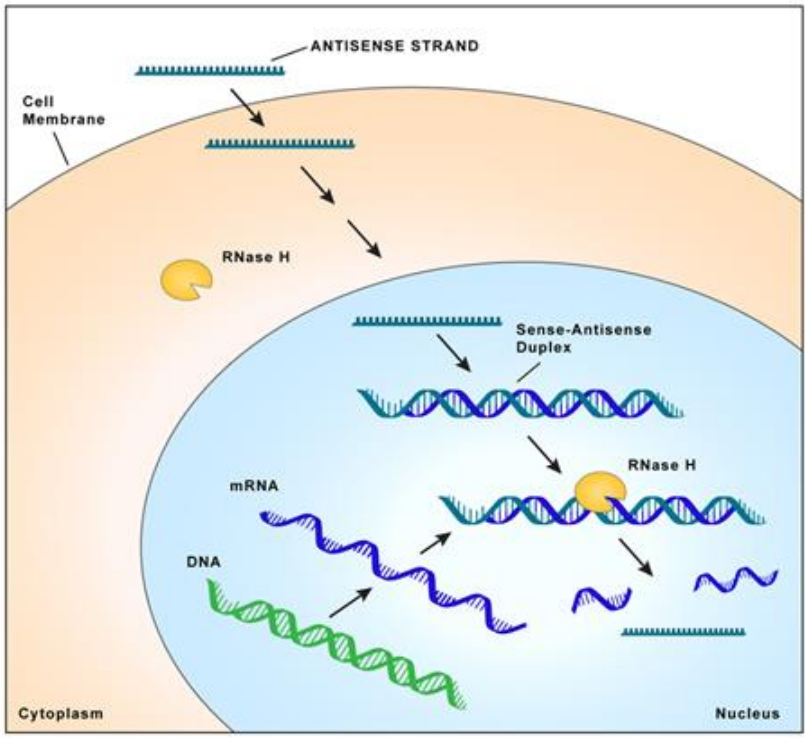


Figure 4: Antisense drug using the RNase H mechanism of action.

Nusinersen is an example of an antisense drug that modulates RNA splicing to increase protein production of the SMN protein (figure 5), which is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular function. The SMN protein is deficient in patients with SMA. There are a number of other diseases, including cystic fibrosis and Duchenne muscular dystrophy, which are the result of splicing disorders. These are diseases we could potentially treat using antisense modulation of splicing.

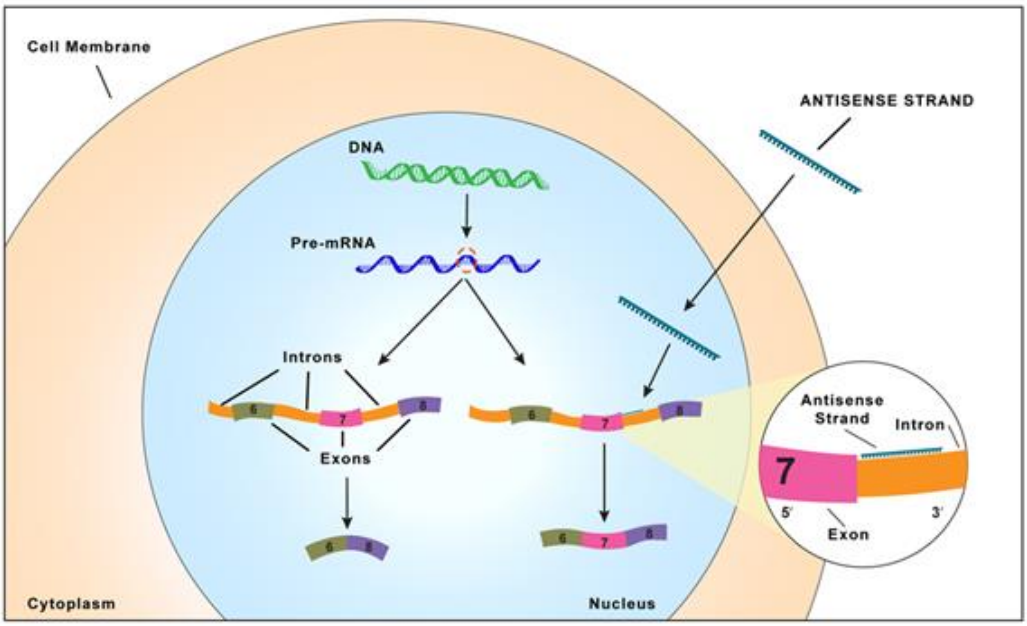


Figure 5: Antisense drug altering splicing of the SMN2 mRNA.

Because there are many different types of RNA that exist within the body, our antisense technology is not limited to RNA sequences that translate into proteins. We can also develop drugs that target non-coding RNAs, such as toxic RNAs. For example, DM1 is a form of muscular dystrophy that is caused by an abnormally long, toxic RNA that accumulates in cells and prevents the production of proteins essential for normal cellular function. We designed IONIS-DMPK-2.5_{Rx} to target and reduce the toxic DMPK RNA that causes this disease. In a mouse model of the disease, we observed effective reductions of the toxic RNA that led to a sustained reversal of disease symptoms for up to one year.

Another RNA target for our antisense technology is microRNAs. To date, scientists have identified more than 700 microRNAs in the human genome, and have shown that the absence or presence of specific microRNAs in various cells is associated with specific human diseases, including cancer, viral infection, metabolic disorders and inflammatory disease. To fully exploit the therapeutic opportunities of targeting microRNAs, we co-founded Regulus Therapeutics as a company focused on the discovery, development and commercialization of microRNA-based therapeutics. Regulus has reported human proof-of-concept data for RG-101 in HCV patients. These data demonstrated that treatment with a single subcutaneous dose of RG-101 as a single agent resulted in significant and sustained reductions in HCV RNA in a varied group of patients.

We are also making progress in designing antisense drugs to target long, non-coding RNAs, or lncRNAs. These lncRNAs do not make proteins but may regulate other genes. In 2014, we published a paper in Nature in which we were the first to show that targeted reduction of an lncRNA with an antisense compound can ameliorate certain cognitive deficits in a mouse model of Angelman syndrome, or AS. Moreover, these studies demonstrate the potential therapeutic benefits of an antisense drugs for the treatment of AS.

Because the efficiency of our core technology platform can support multiple target-based antisense research programs without significantly increasing costs, we can develop antisense drugs to target a broad range of diseases, efficiently producing a large and broad proprietary portfolio of drugs. We are currently pursuing antisense drug discovery programs focused on various severe and rare, cardiovascular, neurologic and metabolic diseases, and cancer.

Collaborative Arrangements and Licensing Agreements

Overview

We are leaders in RNA-targeted therapeutics and we have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our drugs. Our partners bring resources and expertise that augment and build upon our internal capabilities. The depth of our knowledge and expertise with antisense technology provides us the flexibility to partner our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. We have distinct partnering strategies that we employ based on the specific program, therapeutic area and the expertise and resources our potential partners may bring to the collaboration.

- We form strategic partnerships through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas in which our partners can provide tools and resources to complement our drug discovery efforts. For instance, we established a broad strategic alliance with Biogen that pairs Biogen's extensive resources and expertise in neurological diseases with our antisense technology. Together we are creating a franchise of novel potential drugs for neurological diseases that we believe will expand both our pipeline and Biogen's pipeline with promising new drugs.

- We form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas. For example, we established a collaboration with Janssen, which brings together our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation to discover and develop antisense drugs to treat autoimmune disorders in the gastrointestinal, or GI, tract.

- We form late stage development and commercialization partnerships that enable us to leverage our partner's global expertise and resources needed to support large commercial opportunities. For example, we licensed IONIS-FXI_{Rx} to Bayer to develop and commercialize IONIS-FXI_{Rx} for the prevention of thrombosis. As a leader in the antithrombotic market, Bayer has the expertise, resources and commitment to broadly develop IONIS-FXI_{Rx}.

- We also work with a consortium of companies that can exploit our drugs and technologies outside our primary areas of focus. We refer to these companies as satellite companies. Through our satellite company collaborations, we expand the reach and potential of RNA-targeting therapeutics into disease areas that are outside of our core focus.

Through our partnerships we have created a broad and sustaining base of potential license fees, upfront payments, milestone payments, royalties and earn out payments while controlling our drug development expenses. In all of our partnerships, we benefit from the expertise our partners bring to our drugs. By coupling our efficient drug discovery technology with the resources and expertise of our partners we believe we can maximize the value of our drugs and our technology.

Strategic Partnerships

AstraZeneca

Cardiometabolic and Renal Diseases Collaboration

In July 2015, we and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases primarily focused on targets in the kidney, and renal diseases. As part of the agreement, we granted AstraZeneca an exclusive license to a preclinical program and the option to license a drug for each target advanced under this research collaboration. Upon acceptance of a drug development candidate, AstraZeneca will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and substantive milestone payments of up to more than $4 billion. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration agreement.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs for cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize IONIS-STAT3-2.5$_{Rx}$ for the treatment of cancer and an option to license up to three anti-cancer drugs under a separate research program. AstraZeneca is responsible for all global development, regulatory and commercialization activities for IONIS-STAT3-2.5$_{Rx}$. We and AstraZeneca have evaluated IONIS-STAT3-2.5$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma and advanced lymphoma. AstraZeneca is evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with MEDI4736, AstraZeneca's investigational anti-PD-L1 drug, in patients with head and neck cancer. For the research program, we are responsible for identifying a development candidate for each of the three anti-cancer research programs. AstraZeneca has the option to license drugs resulting from each of the three anti-cancer research programs, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities for such drug.

Under the terms of the agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive tiered royalties up to the low to mid-teens on sales from any drugs resulting from these programs. If AstraZeneca successfully develops IONIS-STAT3-2.5$_{Rx}$ and the three drugs under the research program, we could receive license fees and milestone payments of $750 million. From inception through February 2016, we have generated more than $70 million in payments under this oncology collaboration.

For additional details about our collaboration agreements with AstraZeneca, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Biogen

We have established four strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological and neuromuscular disorders. These collaborations combine our expertise in creating antisense drugs with Biogen's expertise in developing therapies for neurological disorders. We and Biogen are currently developing six drugs to treat neurological diseases under these collaborations, including nusinersen, IONIS-DMPK-2.5$_{Rx}$, IONIS-SOD1$_{Rx}$, formerly ISIS-BIIB3$_{Rx}$, and three drugs to treat undisclosed neurodegenerative diseases, IONIS-BIIB4$_{Rx}$, IONIS-BIIB5$_{Rx}$, and IONIS-BIIB6$_{Rx}$. In addition to these six drugs, we and Biogen are evaluating numerous additional targets for the development of drugs to treat neurological diseases.

Nusinersen

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize nusinersen for the treatment of SMA. We are currently conducting a Phase 3 study evaluating nusinersen in infants with SMA, which we expect to be fully enrolled in the second quarter of 2016. We are also conducting a Phase 3 study evaluating nusinersen in children with SMA, for which we have completed target enrollment. In addition, we are evaluating nusinersen in two Phase 2 open-label studies, one in children with SMA and one in infants with SMA. Patients from all of these studies continue to have access to nusinersen through open-label extension dosing. We are responsible for completing the studies we are currently conducting. Biogen has the option to license nusinersen. If Biogen exercises its option, it will pay us a license fee and will assume all other global development, regulatory and commercialization responsibilities. Biogen may exercise this option upon completion of and data review of the first successful Phase 2/3 trial or completion of both Phase 2/3 trials. An amendment in December 2014 provided for additional opt-in scenarios, based on the filing or the acceptance of a new drug application or marketing authorization application with the FDA or EMA. Under the terms of the agreement, we received an upfront payment of $29 million and we are eligible to receive up to $346 million in a license fee and payments. We are also eligible to receive tiered royalties up to the mid-teens on any sales of nusinersen. From inception through February 2016, we have generated nearly $150 million in payments for advancing nusinersen, including a $2 million milestone payment we earned in February 2016 for further advancing the Phase 3 study of nusinersen in infants.

IONIS-DMPK-2.5$_{Rx}$

In June 2012, we and Biogen entered into a second and separate collaboration agreement to develop and commercialize a novel antisense drug, IONIS-DMPK-2.5$_{Rx}$, targeting DMPK for the treatment of DM1. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. We are currently evaluating IONIS-DMPK-2.5$_{Rx}$ in a Phase 1/2 clinical study in patients with DM1. Biogen has the option to license the drug through the completion of the first Phase 2 trial. If Biogen exercises its option, it will assume all other global development, regulatory and commercialization responsibilities. Under the terms of the agreement, we received an upfront payment of $12 million. Over the term of the collaboration, we are eligible to receive up to $263 million in a license fee and substantive milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-teens on any sales of IONIS-DMPK-2.5$_{Rx}$. From inception through February 2016, we have generated more than $35 million in payments for advancing IONIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen entered into a third and separate collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-BIIB4$_{Rx}$ under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any drugs resulting from each of the three programs. From inception through February 2016, we have generated nearly $45 million in payments under this collaboration, including the $3 million milestone payment we earned in February 2016 for the continued development of IONIS-BIIB4$_{Rx}$.

Strategic Neurology

In September 2013, we and Biogen entered into a fourth and separate collaboration agreement, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs being pursued under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs after Phase 2 proof of concept. We are currently advancing three drugs, IONIS-SOD1$_{Rx}$, IONIS-BIIB5$_{Rx}$, and IONIS-BIIB6$_{Rx}$, under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in substantive milestone payments. In addition, we are eligible to receive tiered single-digit royalties on sales from any drugs using non-antisense modalities developed under this collaboration. From inception through February 2016, we have generated more than $140 million in payments under this collaboration.

For additional details about our collaboration agreements with Biogen, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Research, Development and Commercialization Partners

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. We are responsible for completing our ongoing Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis. Bayer is responsible for all other development and commercialization activities for IONIS-FXI$_{Rx}$. Under the terms of the agreement, we are eligible to receive $155 million in near-term payments, including a $100 million upfront payment we received in the second quarter of 2015 and a $55 million milestone payment that we are eligible to receive upon advancement of the program following the Phase 2 study in patients with end-stage renal disease on hemodialysis. Over the term of the agreement, we are eligible to receive up to $375 million in license fees, substantive milestone payments and other payments. In addition, we are eligible to receive tiered royalties in the low-to-high 20 percent range on gross margins of IONIS-FXI$_{Rx}$.

For additional details about our collaboration agreement with Bayer, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Genzyme Corporation, a Sanofi company

In January 2008, we entered into an alliance with Genzyme focused on the licensing and co-development of Kynamro. The license and co-development agreement provided Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to Kynamro. The transaction included a $175 million licensing fee and a $150 million equity investment by Genzyme in our stock. From inception through January 2016, we have generated $375 million in a license fee, milestone payments and an equity investment for advancing Kynamro in development. In January 2016, we terminated our license agreement with Genzyme.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Our alliance currently comprises five drugs in development, including our Phase 3 drug, IONIS-TTR$_{Rx}$. GSK has the exclusive option to license drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee. If GSK exercises its exclusive option for any drugs resulting from this alliance, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received $38 million in upfront and expansion payments.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for IONIS-TTR$_{Rx}$. We are currently evaluating IONIS-TTR$_{Rx}$ in a broad Phase 3 development program. We have completed target enrollment for our Phase 3 study in patients with FAP. In September 2015, we and GSK amended the development plan for IONIS-TTR$_{Rx}$ to support the Phase 3 cardiomyopathy study, which GSK plans to conduct. In addition to IONIS-TTR$_{Rx}$, we have four drugs in development with GSK. We are developing two antisense drugs we designed to reduce the production of viral proteins associated with HBV infection; IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$, a follow-on drug using our LICA technology. We are also developing IONIS-GSK4-L$_{Rx}$ and IONIS-RHO-2.5$_{Rx}$, which are antisense drugs we designed to treat ocular diseases.

Under our agreement, if GSK successfully develops all five drugs for one or more indications and achieves pre-agreed sales targets, we could receive payments of more than $1.0 billion. From inception through February 2016, we have generated more than $150 million in payments under this alliance with GSK, including a $1.5 million payment we generated in January 2016 when GSK further advanced IONIS-HBV-L$_{Rx}$. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

For additional details about our collaboration agreement with GSK, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Janssen Biotech, Inc., a pharmaceutical company of Johnson & Johnson

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the GI tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under the terms of the agreement, we received $35 million in upfront payments. We are eligible to receive nearly $800 million in milestone payments and license fees for these programs. In addition, we are eligible to receive tiered royalties up to the near teenson sales from any drugs resulting from this collaboration.

For additional details about our collaboration agreement with Janssen, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for HD based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Under the agreement, we are responsible for the discovery and development of an antisense drug targeting HTT protein. We are currently evaluating a drug targeting HTT, IONIS-HTT_{Rx}, in a Phase 1/2 clinical study in patients with early stage HD. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013. We are eligible to receive up to $362 million in a license fee and milestone payments. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties up to the mid-teens on product sales from any drugs resulting from this alliance. From inception through February 2016, we have generated nearly $55 million in payments under this alliance with Roche.

For additional details about our collaboration agreement with Roche, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Satellite Company Collaborations

Achaogen, Inc.

In 2006, we exclusively licensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In exchange, Achaogen agreed to certain payment obligations related to aminoglycosides Achaogen developed. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. If Achaogen successfully develops and commercializes two drugs under our agreement, we will receive payments totaling up to $49.3 million for the achievement of key clinical, regulatory and sales events. Through February 2016, we have earned $7 million in milestone payments from Achaogen, including a $4 million milestone payment we earned in September 2014 when Achaogen initiated a Phase 3 study of plazomicin in patients with serious multi-drug resistant, gram-negative bacterial infections. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into an alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam’s partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in milestone payments. We also have the potential to earn a portion of payments that Alnylam receives from licenses of our technology it grants to its partners plus royalties. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, ssRNAi therapeutics, and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam’s technology, we will pay Alnylam up to $3.4 million in milestone payments for specified development and regulatory events, plus royalties. To date, we do not have an RNAi-based drug in development.

In 2015, we and Alnylam entered into an alliance in which we formed an intellectual property cross-license under which we and Alnylam each obtained exclusive license rights to four therapeutic programs. Alnylam granted us an exclusive, royalty-bearing license to its chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four targets. In exchange, we granted Alnylam an exclusive, royalty-bearing license to our chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four targets. Alnylam also granted us a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, we granted Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics. Through February 2016, we have generated nearly $70 million from Alnylam.

Antisense Therapeutics Limited

In 2001, we licensed ATL1102 and ATL1103 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL is currently undertaking a chronic toxicology study in primates to support a potential Phase 2b trial of ATL1102 in patients with MS. In addition, ATL is currently developing ATL1103 for growth and sight disorders. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103.

Atlantic Pharmaceuticals Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006. Atlantic Pharmaceuticals is developing alicaforsen for the treatment of UC and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international named patient supply regulations for patients with IBD for which we receive royalties. Additionally, in 2013 we received an advance payment in the form of equity for the initial royalties that we will earn from Atlantic Pharmaceuticals. Under the agreement, we could receive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications.

OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc.

Custirsen

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize custirsen, an anti-cancer antisense drug that targets clusterin. OncoGenex is currently evaluating custirsen in two Phase 3 studies. In July 2008, we and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely responsible for the costs, development and commercialization of custirsen. In exchange, OncoGenex agreed to pay us royalties on sales of custirsen and to share consideration it receives from licensing custirsen to a third party, except for consideration OncoGenex receives for the fair market value of equity and reimbursement of research and development expenses. Under the amended agreement, we assigned to OncoGenex our rights in the patents claiming the composition and therapeutic methods of using custirsen and granted OncoGenex a worldwide, nonexclusive license to our know-how and patents covering our core antisense technology and manufacturing technology solely for use with custirsen. In addition, we agreed that so long as OncoGenex or its commercialization partner is using commercially reasonable efforts to develop and commercialize custirsen, we will not research, develop or commercialize an antisense compound designed to modulate clusterin. The amended agreement will continue until OncoGenex or its commercialization partner is no longer developing or commercializing custirsen or until we terminate the agreement for OncoGenex's uncured failure to make a payment required under the agreement.

OGX-225

In August 2003, we and OncoGenex entered into a second and separate agreement for the development of an antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities. OncoGenex issued to us $0.8 million of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of key development and regulatory milestones. In addition, we are eligible to receive royalties on future product sales of OGX-225.

Apatorsen

In January 2005, we entered into a third and separate agreement with OncoGenex to allow for the development of an additional antisense anti-cancer drug, apatorsen. OncoGenex and collaborators are evaluating apatorsen in multiple Phase 2 studies in patients with cancer. OncoGenex is responsible for all development costs and activities. OncoGenex will pay us milestone payments totaling up to $5.8 million for the achievement of key development and regulatory milestones. In addition, we are eligible to receive royalties on future product sales of the drug.

Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development. MicroRNAs may also prove to be an attractive new tool for characterizing diseases. Regulus focuses its drug discovery and development efforts in numerous therapeutic areas, including cancer, fibrosis, and viral infections. Regulus currently has three drugs in clinical development. Regulus is evaluating RG-101 in a Phase 2 study in patients with HCV and in a Phase 1 study in patients with severe renal insufficiency or end-stage renal disease. Regulus is also evaluating RG-012 in a Phase 1 study to treat patients with Alport syndrome. Regulus and AstraZeneca are also evaluating RG-125 in a Phase 1 study for the treatment of NASH in patients with type 2 diabetes or pre-diabetes. We are eligible to receive royalties on any future product sales of these drugs.

For additional details about our satellite company arrangements, see Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

External Project Funding

We are pursuing discovery and development projects that provide us with new therapeutic applications for antisense drugs. These programs represent opportunities for us and our technology. In some cases, we have funded these studies through support from our partners or disease advocacy groups and foundations. For example, we received external funding support for our ALS and Huntington's disease programs.

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche. We made payments of $5 million and $3 million to CHDI in 2015 and 2013, respectively, associated with the progression of our Huntington's disease program. If we achieve pre-specified milestones under our collaboration with Roche, we will make additional payments to CHDI up to $4 million, upon which our obligation to CHDI will be complete.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered into a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs for ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration.

Intellectual Property Sale and Licensing Agreements

We have a broad patent portfolio covering our products and technologies. We believe our patent estate represents the largest and most valuable nucleic acid therapeutics-oriented patent estate in the pharmaceutical industry. While the principal purpose of our intellectual property portfolio is to protect our products and those of our partners described above, our intellectual property is a strategic asset that we are exploiting to generate near-term revenues and that we expect will also provide us with revenue in the future. We have an active intellectual property sales and licensing program in which we sell or license aspects of our intellectual property to companies. Through this program, we also license our non-antisense patents. To date, we have generated nearly $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Sales of Intellectual Property

Abbott Molecular Inc.

In January 2009, we sold our former subsidiary, Ibis Biosciences, to Abbott Molecular Inc., or AMI, pursuant to a stock purchase agreement for a total acquisition price of $215 million plus the earn out payments described below. Under the stock purchase agreement, we are eligible to receive earn out payments from AMI equal to a percentage of Ibis' revenue related to sales of Ibis systems, which AMI launched in 2014 as IRIDICA, including instruments, assay kits and successor products. Once cumulative net sales reach $140 million, and through December 31, 2025, we are eligible to earn out payments in any year that net sales exceed $50 million for the applicable year. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events.

In-Licensing Arrangements

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to nusinersen. If we successfully develop and commercialize a drug incorporating the technology we licensed from the University of Massachusetts, we will pay a milestone payment to the University of Massachusetts of $0.3 million for the achievement of a key regulatory milestone. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive in consideration for sublicensing its technology, and a royalty on sales of nusinersen in the United States if our product incorporates the technology we licensed from the University of Massachusetts.

Verva Pharmaceuticals Ltd.

We have a license agreement with Verva under which we acquired an exclusive license to Verva's antisense patent rights related to IONIS-FGFR4$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology Verva licensed to us, we will pay milestone payments to Verva totaling up to $6.1 million for the achievement of key patent, clinical, and regulatory milestones. If we convert our license from an exclusive license to a nonexclusive license we could significantly reduce the milestone payments due to Verva. In addition, we will also pay royalties to Verva on sales of IONIS-FGFR4$_{Rx}$ if our product incorporates the technology we licensed from Verva.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to nusinersen. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay a portion of any sublicense revenue and post licensing milestone payments we receive in consideration for sublicensing the Cold Spring Harbor Laboratory's technology up to $11.3 million and a royalty on sales of nusinersen if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

Manufacturing

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides like the antisense drugs we use in our research and development programs. As a result, we have dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide drugs, we found that the same techniques we used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide drugs. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the drugs. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions.

Our drug substance manufacturing facility is located in a 28,700 square foot building in Carlsbad, California. We lease this building under a lease that has an initial term ending on December 31, 2031 with an option to extend the lease for up to four additional five-year periods. In addition, we have a 25,800 square foot building that houses support functions for our manufacturing activities. We lease this facility under a lease that has an initial term ending in June 2021 with an option to extend the lease for up to two additional five-year periods. Our manufacturing facility is subject to periodic inspections by the FDA to ensure that it is operating in compliance with current Good Manufacturing Practices, or cGMP, requirements.

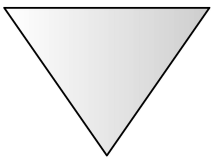
As part of our collaborations we may agree to manufacture clinical trial materials and/or commercial supply for our partners. For example, in the past we have manufactured clinical supply materials for AstraZeneca, Bayer, Biogen, and GSK.

We believe we have sufficient manufacturing capacity to meet our current internal research and development needs, including the Phase 3 clinical trials we have for IONIS-TTR$_{Rx}$, nusinersen, and volanesorsen, as well as our current and future obligations under existing agreements with our partners for commercial, research and development needs. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs, including the initial launch supplies for nusinersen, and volanesorsen. GSK intends to provide the initial launch supplies for IONIS-TTR$_{Rx}$. We also believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we can manufacture antisense drugs at commercially competitive prices.

Patents and Proprietary Rights

Our success depends, in part, on our ability to obtain patent protection for our products in the United States and other countries. As of February 10, 2016, we owned or exclusively licensed more than 1,300 issued patents worldwide. We focus our resources on patents and new patent applications that drive value for our company.

We own or control patents that provide exclusivity for products in our pipeline and patents that provide exclusivity for our core technology in the field of antisense more generally. Our core technology patents include claims to chemically modified nucleosides and oligonucleotides as well as antisense drug designs utilizing these chemically modified nucleosides. These core claims are each independent of specific therapeutic target, nucleic acid sequence, or clinical indication. We also own a large number of patents claiming specific antisense compounds having nucleic acid sequences complementary to therapeutic target nucleic acids, independent of the particular chemical modifications incorporated into the antisense compound. Most importantly, we seek and obtain issued patent claims to specifically protect each of our drugs. For example, we file and seek to obtain claims covering each drug's nucleic acid sequence and precise drug design. In sum, we maintain our competitive advantage in the field of antisense technology by protecting our core platform technology, which applies to most of our drugs, and by creating multiple layers of patent protection for each of our specific drugs in development.

Type of Patent Claim		Description
1. Chemically Modified Nucleosides and Oligonucleotides 1. Antisense Drug Design Motifs 2. Therapeutic Methods 3. Antisense Sequence 4. Drug Composition	**Breadth** Broadly Applicable  Specific	1. Target and sequence independent 2. Sequence independent 3. Chemistry independent 4. Specific claim to drug candidates

Chemically Modified Nucleosides and Oligonucleotides

The most broadly applicable of our patents are those that claim modified nucleosides and oligonucleotides comprising the modified nucleosides that we incorporate into our antisense drugs to increase their therapeutic efficacy. Nucleosides and chemically modified nucleosides are the basic building blocks of our antisense drugs, therefore claims that cover any oligonucleotide incorporating one of our proprietary modified nucleosides can apply to a wide array of antisense mechanisms of action as well as several therapeutic targets. Of particular note are our patents covering our proprietary 2'-O-(2-methoxy) ethyl modified nucleosides, incorporated into many of our development compounds, as well as our Generation 2.5 compounds, the constrained-ethyl nucleosides, or cEt nucleosides.

The following are some of our patents in this category:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,101,993	OLIGONUCLEOTIDES CONTAINING 2'O-MODIFIED PURINES	2023	Covers certain MOE nucleosides and oligonucleotides containing these nucleotides.
United States	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	7,741,457	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	8,022,193	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers methods of synthesizing our cEt nucleosides.
Europe	EP1984381	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.

Antisense Drug Design Motifs

MOE Gapmers

Other Ionis patents claim oligonucleotides comprising specific antisense drug design motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Patent claims covering our antisense drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that optimize oligonucleotides for a particular antisense mechanism of action, such as ribonuclease H, or RNase H, RNAi, or splicing. We have designed oligonucleotides incorporating motifs, which we refer to as chimeric compounds or gapmers to exploit the RNase H mechanism to achieve target RNA reduction. Almost all of our drugs, including volanesorsen and IONIS-TTR$_{Rx}$, contain this gapmer antisense drug design motif. In fact, we own a U.S. patent that covers each of our second generation gapmer antisense drugs until March of 2023. We also have issued patents covering other gapmer drug designs, and methods of lowering a target RNA in an animal with these gapmer compositions. The following patent is one example of our patents in this category.

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
United States	7,015,315	GAPPED OLIGONUCLEOTIDES	2023	Covers 2'-O-alkyl-O-alkyl gapmer oligonucleotides.

Bicyclic Nucleoside Gapmer Oligonucleotides

In addition, we have pursued patent claims to antisense drug design motifs incorporating bicyclic nucleoside analogs, which include locked nucleic acids, or LNAs. In Europe, we have granted claims drawn to short gapmer oligonucleotides with bicyclic nucleosides, which include locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders. We have also successfully obtained issued patent claims covering gapmer antisense drug design motifs that incorporate our cEt modified nucleosides. Santaris opposed granted patent EP2092065 and EP2410053 and in April 2015, the claims of EP2092065 were successfully upheld in amended form. We intend to vigorously defend EP2410053 in future proceedings. The following patents are some examples of our issued patents in this category:

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
Europe	EP2021472	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, 10 to 14 nucleotides in length, with bicyclic nucleosides, which includes cEt locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders
United States	7,750,131	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers cEt containing gapmer compounds
Europe	EP2092065	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2'-MOE and bicyclic nucleosides
Europe	EP2410053	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2'-MOE and bicyclic nucleosides

Ligand-Conjugated Antisense (LICA) Technology

We have also pursued patent claims to new chemistries created to enhance targeting of antisense drugs to specific tissues and cells in order to improve a drug's potency. Our N-acetyl-galactosamine (GalNAc) LICA drugs are designed to provide an increase in potency for targets in the liver. We have successfully obtained issued patent claims covering our primary GalNAc LICA (THA) conjugated to any modified oligonucleotide, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides. The following patents are some examples of our issued patents in this category:

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
United States	9,127,276	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Covers our primary THA LICA conjugate having any type of linker and conjugated to any group of nucleosides, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides
United States	9,181,549	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Covers our primary THA conjugate having our preferred linker and cleavable moiety conjugated to any oligomeric compound or any nucleoside having a 2'-MOE modification or a cEt modification

Therapeutic Methods of Treatment and Antisense Drug Sequences

In addition to our broad core patents, we also own hundreds of patents, worldwide, with claims to antisense sequences and compounds directed to particular therapeutically important targets or methods of achieving clinical endpoints using these antisense compounds. Target patents may also include claims reciting the specific nucleic acid sequences utilized by our products, independent of chemical modifications and motifs. In addition, our product specific patents typically include claims combining specific nucleic acid sequences with nucleoside modifications and motifs. In this way, we seek patent claims narrowly tailored to protect our products specifically, in addition to the broader core antisense patents described above.

Survival Motor Neuron and nusinersen

Nusinersen is protected by a suite of patents in the United States and in Europe from generic competition in the United States until at least 2030 and in Europe until 2026. These issued patents include: (i) the Bennett patent related to methods of altering mRNA processing (i.e., splicing) with a fully modified 2'MOE oligonucleotide, (ii) a patent licensed from the University of Massachusetts drawn to antisense compounds having the sequence of nusinersen, independent of chemical modification and uses of such compounds for treating SMA, and (iii) a joint patent with Cold Spring Harbor Laboratory claiming fully modified 2'MOE compositions targeting SMN2, including the precise composition of matter of nusinersen. Those patents should protect nusinersen from generic and antisense innovator competition in the United States until at least 2030 without patent term extension. The table below lists the key U.S. and European issued patents protecting nusinersen:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	6,210,892	ALTERATION OF CELLULAR BEHAVIOR BY MODULATION OF MRNA PROCESSING	2018	Broad claims of altering mRNA processing with a fully modified 2'MOE oligonucleotide.
United States	8,361,977	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2030	Sequence and chemistry (full 2'-MOE) of nusinersen
Europe	1910395	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Sequence and chemistry (full 2'-MOE) of nusinersen
United States	7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2027	Oligonucleotides having sequence of nusinersen (chemistry independent)
United States	8,110,560	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of using antisense oligonucleotides having sequence of nusinersen to alter splicing of SMN2 and/or to treat SMA
United States	8,980,853	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Methods of administering nusinersen

Transthyretin and IONIS-TTR$_{Rx}$

We obtained issued claims covering IONIS-TTR$_{Rx}$ in the United States. The issued U.S. claims should protect IONIS-TTR$_{Rx}$ from generic competition in the United States until at least 2031. We are also pursuing additional patent applications designed to protect IONIS-TTR$_{Rx}$ in the United States and other foreign jurisdictions, including Europe and Japan. The table below lists the current issued U.S. patents protecting IONIS-TTR$_{Rx}$:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	8,101,743	MODULATION OF TRANSTHYRETIN EXPRESSION	2025	Antisense sequence and chemistry of IONIS-TTR$_{Rx}$
United States	8,697,860	DIAGNOSIS AND TREATMENT OF DISEASE	2031	Composition of IONIS-TTR$_{Rx}$
United States	9,061,044	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Sodium salt composition of IONIS-TTR$_{Rx}$

In some cases, the patent term can be extended to recapture a portion of the term lost during FDA regulatory review.

Apolipoprotein C-III and volanesorsen

We have obtained patent claims in the United States drawn to the use of antisense compounds complementary to a broad active region of human Apo C-III including the site targeted by volanesorsen. Similar claims complementary to any site on human Apo C-III have granted in Australia. We obtained issued patent claims to the specific antisense sequence and chemical composition of volanesorsen in the United States, Australia, and Europe. The issued U.S. claims should protect volanesorsen from generic competition in the United States until at least 2023. In addition, we will seek additional patent term extension to recapture a portion of the term lost during FDA regulatory review, extending the term of this patent beyond 2023. We are also pursuing additional patent applications designed to protect the volanesorsen composition in Canada and additional methods of use in jurisdictions worldwide. The table below lists the key U.S, European and Australian issued patents:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,598,227	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Methods of treating hyperlipidemia, lowering cholesterol levels and lowering triglyceride levels with an antisense compound comprising an antisense oligonucleotide 15-30 linked nucleosides specifically hybridizable within a nucleotide region of apoCIII targeted by volanesorsen
United States	7,750,141	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense sequence and chemistry of volanesorsen
Europe	EP1622597	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense sequence and chemistry of volanesorsen
Australia	2004231550	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Compounds 12-50 nucleobases in length specifically hybridizable with SEQ ID 4 (apoCIII), the antisense sequence and chemistry of volanesorsen and methods of their use in treating hyperlipidemia, lowering cholesterol levels and lowering triglyceride levels
United States	9,157,082	MODULATION OF APOLIPOPROTEIN CIII (APOCIII) EXPRESSION	2032	Methods of using APOCIII antisense oligonucleotides for reducing pancreatitis and chylomicronemia and increasing HDL

ApoB 100 and KYNAMRO

In 2008, we obtained patent claims in the United States drawn to the use of both single-stranded and double-stranded antisense drugs complementary to any site of the mRNA of human apoB, regardless of chemistry or antisense mechanism of action. The patent provides broad protection of the apoB franchise, including KYNAMRO and potential future follow-on compounds. Similar claims granted in Australia and Japan in 2009 and 2010, respectively. Additional claims have granted in Europe covering the use 5-10-5 MOE gapmers targeting ApoB. We obtained issued claims to the specific antisense sequence and chemical composition of KYNAMRO in the United States, Australia, South Africa, India, Japan and the European Union. The issued U.S. claims should protect KYNAMRO from generic competition in the United States until at least 2025. We are also pursuing additional patent applications designed to protect KYNAMRO in these and other jurisdictions including Canada. The table below lists the key issued patent claims designed to protect KYNAMRO in the applicable jurisdiction:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,407,943	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	Methods of inhibiting expression of apoB, decreasing serum cholesterol, decreasing lipoprotein levels, decreasing serum triglycerides in a human with an antisense compound 12 to 30 nucleotide in length and 100% complementary to human apoB wherein the compound is not a ribozyme.
Australia	2002-326481	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2022	An isolated oligonucleotide compound 12 to 30 nucleobases in length 100% complementary to at least a 12-nucleobase portion of a nucleic acid molecule having nucleotides 151-12820 of SEQ ID 3 (apoB) which is not a ribozyme and use of such compound in therapy
Japan	4471650	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2022	Use of an antisense oligonucleotide 12 to 30 nucleobases in length and 100% complementary to human apoB having one or more modifications and inhibiting expression of apoB by at least 90% in primary hepatocytes when present at a concentration of 300 nM for preparation of a medicament for decreasing serum cholesterol, and decreasing lipoprotein levels in a human
Europe	EP2174945	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2022	Use of an antisense oligonucleotide 20 nucleobases in length and 100% complementary to human apoB having a 5-10-5 MOE motif for treating conditions associated with ApoB
United States	7,511,131	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2025	Antisense sequence and composition of matter of Kynamro

Europe	EP1569695	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of Kynamro
Europe	EP2336318	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of Kynamro
India	219847	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of Kynamro
Australia	2003294281	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of Kynamro
South Africa	2005/03690	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of Kynamro
Japan	4986109	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of Kynamro
Europe	EP2409713	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2025	Kynamro for use in treating a human with hypercholesterolemia, wherein the oligonucleotide is administered at 200mg once per week by subcutaneous injection

Custirsen

Issued patent claims have been obtained from an application jointly filed by Ionis and OncoGenex to protect the specific chemical composition of custirsen in the United States. The issued U.S. claims should protect custirsen from generic competition in the United States until at least 2021. The table below lists the U.S. issued patent:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	6,900,187	TRPM-2 ANTISENSE THERAPY USING AN OLIOGNUCLEOTIDE HAVING 2'-O-(2-METHOXY)ETHYL MODIFICATIONS	2021	Antisense sequence and composition of custirsen

RNAi Motifs and Mechanisms - The Crooke Patents

The Crooke Patents, which are the result of the early work by Dr. Crooke and co-workers exploring oligonucleotides that activate double-stranded ribonucleases, or dsRNases, cover chemically modified, RNA-containing oligonucleotides and methods for exploiting the RNAi pathway with these oligonucleotides until June 2016. We licensed the Crooke Patents to Alnylam for the development of double-stranded therapeutics and to Regulus for the development of microRNA-targeting therapeutics. Although these patents do not cover any of the drugs in our development pipeline, these patents are important in the field of ssRNAi compounds, in which we have made great strides to progress this approach toward a viable therapeutic platform. The following patents have issued out of the Crooke Patent family:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	5,898,031	OLIGORIBONUCLEOTIDES FOR CLEAVING RNA	2016	Oligonucleotides comprising regions of RNA nucleosides and regions of nucleosides having stabilizing chemical modifications. Such oligonucleotides are suitable for use in single- and double-stranded applications.
United States	6,107,094	OLIGORIBONUCLEOTIDES AND RIBONUCLEASES FOR CLEAVING RNA	2016	Compounds and methods that use oligonucleotides having both RNA nucleosides and chemically modified nucleosides, including methods that rely on a dsRNase to reduce target RNA and compounds having nucleosides with improved affinity and/or stability.
United States	7,432,249	OLIGORIBONUCLEOTIDES AND RIBONUCLEASES FOR CLEAVING RNA	2016	Pharmaceutical compositions comprising a diluent or carrier and a single-stranded antisense oligonucleotide having a plurality of RNA nucleosides and at least one sugar modification.
United States	7,432,250	OLIGORIBONUCLEOTIDES AND RIBONUCLEASES FOR CLEAVING RNA	2016	Methods for treating a patient by administering an antisense compound having a plurality of RNA nucleosides and at least one sugar modification.
United States	7,629,321	OLIGORIBONUCLEOTIDES AND RIBONUCLEASES FOR CLEAVING RNA	2016	Methods for cleaving a target RNA in a cell by contacting the cell with a single-stranded antisense compound having a plurality of RNA nucleosides and at least one sugar modification.
United States	7,695,902	OLIGORIBONUCLEOTIDES AND RIBONUCLEASES FOR CLEAVING RNA	2016	Methods of activating a dsRNase by contacting the dsRNase with a double-stranded antisense oligonucleotide where at least one strand has a plurality of RNA nucleosides and at least one sugar modification. The methods may be performed inside a cell.

Manufacturing Patents

We also own patents claiming methods of manufacturing and purifying oligonucleotides. These patents claim methods for improving oligonucleotide drug manufacturing, including processes for large-scale oligonucleotide synthesis and purification. These methods allow us to manufacture oligonucleotides at lower cost by, for example, eliminating expensive manufacturing steps.

We also rely on trade secrets, proprietary know-how and continuing technological innovation to develop and maintain a competitive position in antisense therapeutics.

Government Regulation

Regulation by government authorities in the United States and other countries is a significant component in the development, manufacture and commercialization of pharmaceutical products and services. In addition to regulations enforced by the FDA and relevant foreign regulatory authorities, we are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential future federal, state and local regulations.

Extensive regulation by United States and foreign governmental authorities governs our manufacture, development and potential sale of our drugs. In particular, pharmaceutical products are subject to nonclinical and clinical testing, as well as other approval requirements, by the FDA in the United States under the Federal Food, Drug and Cosmetic Act and other laws and by comparable agencies in those foreign countries in which we conduct business. Various federal, state and foreign statutes also govern or influence the manufacture, safety, labeling, storage, record keeping, marketing and quality of our drugs. State, local, and other authorities also regulate pharmaceutical manufacturing facilities and procedures.

Our manufacturing facility is subject to periodic inspection by the FDA and other foreign equivalents to ensure that it is operating in compliance with current good manufacturing practices, or cGMP, requirements. Marketing authorization for each new drug will require a rigorous manufacturing pre-approval inspection by regulatory authorities.

For any approved drug, domestic and foreign sales of the drug will depend, in part, on the availability and amount of reimbursement by third party payors, including governments and private health plans. Governments may regulate coverage, reimbursement and pricing of drugs to control cost or affect use of our drugs. Private health plans may also seek to manage cost and use by implementing coverage and reimbursement limitations. Within the European Union, or EU, a variety of payors pay for drugs, with governments being the primary source of payment. Governments may determine or influence reimbursement of drugs. Governments may also set prices or otherwise regulate pricing. Negotiating prices with governmental authorities can delay commercialization of a drug. These pricing and reimbursement procedures could impact our commercial partners', including our wholly owned subsidiary, Akcea's, ability to successfully commercialize our approved drugs.

Our operations may be directly, or indirectly through our customers, distributors, or other business partners, subject to various federal and state fraud and abuse laws, including, without limitation, anti-kickback statutes and false claims statutes. These laws may impact, among other things, our commercialization partners' proposed sales, marketing and education programs.

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits certain individuals and entities, including us, from promising, paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, directly or indirectly, to obtain or retain business or an improper advantage. If we violate the FCPA, it could result in large civil and criminal penalties and could result in an adverse effect on our reputation, operations, and financial condition. We could also face collateral consequences such as debarment and the loss of export privileges.

Competition

Our Business in General

Some of our drugs may compete with existing therapies for market share. In addition, there are a number of companies pursuing the development of oligonucleotide-based technologies and the development of pharmaceuticals utilizing these technologies. These companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies. Our drugs are differentiated from traditional small molecule drugs by their chemistry, how they move in the body, how they act in the body, delivery technology, and formulations.

Our products under development address numerous markets. The diseases our drugs target for which we have or may receive marketing authorization will determine our competition. For some of our products, an important factor in competition may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and marketing authorization processes and supply commercial quantities of the products to the market are important competitive factors. We expect to compete among products approved for sale based on a variety of factors, including, among other things, product efficacy, safety, mechanism of action, dosing convenience, marketing and sales strategy and tactics, availability, price, and reimbursement.

The current key competition for our three Phase 3 drugs, nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, and our approved drug Kynamro is set forth below.

Nusinersen

We believe that the following drugs could compete with nusinersen:

Drug	Company	Drug Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
AVXS-101	AveXis	Gene therapy that corrects the SMN1 gene using the AAV9 Vector	1	Infusion	All 15 patients enrolled in the study were event free as of Dec 31, 2015. All patients experienced either improvement or stabilization in motor skills relative to their baseline measurement	Well tolerated to date
RG7800	PTC Therapeutics/ Roche/ SMA Foundation	A small molecule drug that modulates splicing of the SMN2 gene	2	Oral	Up to three-fold increases in the ratio of full length SMN2 mRNA to SMN2Δ7 mRNA and up to two-fold increases in SMN protein were observed in plasma versus baseline in SMA patients	RG7800 on clinical hold due to non-clinical safety finding
RG7916	PTC Therapeutics/ Roche/ SMA Foundation	A small molecule drug that modulates splicing of the SMN2 gene	1	Oral	None reported	None reported
LMI070	Novartis	A small molecule drug that modulates splicing of the SMN2 gene	1/2	Oral	None reported	None reported

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations.

We believe that nusinersen's closest competitor is AVXS-101. AVXS-101 is currently in a Phase 1 study for infants with Type 1 SMA. While the data released thus far on the AVXS-101 study is encouraging, it is still early in development. In addition, other gene therapies have had difficulty providing lasting therapeutic benefit. Also AveXis has stated it needs to scale its manufacturing capabilities to be able to manufacture larger quantities of AVXS-101. Further, no company has yet to successfully commercialize a gene therapy, which may create significant barriers for AVXS-101.

IONIS-TTR$_{Rx}$

We believe that the following drugs could compete with IONIS-TTR$_{Rx}$:

Drug	Company	Drug Description	Phase	Admin/Dosing	Efficacy*	Safety*
Patisiran	Alnylam	An RNAi drug formulated with lipid nanoparticles to inhibit TTR mRNA	3	Infusion every 3 weeks with pre-treatment with steroids	~90% mean maximum reduction in TTR	Mild flushing (25.9%) and infusion-related reactions (18.5%) in Phase 2 OLE
Revusiran	Alnylam	An RNAi drug conjugated with GalNAC to inhibit TTR mRNA in liver cells	3	Weekly large volume subcutaneous injection	~87% mean maximum reduction in TTR	Injection site reactions (ISRs) reported in 44% of patients in the Phase 2 OLE, 3 patients discontinued OLE due to ISRs or diffuse rash
Tafamidis	Pfizer	A small molecule drug to stabilize TTR Protein	3, Approved in the EU	Daily oral capsule	In 45% of patients taking Tafamidis, nerve function either improved or stabilized, compared with 30% of patients taking placebo	Urinary tract infection, vaginal infection, upper abdominal pain and diarrhea
Diflunisal	N/A Generic	A non-steroid anti-inflammatory agent	Approved	Daily oral capsule/doses	Improved nerve function as shown by lower Neuropathy Impairment Score plus 7 nerve tests, or NIS+7. The NIS+7 score increased by 25.0 points in the placebo group versus 8.7 points in the diflunisal group	In two studies repurposing diflunisal for use in TTR amyloidosis, drug-related adverse events that led to discontinuation were: gastrointestinal bleeding, low platelets, deterioration of renal function, congestive heart failure, glaucoma and nausea.
Tolcapone	SOM Biotech	Small molecule repurposed generic drug	1/2	Daily oral dose	Shows binding and stabilization of TTR in humans	No drug related adverse events reported
ALN-TTRsc02	Alnylam	An RNAi drug conjugated with	Preclinical	Monthly or quarterly	No data in humans	No data in humans

		GalNAC to inhibit TTR mRNA in liver cells				

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations. Diflunisal efficacy and safety came from the published papers of two investigator sponsored studies, Berk JL, Suhr OB, Obici L, et al. Repurposing Diflunisal for Familial Amyloid Polyneuropathy: A Randomized Clinical Trial. JAMA. 2013;310(24):2658-2667 and Sekijima YS, Toja K, Morita H, et al. Safety and efficacy of long-term diflunisal administration in hereditary transthyretin (ATTR) amyloidosis. Amyloid. 2015;22(2):79-83.

We believe that of the drugs that are in development or on the market, IONIS-TTR$_{Rx}$'s closest competitors are patisiran and revusiran. Alnylam is developing patisiran for the polyneuropathy form of TTR amyloidosis. Patisiran is an intravenously administered RNAi molecule that is formulated with lipid nanoparticles to enable delivery of the drug to the liver. It is administered via an infusion by a healthcare provider every three weeks. Patients receiving patisiran are pretreated with steroids to prevent infusion related reactions. Alnylam is also developing revusiran for the cardiomyopathy form of TTR amyloidosis. Revusiran is a subcutaneously administered RNAi molecule that is Alnylam's first generation GalNAc drug and is dosed at 500 mg per week as two subcutaneous injections. In early clinical studies, IONIS-TTR$_{Rx}$, patisiran and revusiran produced similar TTR reductions in treated subjects. Because we have completed target enrollment in our fifteen month study, ahead of Alnylam's eighteen month study, we believe that IONIS-TTR$_{Rx}$ will be the first RNA-targeted drug on the market. We also believe that the overall product profile of IONIS-TTR$_{Rx}$ as a single, once weekly, subcutaneous injection with no pretreatment is superior to the drugs detailed above.

Volanesorsen

We believe that the following drugs could compete with volanesorsen:

Drug	Company	Drug Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
Glybera	uniQure NV	Adeno-associated Virus Gene therapy	Approved in EU, Suspended development in the US	A single treatment involving multiple injections	Showed a reduction in blood fat levels after meals in some patients. There was also a reduction in the number of pancreatitis attacks in some patients.	Common side effects include: leg pain following injection, headache, tiredness, high body temperature, bruising and potential damage to muscle tissue
Metreleptin	Aegerion	A synthetic form of the hormone leptin	2	Reconstituted subcutaneous injection	44.4% mean reduction in triglycerides at 4 months in patients with abnormal triglyceride levels	Anti-metreleptin antibodies, hypoglycemia, hypersensitivity, risk of T-cell lymphoma

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations.

Glybera is approved only in the EU for a subset of FCS patients whose disease has been confirmed by genetic testing and who have detectable levels of a specific protein in their blood. UniQure NV has announced it is not pursuing marketing authorization in the United States. Metreleptin is being tested in FPL patients who also have NASH. Volanesorsen is currently in Phase 3 development to treat patients with FCS and patients with FPL. To date, volanesorsen has shown the highest percent of triglyceride reductions compared to existing treatments, such as fibrates, regardless of starting triglyceride levels prior to dosing with volanesorsen. Based on our broad Phase 2 data for the treatment of different patients including patients with FCS, we believe that volanesorsen will work equally well as a single agent or in combination with other triglyceride-lowering drugs on the market.

Kynamro

Kynamro is currently approved in the United States and certain other countries to reduce LDL-C, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with HoFH. We believe that the following drugs compete with Kynamro:

Drug	Company	Drug Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
Lomitapide	Aegerion	A small molecule drug that inhibits microsomal triglyceride transfer protein	Approved	Titrate up, 5-60 mg oral daily	40% reduction in LDL-C from baseline (change from mean 336 mg/dL LDL-C to 190 mg/dL LDL-C) at week 26 in Phase 3 study	Hepatic steatosis, risk of steatohepatitis, transaminase abnormalities, risk for drug-induced liver injury, risk for deficiencies in fat-soluble vitamins and essential fatty acids
Evolocumab	Amgen	A monoclonal antibody drug that inhibits PCSK9 protein	Approved	Monthly sub-q	TESLA (phase 2/3 in HOFH): 31% mean reduction in LDL-C from baseline	nasopharyngitis, upper respiratory tract infections, influenza, arthralgia, and back pain

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations

The primary competitor for Kynamro is lomitapide, an oral small molecule that blocks the absorption of fat in the digestive system. In the lomitapide label, concurrent use of lomitapide and common medications for HoFH patients who have cardiovascular disease, including simvastatin and warfarin, need to be closely monitored due to drug-drug interactions with potentially harmful outcomes. Kynamro has no restrictions with these medications or diet restrictions, which may be advantageous for HoFH patients who are on a broad range of therapies due to the severity of their disease. Evolocumab will not work in the HoFH patients that do not have LDL-receptor function and should have variable effect in patients that have variable levels of LDL-receptor activity. Kynamro works in HoFH patients regardless of LDL-receptor function. Kynamro sales could be affected if Kynamro's product profile is not advantageous when compared to these other drugs, as some patients may prefer these other drugs over Kynamro.

Employees

As of February 19, 2016, we employed 428 people, including 14 Akcea employees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Executive Officers of Ionis

The following sets forth certain information regarding our executive officers as of February 19, 2016:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	70	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D.	61	Director, Chief Operating Officer
C. Frank Bennett, Ph.D.	59	Senior Vice President, Antisense Research
Sarah Boyce	44	Chief Business Officer
Richard S. Geary, Ph.D.	58	Senior Vice President, Development
Elizabeth L. Hougen	54	Senior Vice President, Finance and Chief Financial Officer
Brett P. Monia, Ph.D.	54	Senior Vice President, Drug Discovery and Corporate Development
Patrick R. O'Neil, Esq.	42	Senior Vice President, Legal, General Counsel and Corporate Secretary

STANLEY T. CROOKE, M.D., Ph.D.

Chairman, Chief Executive Officer and President

Dr. Crooke is a founder of Ionis and has been Chief Executive Officer and a Director since January 1989. He was elected Chairman of the Board in February 1991. Prior to founding Ionis, from 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories.

B. LYNNE PARSHALL, J.D.

Director, Chief Operating Officer

Ms. Parshall has served as a Director of Ionis since September 2000. She has been our Chief Operating Officer since December 2007 and previously served as our Chief Financial Officer from June 1994 to December 2012. She also served as our Corporate Secretary through 2014 and has served in various executive roles since November 1991. Prior to joining Ionis, Ms. Parshall practiced law at Cooley LLP, outside counsel to Ionis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American, California and San Diego bar associations.

C. FRANK BENNETT, Ph.D.

Senior Vice President, Antisense Research

Dr. Bennett was promoted to Senior Vice President, Antisense Research in January 2006. From June 1995 to January 2006, Dr. Bennett served as our Vice President, Research. From March 1993 to June 1995, he was Director, Molecular Pharmacology, and from May 1992 to March 1993, he was an Associate Director in our Molecular and Cellular Biology department. Prior to joining Ionis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions. He is an external member of the Scientific Advisory Board of Experimental Therapeutics Center in Singapore.

SARAH BOYCE

Chief Business Officer

Ms. Boyce joined Ionis in January 2015 as our Chief Business Officer. Prior to joining Ionis, Ms. Boyce was Vice President, Head of International Business Strategy and Operations at Forest Laboratories, Inc. from 2012 to 2014. She was Vice President, Global Head Nephrology Therapeutics Area of Alexion Pharmaceuticals from 2010 to 2011. She held various positions at Novartis Group AG, including Vice President, Global Program Head, Pediatric and Specialty from 2000 to 2010. Prior to that, Ms. Boyce held positions at Bayer Pharmaceuticals and Roche.

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

Dr. Geary was promoted to Senior Vice President, Development in August 2008. From August 2003 to August 2008, Dr. Geary served as our Vice President, Preclinical Development. From November 1995 to August 2003, he held various positions within the Preclinical Development department. Prior to joining Ionis in 1995, Dr. Geary was Senior Research Scientist and Group Leader for the bioanalytical and preclinical pharmacokinetics group in the Applied Chemistry Department at Southwest Research Institute.

ELIZABETH L. HOUGEN

Senior Vice President, Finance and Chief Financial Officer

Ms. Hougen was promoted to Senior Vice President, Finance and Chief Financial Officer in January 2013. From January 2007 to December 2012, Ms. Hougen served as our Vice President, Finance and Chief Accounting Officer and from May 2000 to January 2007, she served as our Vice President, Finance. Prior to joining Ionis in 2000, Ms. Hougen was Executive Director, Finance and Chief Financial Officer for Molecular Biosystems, Inc., a public biotechnology company.

BRETT P. MONIA, Ph.D.

Senior Vice President, Drug Discovery and Corporate Development

Dr. Monia was promoted to Senior Vice President, Drug Discovery and Corporate Development in January 2012. From February 2009 to January 2012, Dr. Monia served as our Vice President, Drug Discovery and Corporate Development and from October 2000 to February 2009, he served as our Vice President, Preclinical Drug Discovery. From October 1989 to October 2000 he held various positions within our Molecular Pharmacology department.

PATRICK R. O'NEIL, Esq.

Senior Vice President, Legal, General Counsel and Corporate Secretary

Mr. O'Neil was promoted to Senior Vice President, Legal and General Counsel in January 2013. Starting in January 2015, Mr. O'Neil also serves as our Corporate Secretary. From September 2010 to January 2013, Mr. O'Neil served as our Vice President, Legal and General Counsel and from January 2009 to September 2010, he served as our Vice President, Legal and Senior Transactions Counsel. From October 2001 to January 2009 he held various positions within our Legal department. Prior to joining Ionis, Mr. O'Neil was an associate at Cooley LLP.

Item 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

If the market does not accept our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro we are not likely to generate revenues or become consistently profitable.

Even if our drugs are authorized for marketing, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro our success will depend upon the medical community, patients and third party payors accepting our drugs as medically useful, cost-effective and safe. Even when the FDA or foreign regulatory authorities authorize our or our partners' drugs for commercialization, doctors may not prescribe our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

Additionally, in many of the markets where we may sell our drugs in the future, if we cannot agree with the government regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market.

The degree of market acceptance for our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, depends upon a number of factors, including the:

- receipt and scope of marketing authorizations;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price received for our drugs or increase patient coinsurance to a level that makes our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, unaffordable.

If we or our partners fail to compete effectively, our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, will not contribute significant revenues.

Our competitors engage in drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies engage in developing antisense technology. Our competitors may succeed in developing drugs that are:

- priced lower than our drugs;
- safer than our drugs;
- more effective than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other drugs either on their own or in collaboration with others, including our competitors, to treat the same diseases our own collaborative programs target. Competition may negatively impact a partner's focus on and commitment to our drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products and in obtaining FDA and other regulatory authorizations of such products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will rely on our partners and Akcea to provide this capability.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, drugs like AVXS-101, RG7800, RG7916, and LM1070 could compete with nusinersen, drugs like patisiran, revusiran, tafamadis, diflunisal, tolcapone and ALN-TTRsc02 could compete with IONIS-TTR$_{Rx}$, drugs like Glybera and metreleptin could compete with volanesorsen and drugs like lomitapide and evolocumab could compete with Kynamro.

Following approval our drugs, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, could be subject to regulatory limitations. Kynamro is subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our drug products, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro.

The FDA and foreign regulatory authorities have the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. For example Kynamro is subject to a Boxed Warning and is only available through a Risk Evaluation and Mitigation Strategy.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

If we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro.

If we or our partners fail to obtain regulatory approval for our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen, and additional approvals for Kynamro we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that Kynamro will be approved in additional markets outside the United States or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, before they can be approved for sale. We must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. It is possible that regulatory agencies will not approve any of our drugs including, nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen for marketing or additional marketing authorizations for Kynamro. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug.

Failure to receive marketing authorization for our drugs nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, or additional authorizations for Kynamro, or delays in these authorizations could prevent or delay commercial introduction of the drug, and, as a result, could negatively impact our ability to generate revenue from product sales.

If the results of clinical testing indicate that any of our drugs are not suitable for commercial use we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our drugs, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen. If any of our drugs in clinical studies, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

Even if our drugs are successful in preclinical and human clinical studies, the drugs may not be successful in late-stage clinical studies.

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our drugs in development, may not predict the results of subsequent clinical studies, including the Phase 3 studies for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, and subsequent studies for Kynamro. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

Any failure or delay in the clinical studies, including the Phase 3 studies for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, and subsequent studies for Kynamro, could reduce the commercial potential or viability of our drugs.

If we cannot manufacture our drugs or contract with a third party to manufacture our drugs at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.

To successfully commercialize any of our drugs, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We and our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorization for our drugs, including authorizations for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, or result in enforcement action after authorization that could limit the commercial success of our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro.

We depend on third parties to conduct our clinical studies for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our drugs and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our drugs, including authorizations for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen or additional authorizations for Kynamro.

Risks Associated with our Businesses as a Whole

We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2015, we had an accumulated deficit of approximately $1.1 billion and stockholders' equity of approximately $200.8 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

Since corporate partnering is a significant part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

To date, corporate partnering has played a significant role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our unpartnered drugs. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

For example, we do not intend to commercialize Kynamro ourselves. If we cannot find a suitable partner for Kynamro, we will not receive any revenue for Kynamro.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. In the past, based on the disappointing results of Phase 3 clinical studies, we had a partner discontinue its investment in one of our drugs.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our drug development programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical studies;
- seek and obtain marketing authorization; and
- manufacture, market and sell our drugs.

Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with AstraZeneca, Bayer, Biogen, GSK, and Roche these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we first anticipated.

For example, a collaborator such as AstraZeneca, Bayer, Biogen, GSK, or Roche, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the drug that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our drugs than it does for its own drugs.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for marketing authorization. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' expectations, including milestones related to the Phase 3 programs for nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, the price of our securities could decrease.

If we cannot protect our patents or our other proprietary rights, others may compete more effectively against us.

Our success depends to a significant degree upon whether we can continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other partners may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

From time to time we have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we sometimes need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business. For example, in November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court of the Northern District of California. Intellectual property lawsuits may be costly and may not be resolved in our favor.

If a third party claims that our drugs or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of December 31, 2015, we had cash, cash equivalents and short-term investments equal to $779.2 million. If we do not meet our goals to successfully commercialize our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we terminated the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or drugs.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel.

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, 2015, the market price of our common stock ranged from $37.38 to $77.80 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, marketing authorization, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to Kynamro, nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

If a natural or man-made disaster strikes our research, development or manufacturing facilities or otherwise affects our business, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 2/3 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 11.2 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Market. Any such action could adversely affect our financial results and the market price of our common stock.

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. On July 21, 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt, or where the SEC has adopted, additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business.

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have in the past experienced periods of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. It is possible that a crisis in the global credit markets, the U.S. capital markets, the financial services industry or the U.S. economy may adversely affect our business, vendors and prospects, as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 19, 2016, we occupied the following properties, which are all leased:

Property Description	Location	Square Footage	Initial Lease Term End Date	Lease Extension Options
Ionis laboratory and office space facility	Carlsbad, CA	176,000	2031	Four, five-year options to extend
Ionis manufacturing facility	Carlsbad, CA	28,700	2031	Four, five-year options to extend
Ionis adjacent manufacturing facility	Carlsbad, CA	25,800	2021	Two, five-year options to extend
Akcea office space facility	Cambridge, MA	6,100	2018	None
		236,600		

Under our lease agreements for our 176,000 and 28,700 square foot facilities, we have the option to purchase the facilities, independent of each other at the end of each year from 2016 through 2020, and at the end of 2026 and 2031.

We believe our existing facilities are adequate for our requirements in the foreseeable future and that we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and development needs, including for the Phase 3 clinical trials for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen.

Item 3. Legal Proceedings

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of the Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712 that are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead is asking the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents infringes those patents, and requesting monetary damages to compensate for such infringement. Under our agreement with Merck, Merck is responsible for the costs of this suit. Gilead filed a motion for summary judgment alleging invalidity of the asserted patents. In February 2016, the court denied the motion. In the same order, the court granted our motion for summary judgement for a finding of infringement, but noted that Gilead may still pursue its invalidity defenses at trial. The trial for this case is scheduled to begin March 7, 2016.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

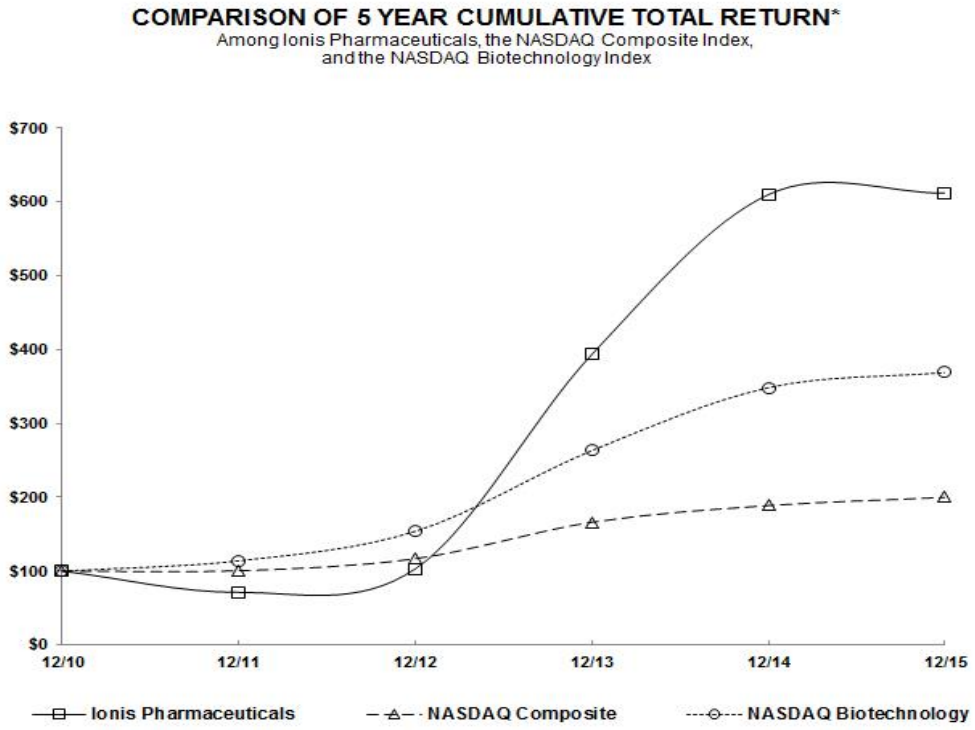
Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "IONS." Prior to our name change in December 2015, we traded under the symbol "ISIS." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by The Nasdaq Global Select Market. These prices do not include retail markups, markdowns or commissions.

	HIGH	LOW
2015		
First Quarter	$ 77.80	$ 57.60
Second Quarter	$ 71.50	$ 55.62
Third Quarter	$ 58.73	$ 37.38
Fourth Quarter	$ 65.34	$ 38.30
2014		
First Quarter	$ 62.66	$ 38.04
Second Quarter	$ 45.04	$ 22.25
Third Quarter	$ 43.42	$ 27.37
Fourth Quarter	$ 67.12	$ 35.26

As of February 19, 2016, there were approximately 606 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2010 in our common stock, the NASDAQ Composite Index (total return) and the NASDAQ Biotechnology Index. The total return assumes reinvestment of dividends.

Performance Graph (1)



*$100 invested on December 31, 2010 in stock or index, including reinvestment of dividends. Fiscal year ending December 31.

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN
Among Ionis Pharmaceuticals, Inc., the NASDAQ Composite Index,
and the NASDAQ Biotechnology Index

	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 71.25	$ 103.16	$ 393.68	$ 610.08	$ 611.96
NASDAQ Composite Index	$ 100.00	$ 100.53	$ 116.92	$ 166.19	$ 188.78	$ 199.95
NASDAQ Biotechnology Index	$ 100.00	$ 113.92	$ 153.97	$ 263.29	$ 348.49	$ 369.06

(1) This section is not "soliciting material," is not deemed "filed" with the SEC, is not subject to the liabilities of Section 18 of the Exchange Act and is not to be incorporated by reference in any of our filings under the Securities Act or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

Item 6. Selected Financial Data

Set forth below are our selected consolidated financial data (in thousands, except per share amounts):

	Years Ended December 31,				
	2015	2014	2013	2012	2011
Consolidated Statement of Operations Data:					
Revenue	$ 283,703	$ 214,161	$ 147,285	$ 102,049	$ 99,086
Research, development and patent expenses	$ 322,292	$ 241,751	$ 184,033	$ 158,458	$ 157,397
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (88,278)	$ (38,984)	$ (60,644)	$ (65,478)	$ (84,801)
Basic and diluted net loss per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (0.74)	$ (0.33)	$ (0.55)	$ (0.65)	$ (0.85)
Shares used in computing basic and diluted net loss per share	119,719	117,691	110,502	100,576	99,656

	As of December 31,				
	2015	2014	2013	2012	2011
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments	$ 779,183	$ 728,832	$ 656,761	$ 374,446	$ 343,664
Working capital	$ 688,127	$ 721,265	$ 637,698	$ 349,116	$ 284,027
Investment in Regulus Therapeutics Inc.(1)	$ 24,792	$ 81,881	$ 52,096	$ 33,622	$ 4,424
Total assets	$ 956,105	$ 955,809	$ 847,156	$ 545,686	$ 484,894
Long-term debt and other obligations, less current portion	$ 606,439	$ 582,697	$ 370,954	$ 288,598	$ 232,924
Accumulated deficit	$ (1,094,872)	$ (1,006,594)	$ (967,610)	$ (906,966)	$ (841,488)
Stockholders' equity	$ 200,790	$ 257,780	$ 378,390	$ 182,766	$ 171,434

(1) In October 2012, Regulus completed an IPO and we changed to accounting for our investment in Regulus at fair value from the equity method because our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. Our investment in Regulus is further described in Note 2, *Investments,* in the Notes to the Consolidated Financial Statements.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

Overview

We are leaders in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform. Using this platform, we have developed a large, diverse and advanced pipeline of potentially first-in-class and/or best-in-class drugs that we believe can provide high value for patients with significant unmet medical needs. In this way, we believe that we are fundamentally changing medicine with the goal to improve the quality of and save lives.

We have discovered and are developing three potentially transformational drugs, nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, which we believe are close to commercialization. We designed each of these three drugs to treat patients with orphan diseases who have limited or no therapeutic options. In total, we are developing these three drugs for six different patient populations. In 2015, we completed target enrollment in the first pivotal Phase 3 study for each of these three drugs, and we anticipate reporting data from these studies in the first half of 2017. We designed nusinersen to treat patients with spinal muscular atrophy, or SMA, a severe motor-neuron disease that is the leading genetic cause of infant mortality. We designed IONIS-TTR$_{Rx}$ to treat patients with transthyretin amyloidosis, or TTR amyloidosis, a fatal disease in which patients experience progressive buildup of amyloid plaque deposits in tissues throughout the body, including peripheral nerves, heart, intestinal tract, kidney and bladder. We designed volanesorsen to treat patients with diseases associated with extremely high levels of triglycerides, including patients with two severe and rare genetic conditions called FCS and FPL. We anticipate that the data from our pivotal Phase 3 studies, if positive, will support global regulatory filings for each drug. We believe that the significant unmet medical need and the severity of these diseases could warrant a rapid path to market. Already our partners for these programs, Biogen for nusinersen and GSK for IONIS-TTR$_{Rx}$, are preparing to commercialize these drugs. Our wholly owned subsidiary, Akcea Therapeutics, is preparing to commercialize volanesorsen. All three companies are engaging in pre-commercialization activities to understand the patient journey, build disease awareness with physicians and patients and develop their launch plans.

In addition to our Phase 3 programs, we have a pipeline of drugs with the potential to be first-in-class and/or best-in-class drugs to treat patients with inadequately treated diseases. Our pipeline has over a dozen drugs in Phase 2 development, many of which we believe have the potential to be significant commercial opportunities. In particular, IONIS-FXI$_{Rx}$ and IONIS-APO(a)-L$_{Rx}$ are representative of the value we have created. IONIS-FXI$_{Rx}$ is the first antithrombotic in development that has shown it can decrease the risk of blood vessel obstruction caused by a blood clot without increasing bleeding risk. Because of the significant commercial opportunities for this drug, we licensed it to Bayer HealthCare, a leader in developing and commercializing antithrombotics. IONIS-APO(a)-L$_{Rx}$ is the first and only drug in clinical development designed to selectively and robustly lower Lp(a), a key driver of cardiovascular disease. We believe that addressing Lp(a) is the next important horizon in lipid-focused cardiovascular disease treatment. With our support, Akcea has designed a broad development program to evaluate IONIS-APO(a)-L$_{Rx}$ in patients who are at significant cardiovascular risk due to their high Lp(a) levels. In addition to these two examples, our Phase 2 pipeline includes drugs to treat patients with severe and rare diseases, viral infections, ocular diseases, metabolic disorders and cardiovascular diseases. We plan to expand the therapeutic reach of our technology by adding three to five new drugs to our pipeline every year.

We believe that our technology is the most versatile and most efficient drug discovery technology today. We can develop drugs to act upon disease targets in many different tissues, including the liver, muscle, kidney, brain, lung, eye, tumors and others. , Many of which are inaccessible with other types of drugs. Our drugs also work through numerous different cellular mechanisms, allowing us to develop drugs that can decrease or increase the production of a target protein involved in disease and remove disease-causing RNAs. In our clinical studies, we have demonstrated that we can administer our drugs by numerous different routes of administration, including oral, local, intrathecal and subcutaneous administration. The recent advances we have made in our technology have already translated into significant value in many of our newer drugs, which patients tolerate better and which are more potent than our earlier Generation 2 drugs. We continue to advance our RNA technology to create even better medicines and to expand the reach of our technology. We actively patent the advances we have made across all areas of our technology and the drugs we are developing. In this way, we have amassed a substantial intellectual property position that provides us with extensive protection for our drugs and our technology.

We have established alliances with a cadre of leading global pharmaceutical companies who are working alongside us in advancing our technology, developing our drugs and preparing to commercialize our drugs. We believe that using our partners' resources, expertise and global commercialization capabilities maximizes the value of our drugs. We have strategic partners, Biogen and AstraZeneca, who partner with us on the development of drugs within specific therapeutic areas. We also have partnerships with GSK, Janssen, Bayer and Roche, who work with us to develop specific drugs in our pipeline. In addition to gaining access to high quality partners, disease and technology-specific expertise and global commercialization reach, our partners provide us with significant revenue through upfront fees, license fees and milestone payments. We have the potential to earn significant revenue from all of our partnerships. Since 2007, we have received more than $1.7 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn nearly $12 billion in future milestone payments and licensing fees from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out or royalty arrangements.

Financial Highlights

The following is a summary of our financial results (in thousands):

	2015	2014	2013
Total revenue	$283,703	$214,161	$147,285
Total operating expenses	$359,465	$261,891	$198,951
Loss from operations	$ (75,762)	$ (47,730)	$ (51,666)
Net loss	$ (88,278)	$ (38,984)	$ (60,644)
Cash, cash equivalents and short-term investments	$779,183	$728,832	$656,761

Our financial highlights above illustrate that over the past several years we have successfully increased our revenue and our cash balance, ending each year in a better financial position than we began. During this time, we advanced three important new drugs into Phase 3 development, initiated five Phase 3 studies on these drugs, advanced 12 Phase 2 drugs and multiple Phase 1 drugs and translated our technological innovations into the next wave of drugs to enter clinical development. During 2015, we received more than $320 million from our partners and increased our cash balance, reflecting the successes of our partnerships. As our drugs successfully advance, we generate cash and revenue from our partners. In addition to cash and revenue, our partners provide expertise and additional resources, which we believe will maximize the commercial value of our partnered drugs.

Business Segments

In 2015, we began reporting our financial results in two reportable segments, Ionis Core, previously referred to as Drug Discovery and Development, and Akcea Therapeutics, our wholly owned subsidiary. Segment loss from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class drugs for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

We formed Akcea to develop and commercialize drugs for cardiometabolic disorders. Moving our lipid drugs into a company that we own and control ensures that our core focus at Ionis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with the audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

The following are our significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Estimating our net deferred income tax asset valuation allowance.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Arrangements with multiple deliverables

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services, and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable.

Identifying deliverables and units of accounting

We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a stand-alone basis. For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment in the second quarter of 2015. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$. We are responsible for completing the ongoing development services for IONIS-FXI$_{Rx}$ and for providing an initial supply of active pharmaceutical ingredient, or API. Bayer is responsible for all other development and commercialization activities for IONIS-FXI$_{Rx}$. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement when we entered into the agreement and determined that certain deliverables have stand-alone value. Below is a list of the three units of accounting under our agreement:

- The exclusive license we granted to Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the treatment of thrombosis;
- The development services we agreed to perform for IONIS-FXI$_{Rx}$; and
- The initial supply of API.

We determined that each of these three units of accounting have stand-alone value. The exclusive license we granted to Bayer has stand-alone value because it is an exclusive license that gives Bayer the right to develop IONIS-FXI$_{Rx}$ or to sublicense its rights. The development services and the initial supply of API each have stand-alone value because Bayer or another third party could provide these items without our assistance.

Measurement and allocation of arrangement consideration

Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees and royalties on product sales. We initially allocate the amount of consideration that is fixed and determinable at the time the agreement is entered into and exclude contingent consideration. We allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

We determined that the allocable arrangement consideration for the Bayer collaboration was $100 million and we allocated it based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the license granted for IONIS-FXI$_{Rx}$ by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for IONIS-FXI$_{Rx}$. We then discounted the projected income to present value. The significant inputs we used to determine the projected income of the license included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the ongoing development services by using our internal estimates of the cost to perform the specific services and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the development services. The significant inputs we used to determine the selling price of the ongoing development services included:

- The number of internal hours we will spend performing these services;
- The estimated cost of work we will perform;
- The estimated cost of work that we will contract with third parties to perform; and
- The estimated cost of drug product we will use.

We determine the selling price of our API consistently for all of our partnerships. On an annual basis, we calculate our fully absorbed cost to manufacture API. We then determine the unit price we will charge our partners by dividing our fully absorbed costs by the quantity of API we expect to produce during the year.

For purposes of determining BESP of the services we will perform and the API in our Bayer transaction, accounting guidance required us to include a markup for a reasonable profit margin.

Based on the units of accounting under the agreement, we allocated the $100 million upfront payment from Bayer as follows:

- $91.2 million to the IONIS-FXI$_{Rx}$ exclusive license;
- $4.3 million for ongoing development services; and
- $4.5 million for the delivery of API.

Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the IONIS-FXI$_{Rx}$ license, we determined that the revenue we would have allocated to the IONIS-FXI$_{Rx}$ license would change by approximately one percent, or $0.9 million, from the amount we recorded.

Timing of revenue recognition

We recognize revenue as we deliver each item under the arrangement and the related revenue is realizable and earned. For example, we recognized revenue for the exclusive license we granted Bayer for IONIS-FXI$_{Rx}$ in the second quarter of 2015 because that was when we delivered the license. We also recognize revenue over time. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We must estimate our period of performance when the agreements we enter into do not clearly define such information. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition. We then recognize revenue ratably over such period. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations change as the development plans for our drugs progress. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of our collaboration agreements, it may affect the timing and amount of revenue that we recognize in future periods.

The following are the periods over which we are recognizing revenue for each of our units of accounting under our Bayer agreement:

- We recognized the portion of the consideration attributed to the IONIS-FXI$_{Rx}$ license immediately because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the ongoing development services for IONIS-FXI$_{Rx}$ over the period of time we are performing the services; and
- We will recognize the amount attributed to the API supply when we deliver it to Bayer.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, since early 2012, we have entered into four collaboration agreements with Biogen:

- In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize nusinersen for SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of nusinersen through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen to develop and commercialize a novel antisense drug targeting DMPK. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of a Phase 2 clinical trial.

- In December 2012, we entered into a third and separate collaboration agreement with Biogen to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets.

- In September 2013, we entered into a fourth and separate collaboration agreement with Biogen to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen exclusive rights to the use of our antisense technology to develop therapies for neurological diseases as part of this broad collaboration. We received a $100 million upfront payment and we are responsible for discovery and early development through the completion of a Phase 2 clinical trial for each antisense drug identified during the six-year term of this collaboration, while Biogen is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen the option to license one or more drugs resulting from the specific collaboration. If Biogen exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the research and/or development of the drugs prior to licensing, milestone payments if Biogen achieves pre-specified regulatory milestones, and royalties on any product sales from any drugs resulting from these collaborations.

We evaluated all four of the Biogen agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent deliverables, there are no provisions in any of these agreements that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. For all four of these agreements, we determined that the options did not have stand-alone value because Biogen cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective estimated period of our performance.

Milestone payments

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and/ or commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraph.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

During the first step of the development stage, we or our partners study our drugs in Investigational New Drug, or IND,-enabling studies, which are animal studies intended to support an IND application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate.

The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing authorization from the FDA and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing authorization. This stage of the drug's life-cycle is the regulatory stage.

If a drug achieves marketing authorization, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the partnered drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow us or our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to marketing authorization and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing authorization such as a New Drug Application, or NDA, in the United States or a Marketing Authorization Application, or MAA, in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Marketing authorization in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain authorization from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment immediately. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. We also consider milestones associated with our alliance with Alnylam substantive because we provide Alnylam ongoing access to our technology to develop and commercialize RNAi therapeutics. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or in part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable. For example, during 2014, we recognized $9.5 million in revenue from Alnylam related to its license of our technology to one of its partners because we had no performance obligations and collectability was reasonably assured.

Valuation of Investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term investments as “available-for-sale” and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investments in equity securities in publicly held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. Our Level 3 investments include investments in the equity securities of publicly held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. Historically, we have determined the lack of marketability discount by using a Black-Scholes model to value a hypothetical put option to approximate the cost of hedging the stock until the restriction ended. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

In November 2014, we participated as a selling shareholder in Regulus' equity offering and as a result we were subject to trading restrictions on our remaining shares through January 2015. Therefore, at December 31, 2014, our equity securities of Regulus included a lack of marketability discount, and as a result, were classified as a Level 3 investment. These securities were transferred to Level 1 in the first quarter of 2015, when the trading restrictions ended. At December 31, 2015 and 2013, we did not have any investments classified as Level 3.

We have equity investments in privately and publicly held biotechnology companies that we have received as part of a technology license or collaboration agreement. We account for our equity investments in publicly held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock price of these publicly held companies as a separate component of comprehensive income (loss). We account for equity investments in privately held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. We hold one cost method investment in Atlantic Pharmaceuticals Limited. Realization of our equity position in this company is uncertain. When realization of our investment is uncertain, we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

During 2015, 2014 and 2013, we realized a net gain on investments we sold of $20.3 million, $21.2 million, and $2.4 million, respectively. Our net gain for 2015 and 2014 was primarily from the $20.2 million and $19.9 million gain we realized when we sold a portion of our stock in Regulus, respectively. We have reflected this gain in a separate line called "Gain on investment in Regulus Therapeutics Inc." on our Consolidated Statements of Operations. See further discussion about our investment in Regulus in Note 2*, Investments,* in the Notes to the Consolidated Financial Statements. Our net gain on investments for 2013 related to the sale of stock in several of our satellite companies.

Estimated Liability for Clinical Development Costs

We record accrued liabilities related to expenses for which service providers have not yet billed us. These liabilities are for products or services that we have received, specifically related to ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We have numerous drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

Valuation Allowance for Net Deferred Tax Assets

We record a valuation allowance to offset any net deferred tax assets if, based upon the available evidence, it is more likely than not that we will not recognize some or all of the deferred tax assets. Except for 2009, we have had net losses since inception, and as a result, we have established a 100 percent valuation allowance for our net deferred tax asset. If we determine that we are able to realize a portion or all of these deferred tax assets in the future, we will record an adjustment to the valuation allowance.

Results of Operations

Years Ended December 31, 2015 and December 31, 2014

Revenue

Total revenue for 2015 was $283.7 million, compared to $214.2 million for 2014. We earned $115.7 million of revenue from milestone payments from our partners, $91.2 million from the license fee we recognized from our Bayer collaboration and $76.8 million primarily from the amortization of upfront fees and manufacturing services we performed for our partners during 2015.

Our revenue fluctuates based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for 2015 was $281.4 million, compared to $202.5 million for 2014. Our revenue for 2015 consisted of the following:

- $91.2 million from Bayer in connection with our exclusive license agreement for IONIS-FXI$_{Rx}$;
- $72.6 million from Biogen for advancing the Phase 3 program for nusinersen, advancing IONIS-DMPK-2.5$_{Rx}$ and IONIS-BIIB4$_{Rx}$, and validating three new targets for neurological disorders;
- $22 million from Roche for initiating a Phase 1/2 study of IONIS-HTT$_{Rx}$;
- $20 million from GSK for advancing the Phase 3 study of IONIS-TTR$_{Rx}$ and initiating a Phase 1 study of IONIS-GSK4-L$_{Rx}$; and
- $75.6 million primarily from the amortization of upfront fees and manufacturing services we performed for our partners.

Already in the first quarter of 2016, we have generated $7.3 million in milestone payments from Biogen for advancing the Phase 3 program for nusinersen, advancing IONIS-BIIB4$_{Rx}$ and from GSK when GSK initiated the Phase 1 study for IONIS-HBV-L$_{Rx}$.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for 2015 was $2.3 million, compared to $11.6 million for 2014. The decrease in 2015 compared to 2014 was primarily a result of the $9.5 million in sublicensing revenue we earned in 2014 from Alnylam related to its license of our technology to one of its partners.

Operating Expenses

Operating expenses for 2015 were $359.5 million, and increased compared to $261.9 million for 2014 as a result of the following:

- We are conducting more later-stage clinical trials in 2015 than we did in 2014, including the continuation of our Phase 3 programs for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the cost of development increases. As our Phase 3 programs continue to progress in 2016, we expect the costs associated with these programs to continue to increase modestly.
- Akcea operating expenses increased in 2015 as it began building its commercial infrastructure and advanced the pre-commercialization activities necessary to successfully launch volanesorsen within the next few years. Akcea's operating expenses for 2016 will increase as it expands these activities.
- Since we grant the majority of our stock-options in January, we had an increase in stock compensation expense because our stock price was higher in January 2015 compared to January 2014.

In 2015, we began disclosing segment information for Akcea, our wholly owned subsidiary. We have revised 2014 for comparative purposes to show operating expenses for Akcea-related projects.

Our operating expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Ionis Core	$256,512	$208,811
Akcea Therapeutics	47,887	21,697
Elimination of intercompany activity	(4,248)	—
Subtotal	300,151	230,508
Non-cash compensation expense related to equity awards	59,314	31,383
Total operating expenses	$359,465	$261,891

In order to analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support expenses.

The following table sets forth information on research, development and patent expenses (in thousands):

	Year Ended December 31,	
	2015	2014
Research, development and patent expenses	$278,654	$215,908
Non-cash compensation expense related to equity awards	43,638	25,843
Total research, development and patent expenses	$322,292	$241,751

Our research, development and patent expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Ionis Core	$240,006	$195,007
Akcea Therapeutics	42,896	20,901
Elimination of intercompany activity	(4,248)	—
Subtotal	278,654	215,908
Non-cash compensation expense related to equity awards	43,638	25,843
Total research, development and patent expenses	$322,292	$241,751

For 2015, our total research, development and patent expenses were $278.7 million, compared to $215.9 for 2014, and were higher primarily due to the progression of our drugs currently in Phase 3 trials. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our partners. Antisense drug discovery is also the function that is responsible for advancing our antisense core technology.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipelines. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs and contribute to the advancement of the science by funding core antisense technology research.

Our antisense drug discovery expenses were as follows (in thousands) and are part of our Ionis Core business segment:

	Year Ended December 31,	
	2015	2014
Antisense drug discovery expenses	$ 49,331	$ 43,620
Non-cash compensation expense related to equity awards	11,914	7,290
Total antisense drug discovery expenses	$ 61,245	$ 50,910

Antisense drug discovery expenses for 2015 were $49.3 million, and were slightly higher as expected, compared to $43.6 million for 2014. Expenses were higher because we conducted more research activities to support our partnerships in 2015 compared to 2014. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Year Ended December 31,	
	2015	2014
Nusinersen	$ 35,164	$ 19,064
Volanesorsen	21,348	9,337
IONIS-TTR$_{Rx}$	19,560	10,927
Other antisense development projects	60,028	50,272
Development overhead expenses	36,117	31,318
Total antisense drug development, excluding non-cash compensation expense related to equity awards	172,217	120,918
Non-cash compensation expense related to equity awards	16,208	9,640
Total antisense drug development expenses	$ 188,425	$ 130,558

Antisense drug development expenses were $172.2 million for 2015, compared to $120.9 million for 2014. Expenses for 2015 were higher compared to 2014 primarily due to the progression of our drugs currently in Phase 3 trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

Our antisense drug development expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Ionis Core	$ 137,092	$ 102,862
Akcea Therapeutics	35,125	18,056
Non-cash compensation expense related to equity awards	16,208	9,640
Total antisense drug development expenses	$ 188,425	$ 130,558

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we may adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous drugs in preclinical and early stage clinical research, the fluctuations in expenses from drug to drug, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. Our manufacturing and operations function is responsible for providing drug supplies to antisense drug development, our Akcea subsidiary and our collaboration partners. Our manufacturing procedures include testing to satisfy good laboratory and good manufacturing practice requirements.

Our manufacturing and operations expenses were as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Manufacturing and operations expenses	$ 28,588	$ 24,763
Non-cash compensation expense related to equity awards	4,563	2,934
Total manufacturing and operations expenses	$ 33,151	$ 27,697

Manufacturing and operations expenses were $28.6 million for 2015, and increased compared to $24.8 million for 2014. The increase in manufacturing and operations expenses was primarily related to the manufacturing activities needed to support the increase in our drug development activities. All amounts exclude non-cash compensation expense related to equity awards.

Our manufacturing and operations expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Ionis Core	$ 25,633	$ 22,425
Akcea Therapeutics	7,203	2,338
Elimination of intercompany activity	(4,248)	—
Subtotal	28,588	24,763
Non-cash compensation expense related to equity awards	4,563	2,934
Total manufacturing and operations expenses	$ 33,151	$ 27,697

R&D Support

In our research, development and patent expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D support expenses.

The following table sets forth information on R&D support expenses (in thousands):

	Year Ended December 31,	
	2015	2014
Personnel costs	$ 10,210	$ 9,875
Occupancy	7,854	7,357
Patent expenses	2,785	2,933
Depreciation and amortization	2,911	2,243
Insurance	1,320	1,197
Other	3,438	3,002
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	28,518	26,607
Non-cash compensation expense related to equity awards	10,953	5,979
Total R&D support expenses	$ 39,471	$ 32,586

R&D support expenses for 2015 were $28.5 million, and increased slightly compared to $26.6 million for 2014. All amounts exclude non-cash compensation expense related to equity awards.

Our R&D support expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Ionis Core	$ 27,950	$ 26,100
Akcea Therapeutics	568	507
Non-cash compensation expense related to equity awards	10,953	5,979
Total R&D support expenses	$ 39,471	$ 32,586

General and Administrative Expenses

General and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of legal, human resources, investor relations, and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above.

The following table sets forth information on general and administrative expenses (in thousands):

	Year Ended December 31,	
	2015	2014
General and administrative expenses	$ 21,497	$ 14,600
Non-cash compensation expense related to equity awards	15,676	5,540
Total general and administrative expenses	$ 37,173	$ 20,140

General and administrative expenses were $21.5 million for 2015, and increased compared to $14.6 million for 2014 primarily due to the addition of Akcea and an increase in personnel costs. Expenses for Akcea will increase as it continues to build the commercial infrastructure and advance the pre-commercialization activities necessary for the commercial launch of volanesorsen. All amounts exclude non-cash compensation expense related to equity awards.

Our general and administrative expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Ionis Core	$ 16,506	$ 13,804
Akcea Therapeutics	4,991	796
Non-cash compensation expense related to equity awards	15,676	5,540
Total general and administrative expenses	$ 37,173	$ 20,140

Akcea Therapeutics, Inc.

The following table sets forth information on operating expenses (in thousands) for our Akcea Therapeutics business segment:

	Year Ended December 31,	
	2015	2014
Development and patent expenses	$ 42,896	$ 20,901
General and administrative expenses	4,991	796
Total operating expenses, excluding non-cash compensation expense related to equity awards	47,887	21,697
Non-cash compensation expense related to equity awards	6,496	—
Total Akcea Therapeutics operating expenses	$ 54,383	$ 21,697

Expenses for Akcea were $47.9 million for 2015, and increased compared to $21.7 million for 2014. The increase in expenses was primarily due to Akcea's Phase 3 program for volanesorsen, which continued to advance, and the progression of its other drugs, including IONIS-APO(a)-L_{Rx} and IONIS-ANGPTL3$_{Rx}$. Also, starting in 2015, Akcea incurred additional general and administrative costs necessary to operate, including costs to begin to build the commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen within the next few years. We expect that these costs will continue to increase in 2016. For 2015 and 2014, we allocated a portion of Ionis' R&D support expenses, which are included in Development and patent expenses in the table above, to Akcea for work we performed on behalf of Akcea. For 2015 and 2014, we also allocated a portion of Ionis' general and administrative expenses, which are included in General and administrative expenses in the table above, to Akcea for work we performed on behalf of Akcea. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for 2015 was $4.3 million, compared to $2.7 million for 2014. The increase in investment income was primarily due to a higher average cash balance and an improvement in the market conditions during 2015 compared to 2014.

Interest Expense

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent notes, non-cash interest expense related to the long-term financing liability for our primary facility and other miscellaneous debt.

The following table sets forth information on interest expense (in thousands):

	Year Ended December 31,	
	2015	2014
2¾ percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 2,530	$ 7,210
Interest expense payable in cash	1,684	5,074
1 percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	20,678	2,364
Interest expense payable in cash	4,999	597
Non-cash interest expense for long-term financing liability	6,665	6,622
Other	176	342
Total interest expense	$ 36,732	$ 22,209

Interest expense for 2015 was $36.7 million, compared to $22.2 million for 2014. The increase in interest expense was primarily due to the increase in non-cash amortization of the debt discount and debt issuance costs for our 1 percent notes we issued in November 2014. In 2015 we had more debt outstanding but our interest expense payable in cash only modestly increased because our 1 percent notes have a lower interest rate than our 2¾ percent notes.

In November 2014, we completed a $500 million convertible debt offering. The notes mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent notes to repurchase $140 million in principal of our 2¾ percent convertible notes. The new principal balance of the 2¾ percent notes is $61.2 million. We record non-cash amortization of the debt discount on our convertible notes because we account for our convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature. This means we recorded our convertible notes at a discount that we are amortizing over the life of the notes as non-cash interest expense.

Gain on Investment in Regulus Therapeutics Inc.

In 2015, we recorded a gain on our investment in Regulus of $20.2 million, compared to a gain of $19.9 million for 2014 related to our sale of a portion of our Regulus common stock in each year.

Early Retirement of Debt

In 2014, we recorded a $8.3 million non-cash loss on early retirement of debt, reflecting the early retirement of a large portion of our 2¾ percent convertible notes in November 2014. We did not recognize any loss on early retirement of debt in 2015.

Income Tax Expense (Benefit)

In 2015, we recorded a net tax expense of $0.4 million due to excess tax benefits related to share-based compensation. In 2014, we recorded a net tax benefit of $15.4 million, of which $12.8 million related to our application of the intraperiod tax allocation rules that required us to record a tax benefit in continuing operations to offset the tax provision we recorded directly to other comprehensive income primarily related to the unrealized gains on our equity investment in Regulus. In addition, $4.3 million of the tax benefit we recorded in 2014 related to a tax refund we received in 2015 from the State of California Franchise Tax Board related to the California franchise taxes we paid for the tax year ended December 31, 2009.

Net Loss and Net Loss per Share

Net loss for 2015 was $88.3 million, compared to $39.0 million for 2014. Basic and diluted net loss per share for 2015 was $0.74, compared to $0.33 for 2014. We had a higher net loss in 2015 primarily due to the increase in expenses related to our three Phase 3 programs.

Net Operating Loss Carryforward

At December 31, 2015, we had federal and California tax net operating loss carryforwards of approximately $734.7 million and $886.5 million, respectively. Our federal tax loss carryforwards begin to expire in 2023. A portion of our California tax loss carryforwards expire in 2015. At December 31, 2015, we also had federal and California research and development tax credit carryforwards of approximately $146.8 million and $44.7 million, respectively. Our Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless we use them prior to expiration. Our California research and development tax credit carryforwards are available indefinitely.

Years Ended December 31, 2014 and December 31, 2013

Revenue

Total revenue for the year ended December 31, 2014 was $214.2 million compared to $147.3 million for 2013. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2014 was $202.5 million compared to $144.2 million for 2013. We earned $135.0 million in milestone payments during 2014 compared to $82.8 million in 2013. The revenue from milestone payments in 2014 was primarily comprised of:

- $80.0 million from Biogen, for advancing nusinersen, initiating a Phase 1 study of IONIS-DMPK-2.5$_{Rx}$, validating two targets to treat neurological disorders, and advancing a third drug into development;
- $28.5 million from GSK related to advancing IONIS-TTR$_{Rx}$, IONIS-HBV$_{Rx}$, IONIS-GSK4-L$_{Rx}$, and IONIS-RHO-2.5$_{Rx}$;
- $22.1 million from AstraZeneca related to the initiation of a Phase 1 clinical study of IONIS-AR-2.5$_{Rx}$ and advancing IONIS-STAT3-2.5$_{Rx}$; and
- $4.0 million from Achaogen when Achaogen initiated a Phase 3 study of plazomicin.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2014 was $11.6 million and increased compared to $3.1 million for 2013. The increase in 2014 was primarily a result of the $9.5 million in revenue we earned from Alnylam related to its license of our technology to one of its partners.

Operating Expenses

Operating expenses for the year ended December 31, 2014 were $261.9 million compared to $199.0 million for 2013. The expected increase in operating expenses was primarily due to higher costs associated with our Phase 3 programs for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen and an increase in stock compensation expense due to the increase in our stock price in January 2014 compared to January 2013.

In 2015, we began disclosing segment information for Akcea, our wholly owned subsidiary. We have revised 2014 and 2013 for comparative purposes to show operating expenses for Akcea-related projects.

Our operating expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2014	**2013**
Ionis Core	$ 208,811	$ 174,631
Akcea Therapeutics	21,697	12,902
Subtotal	230,508	187,533
Non-cash compensation expense related to equity awards	31,383	11,418
Total operating expenses	$ 261,891	$ 198,951

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support expenses.

The following table sets forth information on research, development and patent expenses (in thousands):

	Year Ended December 31,	
	2014	**2013**
Research, development and patent expenses	$ 215,908	$ 174,360
Non-cash compensation expense related to equity awards	25,843	9,673
Total research, development and patent expenses	$ 241,751	$ 184,033

Our research, development and patent expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2014	**2013**
Ionis Core	$ 195,007	$ 162,228
Akcea Therapeutics	20,901	12,132
Subtotal	215,908	174,360
Non-cash compensation expense related to equity awards	25,843	9,673
Total research, development and patent expenses	$ 241,751	$ 184,033

For the year ended December 31, 2014, total research, development and patent expenses were $215.9 million compared to $174.4 million for 2013, and were higher primarily due to more costs incurred in 2014 compared to 2013 associated with the clinical studies of the three drugs we currently have in Phase 3 studies, which we continued to advance. In addition, we progressed numerous drugs in our pipeline into later stage clinical trials. We initiated Phase 2 studies for several of the drugs in our pipeline beginning in the second half of 2013, which were ongoing in 2014, and we have advanced several drugs into clinical development. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

Our antisense drug discovery expenses were as follows (in thousands) and are part of our Ionis Core business segment:

	Year Ended December 31,	
	2014	2013
Antisense drug discovery expenses	$ 43,620	$ 42,402
Non-cash compensation expense related to equity awards	7,290	2,878
Total antisense drug discovery expenses	$ 50,910	$ 45,280

Antisense drug discovery expenses were $43.6 million for the year ended December 31, 2014, and were essentially flat compared to $42.4 million for 2013. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth expenses for our major antisense drug development projects (in thousands):

	Year Ended December 31,	
	2014	2013
Nusinersen	$ 19,064	$ 6,938
IONIS-TTR$_{Rx}$	10,927	4,174
Volanesorsen	9,337	5,730
Other antisense development products	50,272	36,782
Development overhead expenses	31,318	24,171
Total antisense drug development, excluding non-cash compensation expense related to equity awards	120,918	77,795
Non-cash compensation expense related to equity awards	9,640	3,202
Total antisense drug development expenses	$ 130,558	$ 80,997

Antisense drug development expenditures were $120.9 million for the year ended December 31, 2014 compared to $77.8 million for 2013. Expenses in 2014 were higher compared to 2013 primarily due to the progression of numerous drugs in our pipeline into later stage clinical trials, including our three drugs currently in Phase 3 trials. Beginning in the second half of 2013, we initiated Phase 2 studies for several of the drugs in our pipeline, which were ongoing in 2014, and we advanced several drugs into clinical development.

Our antisense drug development expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2014	2013
Ionis Core	$ 102,862	$ 67,006
Akcea Therapeutics	18,056	10,789
Non-cash compensation expense related to equity awards	9,640	3,202
Total antisense drug development expenses	$ 130,558	$ 80,997

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

Our manufacturing and operations expenses were as follows (in thousands):

	Year Ended December 31,	
	2014	2013
Manufacturing and operations expenses	$ 24,763	$ 20,509
Non-cash compensation expense related to equity awards	2,934	1,295
Total manufacturing and operations expenses	$ 27,697	$ 21,804

Our manufacturing and operations expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2014	2013
Ionis Core	$ 22,425	$ 19,614
Akcea Therapeutics	2,338	895
Subtotal	24,763	20,509
Non-cash compensation expense related to equity awards	2,934	1,295
Total manufacturing and operations expenses	$ 27,697	$ 21,804

Manufacturing and operations expenses for the year ended December 31, 2014 were $24.8 million, and increased compared to $20.5 million for 2013, primarily because we manufactured more drug product to support the increase in our drug development activities. In 2014, our manufacturing expenses included drug product to support the Phase 3 trial for volanesorsen and additional costs associated with manufacturing drug product using our LICA technology. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

The following table sets forth information on R&D support expenses (in thousands):

	Year Ended December 31,	
	2014	2013
Personnel costs	$ 9,875	$ 9,571
Occupancy	7,357	6,897
Patent expenses	2,933	10,321
Depreciation and amortization	2,243	2,464
Insurance	1,197	1,108
Other	3,002	3,293
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	26,607	33,654
Non-cash compensation expense related to equity awards	5,979	2,298
Total R&D support expenses	$ 32,586	$ 35,952

R&D support expenses for the year ended December 31, 2014 were $26.6 million compared to $33.7 million for 2013 and decreased primarily due to lower patent expenses in 2014. Patent expenses were higher in 2013 primarily due to non-cash charges for patents and patent applications that we wrote off in 2013 due to a careful restructuring of our patent portfolio to focus our resources on patents and new patent applications that drive value for our company. All amounts exclude non-cash compensation expense related to equity awards.

Our R&D support expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2014	2013
Ionis Core	$ 26,100	$ 33,206
Akcea Therapeutics	507	448
Non-cash compensation expense related to equity awards	5,979	2,298
Total R&D support expenses	$ 32,586	$ 35,952

General and Administrative Expenses

The following table sets forth information on general and administrative expenses (in thousands):

	Year Ended December 31,	
	2014	2013
General and administrative expenses	$ 14,600	$ 13,173
Non-cash compensation expense related to equity awards	5,540	1,745
Total general and administrative expenses	$ 20,140	$ 14,918

General and administrative expenses for the year ended December 31, 2014 were $14.6 million and increased compared to $13.2 million for 2013. The increase was due to consulting expenses we incurred. All amounts exclude non-cash compensation expense related to equity awards.

Our general and administrative expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2014	2013
Ionis Core	$ 13,804	$ 12,403
Akcea Therapeutics	796	770
Non-cash compensation expense related to equity awards	5,540	1,745
Total general and administrative expenses	$ 20,140	$ 14,918

Akcea Therapeutics, Inc.

The following table sets forth information on operating expenses (in thousands) for our Akcea Therapeutics business segment:

	Year Ended December 31,	
	2014	2013
Development and patent expenses	$ 20,901	$ 12,132
General and administrative expenses	796	770
Total Akcea Therapeutics operating expenses	$ 21,697	$ 12,902

Akcea's operating expenses were $21.7 million for the year ended December 31, 2014 and increased compared to $12.9 million for 2013. The increase in expenses was primarily due to Akcea's Phase 3 program for volanesorsen, which continued to advance, and other projects, including IONIS-APO(a)-L_{Rx} and IONIS-ANGPTL3$_{Rx}$. For 2014 and 2013, we allocated a portion of Ionis' R&D support expenses, which are included in Development and patent expenses in the table above, to Akcea for work we performed on behalf of Akcea. For 2014 and 2013, we also allocated a portion of Ionis' general and administrative expenses, which are included in General and administrative expenses in the table above, to Akcea for work we performed on behalf of Akcea.

Investment Income

Investment income for the year ended December 31, 2014 totaled $2.7 million compared to $2.1 million for 2013. The increase in investment income was primarily due to a higher average cash balance and increased yields.

Interest Expense

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent convertible notes, non-cash interest expense related to the long-term financing liability for our primary facility and other miscellaneous debt.

The following table sets forth information on interest expense (in thousands):

	Year Ended, December 31	
	2014	2013
2¾ percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 7,210	$ 6,759
Interest expense payable in cash	5,074	5,534
1 percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	2,364	—
Interest expense payable in cash	597	—
Non-cash interest expense for long-term financing liability	6,622	6,568
Other	342	494
Total interest expense	$ 22,209	$ 19,355

Interest expense for the year ended December 31, 2014 was $22.2 million compared to $19.4 million in 2013. The increase in interest expense was primarily due to a higher average carrying value of the liability portion of our debt and a slight increase in interest expense payable in cash because we had more debt outstanding in 2014 compared to 2013.

Gain on Investments, Net

Net gain on investments for the year ended December 31, 2014 was $1.3 million compared to $2.4 million for 2013. The net gain on investments in 2014 was primarily due to the $1.3 million gain we realized when we sold the common stock of Achaogen we owned. During 2013, the gain consisted of sales of stock we held in several satellite companies.

Gain on Investment in Regulus Therapeutics Inc.

In 2014, we realized a gain on our investment in Regulus of $19.9 million when we sold a portion of our stock. We did not sell any of our stock in Regulus in 2013.

Early Retirement of Debt

In 2014, we recorded a $8.3 million non-cash loss on early retirement of debt, reflecting the early retirement of a large portion of our 2¾ percent convertible notes in November 2014. We did not recognize any loss on early retirement of debt in 2013.

Income Tax Benefit

In 2014, we recorded a net tax benefit of $15.4 million, of which $12.8 million related to our application of the intraperiod tax allocation rules that required us to record a tax benefit in continuing operations to offset the tax provision we recorded directly to other comprehensive income primarily related to the unrealized gains on our equity investment in Regulus. In addition, $4.3 million of the tax benefit we recorded in 2014 related to a tax refund we received in 2015 from the State of California Franchise Tax Board related to the California franchise taxes we paid for the tax year ended December 31, 2009. The increase in 2014 compared to 2013 was due to larger unrealized gains year over year and the tax refund we recorded in 2014.

Net Loss and Net Loss Per Share

Net loss for the year ended December 31, 2014 was $39.0 million compared $60.6 million for 2013. Basic and diluted net loss per share for the year ended December 31, 2014 was $0.33 compared to $0.55 for 2013. Our net loss for the year ended December 31, 2014 decreased significantly compared to 2013 due to the significant increase in revenue that we earned from our partners in 2014, offset mostly by the planned increase in operating expenses associated with our advancing pipeline of drugs. The decrease in our net loss was further impacted by the $19.9 million gain we realized in 2014 from the sale of a portion of our stock in Regulus, the $15.4 million net tax benefit we recorded in 2014 offset, in part, by the $8.3 million non-cash loss we recorded in 2014 on the early retirement of a large portion of our 2¾ percent convertible notes.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through December 31, 2015, we have earned approximately $1.8 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through December 31, 2015, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $1.3 billion under long-term debt arrangements to finance a portion of our operations.

At December 31, 2015, we had cash, cash equivalents and short-term investments of $779.2 million and stockholders' equity of $200.8 million. In comparison, we had cash, cash equivalents and short-term investments of $728.8 million and stockholders' equity of $257.8 million at December 31, 2014. We received a substantial amount of cash in 2015, including more than $320 million in payments from our partners.

At December 31, 2015, we had consolidated working capital of $688.1 million compared to $721.3 million at December 31, 2014. Working capital decreased in 2015 primarily due to the decrease in our investment in Regulus and an increase in payables. The decrease in our investment in Regulus was a result of us selling a portion of our stock in Regulus, in which we received $25.5 million in proceeds in 2015 and Regulus' stock price declining at December 31, 2015 compared to December 31, 2014, as other biotech companies have also experienced declines over this same time period.

As of December 31, 2015, our debt and other obligations totaled $644.8 million compared to $643.5 million at December 31, 2014.

The following table summarizes our contractual obligations as of December 31, 2015. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
1 percent convertible senior notes (principal and interest payable)	$ 530.0	$ 5.0	$ 10.0	$ 10.0	$ 505.0
2¾ percent convertible senior notes (principal and interest payable)	$ 68.0	$ 1.7	$ 3.4	$ 62.9	$ —
Financing arrangements (principal and interest payable)	$ 9.0	$ 9.0	$ —	$ —	$ —
Facility rent payments	$ 125.6	$ 6.5	$ 13.5	$ 14.3	$ 91.3
Other obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Operating leases	$ 24.6	$ 2.0	$ 3.5	$ 3.0	$ 16.1
Total	$ 758.5	$ 24.3	$ 30.5	$ 90.3	$ 613.4

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility leases, equipment financing arrangements and other obligations.

Convertible Debt Summary

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent notes convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes. As a result, the new principal balance of the 2¾ percent notes is $61.2 million.

At December 31, 2015 our outstanding convertible debt was as follows (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes	2¾ Percent Convertible Senior Notes
Outstanding principal balance	$ 500.0	$ 61.2
Issue date	November 2014	August 2012
Maturity date	November 2021	October 2019
Interest rate	1 percent	2¾ percent
Conversion price per share	$ 66.81	$ 16.63
Total shares of common stock subject to conversion	7.5	3.7

Interest is payable semi-annually for both the 1 percent and 2¾ percent notes. The notes are convertible under certain conditions, at the option of the note holders. We settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both.

1 Percent Convertible Senior Notes

We may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 1 percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

2¾ Percent Convertible Senior Notes

We may redeem the 2¾ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion price for the 2¾ percent notes on each such day. The redemption price for the 2¾ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus $90 per each $1,000 principal amount being redeemed. Holders of the 2¾ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 2¾ percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Financing Arrangements

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, Morgan Stanley will provide a maximum of $30 million of revolving credit for general working capital purposes. Any loans under the credit agreement have interest payable monthly in arrears at a rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, we will pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility beginning after June 2016. As of December 31, 2015 we had $8.5 million in outstanding borrowings under the credit facility, which were used to fund our capital equipment needs and is consistent with our historical practice to finance these costs. As of December 31, 2015, our outstanding borrowings under this credit facility were at a weighted average interest rate of 1.67 percent.

The credit agreement includes customary affirmative and negative covenants and restrictions. We are in compliance with all covenants of the credit agreement.

In October 2008, we entered into an equipment financing loan agreement. As of December 31, 2015, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.39 percent. The carrying balance under this loan agreement at December 31, 2015 and 2014 was $0.5 million and $3.2 million, respectively. Our remaining outstanding balance is due in June 2016 and interest is payable monthly.

Research and Development Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed constructed our facility in Carlsbad, California. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under this lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the facility. Accounting rules required us to record the cost of the facility as a fixed asset with a corresponding liability. We are depreciating the building over its economic life and we apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2015 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

As part of Akcea's formation, we made an initial cash investment in the company to fund Akcea's operations. As Akcea continues to progress we may seek additional capital to fund Akcea's future operating needs. As such, we may pursue various financing alternatives, like issuing shares of Ionis' or Akcea's stock in private or public financings, issuing Ionis or Akcea debt instruments, or securing lines of credit. We may also consider entering into collaborations specific to Akcea's pipeline with partners to provide for additional operating cash.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury, reputable financial institutions, corporations, U.S. government agencies and securities issued by states of the United States and political subdivisions of the states with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

Item 8. Financial Statements and Supplementary Data

We filed our consolidated financial statements and supplementary data required by this item as exhibits hereto, and listed them under Item 15(a) (1) and (2), and incorporate them herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

There have been no reported disagreements on any matter of accounting principles or procedures or financial statement disclosure in 2015 with our Independent Registered Public Accounting Firm.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

We maintain disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or Exchange Act) that are designed to ensure that information we are required to disclose in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We designed and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of the end of the period covered by this report on Form 10-K, we carried out an evaluation of our disclosure controls and procedures under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2015.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f). Our internal control over financial reporting is a process designed under the supervision of our Chief Executive Officer and Chief Financial Officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external purposes in accordance with United States generally accepted accounting principles.

As of December 31, 2015, we assessed the effectiveness of our internal control over financial reporting based on the criteria for effective internal control over financial reporting under the 2013 "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations, or COSO, of the Treadway Commission, under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on that assessment, our management concluded that we maintained effective internal control over financial reporting as of December 31, 2015.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2015, as stated in their attestation report, which is included elsewhere herein.

Changes in Internal Control over Financial Reporting

The above assessment did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.)

We have audited Ionis Pharmaceuticals, Inc.'s (formerly Isis Pharmaceuticals, Inc.) internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). Ionis Pharmaceuticals, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, Ionis Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2015, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of Ionis Pharmaceuticals, Inc. as of December 31, 2015 and 2014, and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2015 of Ionis Pharmaceuticals, Inc. and our report dated February 25, 2016 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 25, 2016

Item 9B. Other Information

In June 2015 we and Morgan Stanley Private Bank, National Association entered into a Line of Credit Agreement.

In February 2016, we and Morgan Stanley amended the loan documents to increase the amount available under the agreement to $30 million and revise a financial covenant relating to our debt to net worth ratio.

Item 10. Directors, Executive Officers and Corporate Governance

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption "ELECTION OF DIRECTORS," including in particular the information under "Nominating, Governance and Review Committee" and "Audit Committee," contained in our definitive Proxy Statement (the "Proxy Statement"), which we will file on or about April 15, 2016 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2016 Annual Meeting of Stockholders to be held on June 3, 2016.

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption "Code of Ethics and Business Conduct" contained in the Proxy Statement. Our Code of Ethics and Business Conduct is posted on our website at www.ionispharma.com(1). We intend to disclose future amendments to, or waivers from, our Code of Ethics and Business Conduct on our website.

Item 1, Part I of this Report contains information concerning our executive officers. We incorporate by reference the information required by this Item concerning compliance with Section 16(a) of the Securities Exchange Act of 1934, as amended, from the information under the caption "Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Proxy Statement.

(1) Any information that is included on or linked to our website is not part of this Form 10-K.

Item 11. Executive Compensation

We incorporate by reference the information required by this item to the information under the caption "EXECUTIVE COMPENSATION," "Compensation Committee Interlocks and Insider Participation" and "COMPENSATION COMMITTEE REPORT" contained in the Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

We incorporate by reference the information required by this item to the information under the captions "SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT" contained in the Proxy Statement.

Securities Authorized for Issuance under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2015.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance	
Equity compensation plans approved by stockholders(a)	7,996,753	$ 33.31	6,863,085	(c)
Equity compensation plans not approved by stockholders(b)	44,025	$ 14.66	-	
Total	8,040,778	$ 33.21	6,863,085	

(a) Consists of four Ionis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, 2011 Equity Incentive Plan and Employee Stock Purchase Plan, or ESPP.

(b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below. The 2000 Broad-Based Equity Incentive Plan expired on January 5, 2010.

(c) Of these shares, 481,764 remained available for purchase under the ESPP as of December 31, 2015. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year, we automatically increase the aggregate number of shares reserved for issuance under the plan by 150,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Broad-Based Equity Incentive Plan, or the 2000 Plan, to provide our employees, officers, directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of non-statutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. The Board delegated administration of the 2000 Plan to the Compensation Committee of the Board. The Board has the power to construe and interpret the 2000 Plan.

As of December 31, 2015, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 44,025 shares were granted and outstanding under the 2000 Plan, option holders had exercised options to purchase an aggregate of 5,492,172 shares under the 2000 Plan, and no shares remained available for grant thereunder. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Options granted under the 2000 Plan generally have a term of seven or ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25 percent per year after the first year and then at the rate of 2.08 percent per month thereafter during the option holder's employment or service as a consultant, employee or director. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our board of directors will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, all outstanding stock awards will terminate immediately prior to such event.

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise;

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

Item 13. Certain Relationships and Related Transactions, and Director Independence

We incorporate by reference the information required by this item to the information under the captions "Independence of the Board of Directors" and "Certain Relationships and Related Transactions" contained in the Proxy Statement.

Item 14. Principal Accounting Fees and Services

We incorporate by reference the information required by this item to the information under the caption "Ratification of Selection of Independent Auditors" contained in the Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Index to Financial Statements

We submitted the consolidated financial statements required by this item in a separate section beginning on page F-1 of this Report.

(a)(2) Index to Financial Statement Schedules

We omitted these schedules because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

(a)(3) Index to Exhibits

See Index to Exhibits beginning on page 68.

(b) Exhibits

We listed the exhibits required by this Item under Item 15(a)(3).

(c) Financial Statement Schedules

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 25th day of February, 2016.

IONIS PHARMACEUTICALS, INC.

By: /s/ STANLEY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer
(Principal executive officer)

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Stanley T. Crooke and Elizabeth L. Hougen, or any of them, his or her attorney-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	February 25, 2016
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Chief Operating Officer and Secretary	February 25, 2016
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 25, 2016
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 25, 2016
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	February 25, 2016
/s/ JOSEPH KLEIN Joseph Klein, III	Director	February 25, 2016
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	February 25, 2016
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 25, 2016
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 25, 2016

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed June 17, 2014. (35)
3.3	Certificate of Amendment to Restated Certificate of Incorporation filed December 18, 2015. (41)
3.4	Amended and Restated Bylaws. (41)
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock. (9)
4.2	Specimen Common Stock Certificate. (1)
4.3	Indenture, dated as of August 13, 2012, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 2¾ percent Convertible Senior Note due 2019. (24)
4.4	Indenture, dated as of November 17, 2014, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 1.00 percent Convertible Senior Note due 2021. (34)
10.1	Form of Indemnity Agreement entered into between the Registrant and its Directors and Officers with related schedule. (30)
10.2*	Registrant's 1989 Stock Option Plan, as amended. (21)
10.3*	Registrant's Amended and Restated 2000 Employee Stock Purchase Plan. (11)
10.4	Form of Employee Assignment of Patent Rights. (1)
10.5*	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement. (5)
10.6	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (4)
10.7	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (10)
10.8	License and Co-Development Agreement between the Registrant and Genzyme Corporation dated June 24, 2008. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (6)
10.9	Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (7)
10.10	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (3)
10.11	Amended and Restated License Agreement between the Registrant and Atlantic Pharmaceuticals Limited dated November 30, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (19)
10.12	Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (13)
10.13	Lease Agreement between the Registrant and BMR-Gazelle Court LLC dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (20)
10.14	Second Amendment to Lease Agreement dated May 15, 2011 between the Registrant and BMR-Gazelle Court LLC, with First Amendment to Lease Agreement included. (7)
10.15	Registrant's Amended and Restated 10b5-1 Trading Plan dated September 12, 2013. (27)
10.16*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended. (35)
10.17*	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement. (16)

10.18* Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan. (26)

10.19* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and Stanley T. Crooke. (12)

10.20* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and B. Lynne Parshall. (12)

10.21* Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (15)

10.22 Loan Agreement dated October 15, 2008 between the Registrant and RBS Asset Finance, Inc. (18)

10.23* Form of Option Agreement under the 2011 Equity Incentive Plan. (37)

10.24* Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan. (23)

10.25 Second Amendment to Lease Agreement between the Registrant and BMR-2282 Faraday Avenue LLC dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (20)

10.26* Form of Option Agreement under the 1989 Stock Option Plan. (37)

10.27* Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan. (8)

10.28* Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan. (8)

10.29 Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (20)

10.30 First Amendment to Loan Agreement between the Registrant and RBS Asset Finance, Inc. dated September 30, 2009. (19)

10.31 Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC. (14)

10.32 Stock Purchase Agreement dated December 17, 2008, among the Registrant, Ibis Biosciences, Inc. and Abbott Molecular Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (18)

10.33 Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (2)

10.34 Amendment No. 1 to Amended and Restated License Agreement between the Registrant and OncoGenex Technologies Inc. dated December 18, 2009. (19)

10.35 Second Amendment to Loan Agreement dated November 15, 2010 between the Registrant and RBS Asset Finance, Inc. (17)

10.36 Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (25)

10.37 Third Amendment to Loan Agreement dated June 24, 2012 between the Registrant and RBS Asset Finance, Inc. (26)

10.38 DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (26)

10.39 Amendment #2 to Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated October 30, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (30)

10.40 Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (30)

10.41 Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated December 10, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (30)

10.42 HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (28)

10.43 Letter Agreement between the Registrant and CHDI Foundation, Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (28)

10.44 Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated September 5, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (27)

10.45 Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (27)

10.46 Letter Agreement Amendment between the Registrant and Biogen Idec International Holding Ltd dated January 27, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (31)

10.47 Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (32)

10.48 Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (32)

10.49 Amendment #5 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (32)

10.50 Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)

10.51 Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)

10.52 Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)

10.53 Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (36)

10.54 Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 22, 2014. Portions of this exhibit have been omitted and separately filed with the SEC. (36)

10.55 Amendment No.2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (36)

10.56 Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 2015. Portions of this exhibit have been omitted and separately filed with the SEC. (37)

10.57 Amendment #6 to Research, Development and License Agreement between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 2015. Portions of this exhibit have been omitted and separately filed with the SEC. (37)

10.58 Amendment Number One to the Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated July 13, 2015. Portions of this exhibit have been omitted and separately filed with the SEC. (37)

10.59 License Agreement between the Registrant and Bayer Pharma AG dated May 1, 2015. Portions of this exhibit have been omitted and separately filed with the SEC. (38)

10.60	Line of Credit Agreement between the Registrant and Morgan Stanley Private Bank, National Association dated June 16, 2015. (38)
10.61	Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated January 8, 2015. Portions of this exhibit have been omitted and separately filed with the SEC. (39)
10.62	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015. Portions of this exhibit have been omitted and separately filed with the SEC. (39)
10.63	Amendment No.1 to Loan Documents between the Registrant and Morgan Stanley Private Bank, National Association dated December 30, 2015. (40)
10.64	Amendment No.2 to Line of Credit Agreement between the Registrant and Morgan Stanley Private Bank, National Association dated February 24, 2016.
14.1	Registrant's Code of Ethics and Business Conduct. (29)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney (22)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2015, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of stockholders' equity, (iv) consolidated statements of cash flows, and (v) notes to consolidated financial statements (detail tagged).

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.

(2) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011 and incorporated herein by reference.

(3) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008 and incorporated herein by reference.

(4) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1999 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008 and incorporated herein by reference.

(7) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2011 and incorporated herein by reference.

(8) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2004 and incorporated herein by reference.

(9) Filed as an exhibit to Registrant's Report on Form 8-K dated filed December 13, 2000 and incorporated herein by reference.

(10) Filed as an exhibit to the Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 and incorporated herein by reference.

(11) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2009 Annual Meeting of Stockholders, filed with the SEC on April 20, 2009, and incorporated herein by reference.

(12) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 5, 2008 and incorporated herein by reference.

(13) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2008 and incorporated herein by reference.

(14) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2005 and incorporated herein by reference.

(15) Filed as an exhibit to the Registrant's Notice of 2011 Annual Meeting of Stockholders and Proxy Statement filed with the SEC on April 28, 2011, and incorporated herein by reference.

(16) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2001 and incorporated herein by reference.

(17) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2010 and incorporated herein by reference.

(18) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2008 and incorporated herein by reference.

(19) Filed as an exhibit to the Registrant's Annual Report as Form 10-K for the year ended December 31, 2009 and incorporated herein by reference.

(20) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2010 and incorporated herein by reference.

(21) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2012 Annual Meeting of Stockholders, filed with the SEC on April 16, 2012, and incorporated herein by reference.

(22) Filed as part of the Annual Report on Form 10-K for the year ended December 31, 2013, and incorporated herein by reference.

(23) Filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed with the SEC on August 8, 2011, and incorporated herein by reference.

(24) Filed as an exhibit to the Registrant's Report on Form 8-K filed August 13, 2012 and incorporated herein by reference.

(25) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2012 and incorporated herein by reference.

(26) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference.

(27) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference.

(28) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference.

(29) Filed as an exhibit to the Registrant's Report on Form 8-K filed on December 9, 2013 and incorporated herein by reference.

(30) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference.

(31) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2014 and incorporated herein by reference.

(32) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference.

(33) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference.

(34) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 21, 2014 and incorporated herein by reference.

(35) Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014, and incorporated herein by reference.

(36) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference.
(37) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference.
(38) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015 and incorporated herein by reference.
(39) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference.
(40) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed January 5, 2016 and incorporated herein by reference.
(41) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
* Indicates management compensatory plans and arrangements as required to be filed as exhibits to this Report pursuant to Item 14(c).

IONIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.)

We have audited the accompanying consolidated balance sheets of Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.) as of December 31, 2015 and 2014, and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2015. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Ionis Pharmaceuticals, Inc. at December 31, 2015 and 2014, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), Ionis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 25, 2016 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 25, 2016

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	December 31,	
	2015	**2014**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 128,797	$ 142,998
Short-term investments	650,386	585,834
Contracts receivable	11,356	3,903
Inventories	6,899	6,290
Investment in Regulus Therapeutics Inc.	24,792	81,881
Other current assets	14,773	15,691
Total current assets	837,003	836,597
Property, plant and equipment, net	90,233	88,958
Patents, net	19,316	17,186
Deposits and other assets	9,553	13,068
Total assets	$ 956,105	$ 955,809
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 28,355	$ 17,984
Accrued compensation	16,065	12,302
Accrued liabilities	28,105	30,451
Current portion of long-term obligations	9,029	2,882
Current portion of deferred contract revenue	67,322	51,713
Total current liabilities	148,876	115,332
Long-term deferred contract revenue	134,306	127,797
1 percent convertible senior notes	347,214	327,486
2¾ percent convertible senior notes	50,361	48,014
Long-term obligations, less current portion	2,341	7,669
Long-term financing liability for leased facility	72,217	71,731
Total liabilities	755,315	698,029
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 120,351,480 and 118,442,726 shares issued and outstanding at December 31, 2015 and December 31, 2014, respectively	120	118
Additional paid-in capital	1,309,107	1,224,509
Accumulated other comprehensive income (loss)	(13,565)	39,747
Accumulated deficit	(1,094,872)	(1,006,594)
Total stockholders' equity	200,790	257,780
Total liabilities and stockholders' equity	$ 956,105	$ 955,809

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except for per share amounts)

	Years Ended December 31,		
	2015	**2014**	**2013**
Revenue:			
Research and development revenue under collaborative agreements	$ 281,360	$ 202,514	$ 144,194
Licensing and royalty revenue	2,343	11,647	3,091
Total revenue	283,703	214,161	147,285
Expenses:			
Research, development and patent expenses	322,292	241,751	184,033
General and administrative	37,173	20,140	14,918
Total operating expenses	359,465	261,891	198,951
Loss from operations	(75,762)	(47,730)	(51,666)
Other income (expense):			
Investment income	4,302	2,682	2,085
Interest expense	(36,732)	(22,209)	(19,355)
Gain on investments, net	75	1,256	2,378
Gain on investment in Regulus Therapeutics Inc.	20,211	19,902	—
Loss on early retirement of debt	—	(8,292)	—
Loss before income tax (expense) benefit	(87,906)	(54,391)	(66,558)
Income tax (expense) benefit	(372)	15,407	5,914
Net loss	$ (88,278)	$ (38,984)	$ (60,644)
Basic and diluted net loss per share	$ (0.74)	$ (0.33)	$ (0.55)
Shares used in computing basic and diluted net loss per share	119,719	117,691	110,502

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	Years Ended December 31,		
	2015	**2014**	**2013**
Net loss	$ (88,278)	$ (38,984)	$ (60,644)
Unrealized (losses) gains on investments, net of tax	(33,101)	40,079	10,253
Reclassification adjustment for realized gains included in net loss	(20,211)	(21,412)	(1,653)
Comprehensive loss	$ (141,590)	$ (20,317)	$ (52,044)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2015, 2014 and 2013
(In thousands)

Description	Common stock Shares	Common stock Amount	Additional Paid In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2012	101,481	$ 102	$ 1,077,150	$ 12,480	$ (906,966)	$ 182,766
Net loss	—	—	—	—	(60,644)	(60,644)
Change in unrealized gains (losses), net of tax	—	—	—	8,600	—	8,600
Issuance of common stock in connection with employee stock plans	5,372	5	62,953	—	—	62,958
Issuance of public common stock	9,618	9	173,283	—	—	173,292
Share-based compensation expense	—	—	11,418	—	—	11,418
Balance at December 31, 2013	116,471	$ 116	$ 1,324,804	$ 21,080	$ (967,610)	$ 378,390
Net loss	—	—	—	—	(38,984)	(38,984)
Change in unrealized gains (losses), net of tax	—	—	—	18,667	—	18,667
Issuance of common stock in connection with employee stock plans	1,972	2	23,071	—	—	23,073
2¾ percent convertible senior notes redemption, equity portion	—	—	(326,444)	—	—	(326,444)
1 percent convertible senior notes, equity portion, net of issuance costs	—	—	170,232	—	—	170,232
Share-based compensation expense	—	—	31,383	—	—	31,383
Excess tax benefits from share-based compensation awards	—	—	1,463	—	—	1,463
Balance at December 31, 2014	118,443	$ 118	$ 1,224,509	$ 39,747	$ (1,006,594)	$ 257,780
Net loss	—	—	—	—	(88,278)	(88,278)
Change in unrealized gains (losses), net of tax	—	—	—	(53,312)	—	(53,312)
Issuance of common stock in connection with employee stock plans	1,908	2	24,888	—	—	24,890
Share-based compensation expense	—	—	59,314	—	—	59,314
Excess tax benefits from share-based compensation awards	—	—	396	—	—	396
Balance at December 31, 2015	120,351	$ 120	$ 1,309,107	$ (13,565)	$ (1,094,872)	$ 200,790

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Years Ended December 31,		
	2015	**2014**	**2013**
Operating activities:			
Net loss	$ (88,278)	$ (38,984)	$ (60,644)
Adjustments to reconcile net loss to net cash provided by operating activities:			
Depreciation	6,984	6,380	6,591
Amortization of patents	1,381	1,142	1,184
Amortization of licenses	1,873	1,882	2,007
Amortization of premium on investments, net	7,812	7,470	5,572
Amortization of debt issuance costs	1,133	595	415
Amortization of 2¾ convertible senior notes discount	2,347	6,723	6,344
Amortization of 1 percent convertible senior notes discount	19,728	2,256	—
Amortization of long-term financing liability for leased facility	6,665	6,622	6,567
Share-based compensation expense	59,314	31,383	11,418
Gain on investment in Regulus Therapeutics Inc.	(20,211)	(19,902)	—
Loss on early retirement of debt	—	8,292	—
Gain on investments, net	(75)	(1,256)	(2,378)
Non-cash losses related to patents, licensing and property, plant and equipment	1,881	1,305	6,306
Tax benefit from other unrealized gains on securities	—	(12,835)	(5,914)
Changes in operating assets and liabilities:			
Contracts receivable	(7,453)	7,199	(10,580)
Inventories	(609)	1,743	(1,912)
Other current and long-term assets	(4,319)	(1,750)	(1,091)
Accounts payable	9,211	4,824	66
Income taxes	—	(4,034)	—
Accrued compensation	3,763	134	4,290
Deferred rent	205	153	217
Accrued liabilities	(2,345)	8,358	6,691
Deferred contract revenue	22,118	(11,415)	88,344
Net cash provided by operating activities	21,125	6,285	63,493
Investing activities:			
Purchases of short-term investments	(493,467)	(391,883)	(425,554)
Proceeds from the sale of short-term investments	419,584	294,727	172,762
Purchases of property, plant and equipment	(7,692)	(7,518)	(1,552)
Acquisition of licenses and other assets, net	(4,056)	(3,586)	(3,810)
Proceeds from the sale of Regulus Therapeutics, Inc.	25,527	22,949	—
Proceeds from the sale of strategic investments	52	2,463	2,428
Net cash used in investing activities	(60,052)	(82,848)	(255,726)
Financing activities:			
Proceeds from equity awards	24,888	23,071	62,958
Proceeds from issuance of 1 percent convertible senior notes, net of issuance costs	—	487,035	—
Repurchase of $140 million principal amount of the 2¾ percent convertible senior notes	—	(441,394)	—
Proceeds from borrowing on line of credit facility	8,500	—	—
Proceeds from public common stock offering	—	—	173,292
Proceeds from equipment financing arrangement	—	—	2,513
Excess tax benefits from share-based compensation awards	396	1,463	—
Principal payments on debt and capital lease obligations	(9,058)	(10,587)	(11,039)
Net cash provided by financing activities	24,726	59,588	227,724
Net (decrease) increase in cash and cash equivalents	(14,201)	(16,975)	35,491
Cash and cash equivalents at beginning of year	142,998	159,973	124,482
Cash and cash equivalents at end of year	$ 128,797	$ 142,998	$ 159,973

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

Supplemental disclosures of cash flow information:			
Interest paid	$ 6,800	$ 6,353	$ 6,000
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 1,162	$ 2,151	$ 704

See accompanying notes.

1. Organization and Significant Accounting Policies

Basis of presentation

The consolidated financial statements include the accounts of Ionis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiary, Akcea Therapeutics, Inc., which we formed in December 2014. In December 2015, we changed our name from Isis Pharmaceuticals, Inc. to Ionis Pharmaceuticals, Inc.

Organization and business activity

We incorporated in California on January 10, 1989. In conjunction with our initial public offering, we reorganized as a Delaware corporation in April 1991. We were organized principally to develop human therapeutic drugs using antisense technology.

Basic and diluted net loss per share

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a net loss for 2015, 2014 and 2013, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- .ıpercent convertible senior notes (for 2014 and 2015);
- 2¾ percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

Revenue recognition

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Arrangements with multiple deliverables

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services, and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable.

Identifying deliverables and units of accounting

We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a stand-alone basis. For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment in the second quarter of 2015. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$. We are responsible for completing the ongoing development services for IONIS-FXI$_{Rx}$ and for providing an initial supply of active pharmaceutical ingredient, or API. Bayer is responsible for all other development and commercialization activities for IONIS-FXI$_{Rx}$. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement when we entered into the agreement and determined that certain deliverables have stand-alone value. Below is a list of the three units of accounting under our agreement:

- The exclusive license we granted to Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the treatment of thrombosis;
- The development services we agreed to perform for IONIS-FXI$_{Rx}$; and
- The initial supply of API.

We determined that each of these three units of accounting have stand-alone value. The exclusive license we granted to Bayer has stand-alone value because it is an exclusive license that gives Bayer the right to develop IONIS-FXI$_{Rx}$ or to sublicense its rights. The development services and the initial supply of API each have stand-alone value because Bayer or another third party could provide these items without our assistance.

Measurement and allocation of arrangement consideration

Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees and royalties on product sales. We initially allocate the amount of consideration that is fixed and determinable at the time the agreement is entered into and exclude contingent consideration. We allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

We determined that the allocable arrangement consideration for the Bayer collaboration was $100 million and we allocated it based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the license granted for IONIS-FXI$_{Rx}$ by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for IONIS-FXI$_{Rx}$. We then discounted the projected income to present value. The significant inputs we used to determine the projected income of the license included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the ongoing development services by using our internal estimates of the cost to perform the specific services and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the development services. The significant inputs we used to determine the selling price of the ongoing development services included:

- The number of internal hours we will spend performing these services;
- The estimated cost of work we will perform;
- The estimated cost of work that we will contract with third parties to perform; and
- The estimated cost of drug product we will use.

We determine the selling price of our API consistently for all of our partnerships. On an annual basis, we calculate our fully absorbed cost to manufacture API. We then determine the unit price we will charge our partners by dividing our fully absorbed costs by the quantity of API we expect to produce during the year.

For purposes of determining BESP of the services we will perform and the API in our Bayer transaction, accounting guidance required us to include a markup for a reasonable profit margin.

Based on the units of accounting under the agreement, we allocated the $100 million upfront payment from Bayer as follows:

- $91.2 million to the IONIS-FXI$_{Rx}$ exclusive license;
- $4.3 million for ongoing development services; and
- $4.5 million for the delivery of API.

Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the IONIS-FXI$_{Rx}$ license, we determined that the revenue we would have allocated to the IONIS-FXI$_{Rx}$ license would change by approximately one percent, or $0.9 million, from the amount we recorded.

Timing of revenue recognition

We recognize revenue as we deliver each item under the arrangement and the related revenue is realizable and earned. For example, we recognized revenue for the exclusive license we granted Bayer for IONIS-FXI$_{Rx}$ in the second quarter of 2015 because that was when we delivered the license. We also recognize revenue over time. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We must estimate our period of performance when the agreements we enter into do not clearly define such information. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition. We then recognize revenue ratably over such period. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations change as the development plans for our drugs progress. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of our collaboration agreements, it may affect the timing and amount of revenue that we recognize in future periods.

The following are the periods over which we are recognizing revenue for each of our units of accounting under our Bayer agreement:

- We recognized the portion of the consideration attributed to the IONIS-FXI$_{Rx}$ license immediately because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the ongoing development services for IONIS-FXI$_{Rx}$ over the period of time we are performing the services; and
- We will recognize the amount attributed to the API supply when we deliver it to Bayer.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, since early 2012, we have entered into four collaboration agreements with Biogen:

- In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize nusinersen for spinal muscular atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of nusinersen through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen to develop and commercialize a novel antisense drug targeting DMPK, or dystrophia myotonica-protein kinase. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of a Phase 2 clinical trial.

- In December 2012, we entered into a third and separate collaboration agreement with Biogen to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets.

- In September 2013, we entered into a fourth and separate collaboration agreement with Biogen to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen exclusive rights to the use of our antisense technology to develop therapies for neurological diseases as part of this broad collaboration. We received a $100 million upfront payment and we are responsible for discovery and early development through the completion of a Phase 2 clinical trial for each antisense drug identified during the six-year term of this collaboration, while Biogen is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen the option to license one or more drugs resulting from the specific collaboration. If Biogen exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the research and/or development of the drugs prior to licensing, milestone payments if Biogen achieves pre-specified regulatory milestones, and royalties on any product sales from any drugs resulting from these collaborations.

We evaluated all four of the Biogen agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent deliverables, there are no provisions in any of these agreements that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. For all four of these agreements, we determined that the options did not have stand-alone value because Biogen cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective estimated period of our performance.

Milestone payments

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and/ or commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraph.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

During the first step of the development stage, we or our partners study our drugs in Investigational New Drug, or IND, -enabling studies, which are animal studies intended to support an IND application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate.

The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing authorization from the FDA and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing authorization. This stage of the drug's life-cycle is the regulatory stage.

If a drug achieves marketing authorization, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the partnered drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow us or our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to marketing authorization and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing authorization such as a New Drug Application, or NDA, in the United States or a Marketing Authorization Application, or MAA, in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Marketing authorization in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain authorization from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment immediately. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. We also consider milestones associated with our alliance with Alnylam Pharmaceuticals, Inc. substantive because we provide Alnylam ongoing access to our technology to develop and commercialize RNA interference, or RNAi, therapeutics. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or in part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements*.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable. For example, during 2014, we recognized $9.5 million in revenue from Alnylam related to its license of our technology to one of its partners because we had no performance obligations and collectability was reasonably assured.

Research, development and patent expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs and other expenses that are directly related to our research and development operations. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our consolidated balance sheet and we expense them as the services are provided. For the years ended December 31, 2015, 2014 and 2013, research and development expenses were $319.5 million, $238.9 million and $173.7 million, respectively. A portion of the costs included in research and development expenses are costs associated with our collaboration agreements. For the years ended December 31, 2015, 2014 and 2013, research and development costs of approximately $161.7 million, $85.6 million and $51.0 million, respectively, were related to our collaborative agreements.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. The weighted average remaining amortizable life of our issued patents was 10.2 years at December 31, 2015.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2015 and 2014 was $27.5 million and $25.0 million, respectively. Accumulated amortization related to patents was $8.2 million and $7.8 million at December 31, 2015 and 2014, respectively.

Based on existing patents, estimated amortization expense related to patents in each of the next five years is as follows:

Years Ending December 31,	Amortization (in millions)
2016	$ 1.4
2017	$ 1.3
2018	$ 1.2
2019	$ 1.1
2020	$ 1.0

We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. When we identify patents and patent applications that we are not actively pursuing, we write off any associated costs. In 2015, 2014 and 2013, patent expenses were $2.8 million, $2.9 million and $10.3 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $1.1 million, $1.3 million and $6.4 million, respectively.

Concentration of credit risk

Financial instruments that potentially subject us to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. We place our cash equivalents and short-term investments with reputable financial institutions. We primarily invest our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or S&P, or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

Cash, cash equivalents and short-term investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term investments as "available-for-sale" and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We have equity investments in privately and publicly held biotechnology companies that we have received as part of a technology license or collaboration agreement. At December 31, 2015, we held ownership interests of less than 20 percent in each of the respective companies.

We account for our equity investments in publicly held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock of these publicly held companies as a separate component of comprehensive income (loss). We account for equity investments in privately held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. We hold one cost method investment in Atlantic Pharmaceuticals Limited. Realization of our equity position in this company is uncertain. When realization of our investment is uncertain, we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs. We did not record any inventory write-offs for the years ended December 31, 2015, 2014 or 2013. Total inventory was $6.9 million and $6.3 million as of December 31, 2015 and 2014, respectively.

Property, plant and equipment

We carry our property, plant and equipment at cost and depreciate it on the straight-line method over its estimated useful life, which consists of the following (in thousands):

	Estimated Useful Lives (in years)	December 31, 2015	December 31, 2014
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 56,822	$ 49,772
Building and building systems	25 to 40	48,163	48,521
Land improvements	20	2,853	2,853
Leasehold improvements	5 to 20	39,061	37,935
Furniture and fixtures	5 to 10	5,842	5,732
		152,741	144,813
Less accumulated depreciation		(72,706)	(66,053)
		80,035	78,760
Land		10,198	10,198
Total		$ 90,233	$ 88,958

We depreciate our leasehold improvements using the shorter of the estimated useful life or remaining lease term.

Fair value of financial instruments

We have estimated the fair value of our financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. We report our investment securities at their estimated fair value based on quoted market prices for identical or similar instruments.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and exclusive licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets. We recorded charges of $1.9 million, $1.3 million and $6.4 million for the years ended December 31, 2015, 2014 and 2013, respectively, related primarily to the write-down of intangible assets.

Use of estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Stock-based compensation expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our ESPP based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our Consolidated Statements of Operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We use the Black-Scholes model as our method of valuing option awards and stock purchase rights under our ESPP. On the grant date, we use our stock price and assumptions regarding a number of highly complex and subjective variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because our employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of our employee stock options. Although we determine the estimated fair value of employee stock options using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

We recognize compensation expense for option awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted vest annually over a four-year period.

See Note 4, *Stockholders' Equity,* for additional information regarding our share-based compensation plans.

Accumulated other comprehensive income (loss)

Accumulated other comprehensive income (loss) is comprised of unrealized gains and losses on investments, net of taxes, and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive income to our Consolidated Statement of Operations. The following table summarizes changes in accumulated other comprehensive income for the years ended December 31, 2015, 2014 and 2013 (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Beginning balance accumulated other comprehensive income	$ 39,747	$ 21,080	$ 12,480
Unrealized (losses) gains on securities, net of tax (1)	(33,101)	40,079	10,253
Amounts reclassified from accumulated other comprehensive (loss) income (2)	(20,211)	(21,412)	(1,653)
Net other comprehensive (loss) income for the period	(53,312)	18,667	8,600
Ending balance accumulated other comprehensive (loss) income	$ (13,565)	$ 39,747	$ 21,080

(1) Other comprehensive income includes income tax expense of $12.8 million and $5.9 million for the years ended December 31, 2014 and 2013, respectively. There was no tax expense for other comprehensive income for the year ended December 31, 2015.

(2) Amounts for 2015 are included in the separate line called "Gain on investment in Regulus Therapeutics Inc." on our Consolidated Statement of Operations. For 2014, $19.9 million is included in a separate line called "Gain on investment in Regulus Therapeutics Inc.", with the remaining amount included in a separate line called "Gain on investments, net" on our Consolidated Statement of Operations. Amounts for 2013 are included in a separate line called "Gain on investments, net" on our Consolidated Statement of Operations.

Convertible debt

We account for convertible debt instruments, including our 1 percent and 2¾ percent notes, that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component, and the associated non-cash interest expense.

We assign a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing the debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method. For additional information, see Note 3, *Long-Term Obligations and Commitments*.

Segment information

In 2015, we began operating as two segments, our Ionis Core segment, previously referred to as Drug Discovery and Development, and Akcea Therapeutics, which consists of the operations of our wholly owned subsidiary, Akcea Therapeutics, Inc. We formed Akcea to develop and commercialize drugs for cardiometabolic disorders. We provide segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments.

Fair value measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. Our Level 3 investments include our investments in the equity securities of publicly held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. Historically, we have determined the lack of marketability discount by using a Black-Scholes model to value a hypothetical put option to approximate the cost of hedging the stock until the restriction ends. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During 2015 and 2014, there were no transfers between our Level 1 and Level 2 investments. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

We measure the following major security types at fair value on a recurring basis. The following summary breaks down the fair-value hierarchy that we valued each security with at December 31, 2015 and 2014 (in thousands):

	At December 31, 2015	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 88,902	$ 88,902	$ —	$ —
Corporate debt securities (2)	438,426	—	438,426	—
Debt securities issued by U.S. government agencies (2)	89,253	—	89,253	—
Debt securities issued by the U.S. Treasury (2)	2,601	2,601	—	—
Debt securities issued by states of the United States and political subdivisions of the states (3)	127,656	—	127,656	—
Investment in Regulus Therapeutics Inc.	24,792	24,792	—	—
Total	$ 771,630	$ 116,295	$ 655,335	$ —

	At December 31, 2014	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 104,680	$ 104,680	$ —	$ —
Corporate debt securities (4)	372,002	—	372,002	—
Debt securities issued by U.S. government agencies (2)	109,855	—	109,855	—
Debt securities issued by the U.S. Treasury (5)	19,017	19,017	—	—
Debt securities issued by states of the United States and political subdivisions of the states (6)	105,033	—	105,033	—
Investment in Regulus Therapeutics Inc.	81,881	—	—	81,881
Total	$ 792,468	$ 123,697	$ 586,890	$ 81,881

(1) Included in cash and cash equivalents on our consolidated balance sheet.

(2) Included in short-term investments on our consolidated balance sheet.

(3) $7.5 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(4) $0.8 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(5) $10 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(6) $9.3 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

In the first quarter of 2014, Achaogen completed an initial public offering. As a result, we stopped using the cost method of accounting for our equity investment in Achaogen and instead we began accounting for it at fair value. Until September 2014, the fair value of our investment in Achaogen included a lack of marketability discount because there were restrictions on when we could trade the securities. As such, we classified our Achaogen stock as a Level 3 investment. In September 2014, we reclassified our investment in Achaogen to a Level 1 investment because the contractual trading restrictions on the shares we owned ended and we subsequently sold all of our shares in 2014.

In November 2014, Regulus completed a public offering. As part of the offering, we sold shares of Regulus' common stock and became subject to trading restrictions on our remaining shares through January 2015. Therefore, at December 31, 2014, we recorded a lack of marketability discount on our investment in Regulus and classified it as a Level 3 investment. At the end of January 2015, we reclassified our investment in Regulus to a Level 1 investment because the contractual trading restrictions on the shares we owned ended.

The following is a summary of our investments measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the years ended December 31, 2015 and 2014 (in thousands):

	Year Ended December 31,	
	2015	2014
Beginning balance of Level 3 investments	$ 81,881	$ —
Transfers into Level 3 investments	—	108,009
Total gains (losses) included in accumulated other comprehensive income (loss)	22,377	(24,897)
Transfers out of Level 3 investments	(104,258)	(1,231)
Ending balance of Level 3 investments	$ —	$ 81,881

Impact of recently issued accounting standards

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects in exchange for the goods or services. This guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance as originally issued is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016.
In July 2015, the FASB issued updated accounting guidance to allow for an optional one year deferral from the original effective date. As a result, we will adopt this guidance beginning on January 1, 2018. The guidance allows us to select one of two methods of adoption, either the full retrospective approach, meaning the guidance would be applied to all periods presented, or modified retrospective, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to our opening retained earnings balance. We are currently determining the adoption method and timing as well as the effects the adoption will have on our consolidated financial statements and disclosures.

In August 2014, the FASB issued accounting guidance on how and when to disclose going-concern uncertainties in the financial statements. This guidance will require us to perform interim and annual assessments to determine our ability to continue as a going concern within one year from the date that we issue our financial statements. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. We will adopt this guidance in our fiscal year beginning January 1, 2017. We do not expect this guidance to have any effect on our consolidated financial statements.

In February 2015, the FASB issued accounting guidance which amends existing consolidation guidance for entities that are required to evaluate whether they should consolidate certain legal entities. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have any effect on our consolidated financial statements.

In April 2015, the FASB issued accounting guidance to simplify the presentation of debt issuance costs. The amended guidance requires us to present debt issuance costs as a direct deduction from the carrying amount of the related debt liability rather than as an asset. The guidance does not require us to change how we recognize and measure our debt issuance costs. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015, with early adoption permitted. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have a material impact on our consolidated financial statements.

In April 2015, the FASB issued accounting guidance to clarify the accounting for fees paid in cloud computing arrangements. The amendment provides guidance to customers about whether a cloud computing arrangement includes a software license element consistent with the acquisition of other software licenses or if the arrangement excludes a software license and should be accounted for as a service contract. The guidance does not change the accounting for service contracts. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We will adopt this guidance in our fiscal year beginning January 1, 2016 on a prospective basis. We do not expect this guidance to have a material impact on our consolidated financial statements.

In July 2015, the FASB issued accounting guidance to simplify the remeasurement of inventory. The amended guidance applies to entities that value inventory under methods other than last-in first-out (LIFO) or the retail inventory method and applies to us because we value our inventory under the FIFO method. The amended guidance requires us to measure our inventory at the lower of cost and net realizable value. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015 on a prospective basis. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have any effect on our consolidated financial statements.

In November 2015, the FASB issued accounting guidance to simplify the classification of deferred income tax assets and liabilities to always be classified as current, compared to the previous treatment, which required us to allocate our deferred tax assets between current and noncurrent. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016 on a prospective or retrospective basis, with early adoption permitted. We adopted this guidance on a prospective basis and reflected it in our consolidated balance sheet at December 31, 2015.

In January 2016, the FASB issued amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires us to measure and record equity investments, except those accounted for under the equity method of accounting that have a readily determinable fair value, at fair value and for us to recognize the changes in fair value in our net income (loss), instead of recognizing changes in value through accumulated other comprehensive income, as we currently do under the existing guidance. The amended guidance also changes several disclosure requirements for financial instruments, including the methods and significant assumptions we use to estimate fair value. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2017. We will adopt this guidance on January 1, 2018 and we will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. We are currently determining the effects the adoption will have on our consolidated financial statements and disclosures.

2. Investments

As of December 31, 2015, we have primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, S&P or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2015:

One year or less	49 %
After one year but within two years	27 %
After two years but within three and a half years	24 %
Total	100 %

As illustrated above, at December 31, 2015, 76 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

At December 31, 2015, we had an ownership interest of less than 20 percentin one private company and two public companies with which we conduct business. The privately held company is Atlantic Pharmaceuticals Limited and the publicly traded companies are Antisense Therapeutics Limited and Regulus. We account for equity investments in the privately held company under the cost method of accounting and we account for equity investments in the publicly traded companies at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments.

During 2015, 2014 and 2013, we realized a net gain on investments we sold of $20.3 million, $21.2 million, and $2.4 million, respectively. Our net gain for 2015 and 2014 was primarily from the $20.2 million and $19.9 million gain we realized when we sold a portion of our stock in Regulus, respectively. We have reflected this gain in a separate line called “Gain on investment in Regulus Therapeutics Inc.”, on our Consolidated Statements of Operations. Our net gain on investments for 2013 related to the sale of stock in several of our satellite companies. As of December 31, 2015, we owned approximately five percent of Regulus’ equity, with a carrying balance of $24.8 million on our consolidated balance sheet.

The following is a summary of our investments (in thousands):

		Gross Unrealized		
December 31, 2015	**Cost**	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities (1):				
Corporate debt securities	$ 181,670	$ 5	$ (250)	$ 181,425
Debt securities issued by U.S. government agencies	50,559	1	(19)	50,541
Debt securities issued by the U.S. Treasury	2,604	—	(3)	2,601
Debt securities issued by states of the United States and political subdivisions of the states (2)	79,414	18	(88)	79,344
Total securities with a maturity of one year or less	314,247	24	(360)	313,911
Corporate debt securities	258,703	3	(1,705)	257,001
Debt securities issued by U.S. government agencies	38,956	—	(244)	38,712
Debt securities issued by states of the United States and political subdivisions of the states	48,552	3	(243)	48,312
Total securities with a maturity of more than one year	346,211	6	(2,192)	344,025
Total available-for-sale securities	$ 660,458	$ 30	$ (2,552)	$ 657,936
Equity securities:				
Regulus Therapeutics Inc.	$ 7,162	$ 17,630	$ —	$ 24,792
Total equity securities	$ 7,162	$ 17,630	$ —	$ 24,792
Total available-for-sale and equity securities	$ 667,620	$ 17,660	$ (2,552)	$ 682,728

		Gross Unrealized		
December 31, 2014	**Cost**	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities (1):				
Corporate debt securities (2)	$ 219,856	$ 89	$ (89)	$ 219,856
Debt securities issued by U.S. government agencies	47,496	7	(27)	47,476
Debt securities issued by the U.S. Treasury (2)	19,008	9	—	19,017
Debt securities issued by states of the United States and political subdivisions of the states (2)	45,196	19	(53)	45,162
Total securities with a maturity of one year or less	331,556	124	(169)	331,511
Corporate debt securities	152,730	16	(600)	152,146
Debt securities issued by U.S. government agencies	62,530	—	(151)	62,379
Debt securities issued by states of the United States and political subdivisions of the states	60,073	32	(234)	59,871
Total securities with a maturity of more than one year	275,333	48	(985)	274,396
Total available-for-sale securities	$ 606,889	$ 172	$ (1,154)	$ 605,907
Equity securities:				
Regulus Therapeutics Inc.	$ 12,477	$ 69,404	$ —	$ 81,881
Total equity securities	$ 12,477	$ 69,404	$ —	$ 81,881
Total available-for-sale and equity securities	$ 619,366	$ 69,576	$ (1,154)	$ 687,788

(1) Our available-for-sale securities are held at amortized cost.

(2) Includes investments classified as cash equivalents on our consolidated balance sheet.

Investments we consider to be temporarily impaired at December 31, 2015 are as follows (in thousands):

		Less than 12 months of Temporary Impairment		More than 12 months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	397	$ 406,098	$ (1,908)	$ 16,066	$ (47)	$ 422,164	$ (1,955)
Debt securities issued by U.S. government agencies	19	71,842	(262)	1,001	(1)	72,843	(263)
Debt securities issued by the U.S. Treasury	2	2,601	(3)	—	—	2,601	(3)
Debt securities issued by states of the United States and political subdivisions of the states	230	59,882	(173)	29,634	(158)	89,516	(331)
Total temporarily impaired securities	648	$ 540,423	$ (2,346)	$ 46,701	$ (206)	$ 587,124	$ (2,552)

We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold these securities to maturity. Therefore, we anticipate full recovery of their amortized cost basis at maturity.

3. Long-Term Obligations and Commitments

The carrying value of our long-term obligations was as follows (in thousands):

	December 31,	
	2015	2014
1 percent convertible senior notes	$ 347,214	$ 327,486
2¾ percent convertible senior notes	50,361	48,014
Long-term financing liability for leased facility	72,217	71,731
Equipment financing arrangement	515	3,226
Leases and other obligations	2,341	7,325
Total	$ 472,648	$ 457,782
Less: current portion	(515)	(2,882)
Total Long-Term Obligations	$ 472,133	$ 454,900

Convertible Notes

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We raised $487 million of proceeds, net of issuance costs. We used a substantial portion of the net proceeds from the issuance of the 1 percent convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes at a price of $441.9 million, including accrued interest. As a result, the new principal balance of the 2¾ percent notes is $61.2 million. We recognized an $8.3 million non-cash loss as a result of the early retirement of a portion of the 2¾ percent notes.

At December 31, 2015 we had the following convertible debt outstanding (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes	2¾ Percent Convertible Senior Notes
Outstanding balance	$ 500	$ 61
Issue date	November 2014	August 2012
Maturity date	November 2021	October 2019
Interest rate	1 percent	2¾ percent
Conversion price per share	$ 66.81	$ 16.63
Total shares of common stock subject to conversion	7.5	3.7

Interest is payable semi-annually in arrears on May 15 and November 15 of each year for the 1 percent notes and on April 1 and October 1 for the 2 ¾ percent notes.

The 1 percent notes are convertible at the option of the note holders prior to July 1, 2021 only under certain conditions. On or after July 1, 2021, the notes are initially convertible into approximately 7.5 million shares of common stock at a conversion price of approximately $66.81 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. If we undergo a fundamental change, holders may require us to purchase for cash all or any portion of their 1 percent notes at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest to, but excluding, the fundamental change purchase date.

The 2¾ percent notes are convertible at the option of the note holders prior to July 1, 2019 only under certain conditions. On or after July 1, 2019, the notes are convertible into approximately 3.7 million shares of common stock at a conversion price of approximately $16.63 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We can redeem the 2¾ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion price for the 2¾ percent notes on each such day. The redemption price for the 2¾ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus $90 per each $1,000 principal amount being redeemed. Holders of the 2¾ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing these notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

For the 2¾ percent notes, the price of our common stock exceeded the conversion threshold price during the quarter ended December 31, 2015. As a result, the 2¾ percent notes are convertible at the option of the holders during the quarter ending March 31, 2016. As of December 31, 2015, the if-converted value of the 2¾ percent notes, which assumes that the notes will be converted into shares of our common stock, exceeded the principal amount by $166.9 million. We did not include the potential effect of the conversion of our convertible notes into our common stock in the computation of diluted net loss per share because the effect would have been anti-dilutive.

We account for our convertible notes using an accounting standard that requires us to assign a value to our convertible debt equal to the estimated fair value of similar debt instruments without the conversion feature and to record the remaining portion in equity. As a result, we recorded our convertible notes at a discount, which we are amortizing as additional non-cash interest expense over the expected life of the respective debt. We determined our nonconvertible debt borrowing rate using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model. The following table summarizes the nonconvertible borrowing rate, effective interest rate and amortization period of our debt discount for our convertible notes:

	1 Percent Convertible Senior Notes	2¾ Percent Convertible Senior Notes
Nonconvertible debt borrowing rate	7.4 percent	8.0 percent
Effective interest rate	7.8 percent	8.8 percent
Amortization period of debt discount	7 years	7 years

Interest expense for the year ended December 31, 2015, 2014 and 2013 included $23.2 million, $9.6 million and $6.8 million, respectively, of non-cash interest expense related to the amortization of the debt discount and debt issuance costs for our convertible notes.

The following table summarizes information about the equity and liability components of our outstanding convertible notes, (in thousands). We measured the fair values of the convertible notes outstanding based on quoted market prices, which is a Level 2 measurement:

	December 31,	
	2015	2014
2¾ Percent Convertible Senior Notes		
Fair value of outstanding notes	$ 215,320	$ 223,900
Principal amount of convertible notes outstanding	$ 61,247	$ 61,247
Unamortized portion of debt discount	$ 10,886	$ 13,233
Long-term debt	$ 50,361	$ 48,014
Carrying value of equity component	$ 18,714	$ 18,714
1 Percent Convertible Senior Notes		
Fair value of outstanding notes	$ 555,000	$ 568,000
Principal amount of convertible notes outstanding	$ 500,000	$ 500,000
Unamortized portion of debt discount	$ 152,786	$ 172,514
Long-term debt	$ 347,214	$ 327,486
Carrying value of equity component	$ 174,770	$ 174,770

Financing Arrangements

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, we can borrow up to a maximum of $30 million of revolving credit for general working capital purposes. Under the credit agreement interest is payable monthly in arrears on the outstanding principal at a rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, we will pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility beginning after June 1, 2016. As of December 31, 2015 we had $8.5 million in outstanding borrowings under the credit facility, which were used to fund our capital equipment needs and is consistent with our historical practice to finance these costs. As of December 31, 2015, our outstanding borrowings under this credit facility were at a weighted average interest rate of 1.67 percent.

The credit agreement includes customary affirmative and negative covenants and restrictions. We are in compliance with all covenants of the credit agreement.

In October 2008, we entered into an equipment financing loan agreement. As of December 31, 2015, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.39 percent. The carrying balance under this loan agreement at December 31, 2015 and 2014 was $0.5 million and $3.2 million, respectively. Our remaining outstanding balance is due in June 2016 and interest is payable monthly.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2015 are as follows (in thousands):

2016	$ 15,767
2017	6,744
2018	6,744
2019	6,744
2020	66,304
Thereafter	505,960
Subtotal	$ 608,263
Less: current portion	(9,029)
Less: fixed and determinable interest	(37,655)
Less: unamortized portion of debt discount	(163,672)
Plus: Deferred rent	2,006
Total	$ 399,913

Operating Leases

We lease office, laboratory and manufacturing space under non-cancelable operating leases with terms through December 2031. We are located in three buildings in Carlsbad, California, which consists of laboratory, manufacturing and office space. Our facilities include a primary research and development facility, a manufacturing facility and a building adjacent to our manufacturing facility. We account for the lease of our primary research and development facility as a financing obligation as discussed below. Our manufacturing facility is used for our drug development business and was built to meet current Good Manufacturing Practices and the facility adjacent to our manufacturing facility has laboratory and office space that we use to support our manufacturing activities. The lease for our manufacturing facility expires in 2031 and has four five-year options to extend. Under the lease agreement, we have the option to purchase the facility at the end of each year from 2016 through 2020, and at the end of 2026 and 2031. The lease for the facility adjacent to our manufacturing facility has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods. Additionally, Akcea leases office space in a building in Cambridge, Massachusetts. The lease for Akcea has a three-year term and expires in July 2018. We also lease office equipment under non-cancelable operating leases with terms through June 2017.

Annual future minimum payments under operating leases as of December 31, 2015 are as follows (in thousands):

	Operating Leases
2016	$ 1,879
2017	1,878
2018	1,597
2019	1,474
2020	1,527
Thereafter	16,125
Total minimum payments	$ 24,480

Rent expense for the year ended December 31, 2015 was $2.0 million and was $1.8 million each of the years ended December 31, 2014 and 2013. We recognize rent expense on a straight line basis over the lease term for the lease on our manufacturing facility, the lease on our building adjacent to our manufacturing facility and Akcea's office space, which resulted in a deferred rent balance of $2.0 million and $1.8 million at December 31, 2015 and 2014, respectively.

Research and Development Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P., or BioMed. Under the lease, BioMed constructed our primary research and development facility in Carlsbad, California. The lease expires in 2031 and has four five-year options to extend. Under the lease agreement, we have the option to purchase the facility and land at the end of each year from 2016 through 2020, and at the end of 2026 and 2031. To gain early access to the facility, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, we recorded the costs for the facility as a fixed asset and we also recorded a corresponding liability in our non-current liabilities as a long-term financing obligation. In July 2011, we took possession of the facility and began depreciating the cost of the facility over its economic useful life. At December 31, 2015 and 2014, the facility and associated parcel of land had a net book value of $62.2 million and $64.4 million, respectively, which included $9.9 million and $7.7 million, respectively, of accumulated depreciation. We are applying our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In conjunction with the lease agreement with BioMed, we purchased a parcel of land for $10.1 million and subsequently sold it to BioMed. Since we have the option to purchase the facility, including the land, we have continuing involvement in the land, which requires us to account for the purchase and sale of the land as a financing transaction. As such, our property, plant and equipment at December 31, 2015 and 2014 included the value of the land. Additionally, we have recorded a corresponding amount in our non-current liabilities as a long-term financing obligation. Since land is not a depreciable asset, the value of the land and financing obligation we recorded will not change until we exercise our purchase option or the lease terminates.

Annual future rent payments as of December 31, 2015 for our primary research and development facility are as follows (in thousands):

	Future Rent Payments
2016	$ 6,550
2017	6,550
2018	6,943
2019	6,943
2020	7,359
Thereafter	91,205
Total minimum payments	$ 125,550

4. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2015, there were no shares of Preferred Stock outstanding. We have designated Series C Junior Participating Preferred Stock but have no issued or outstanding shares as of December 31, 2015.

Common Stock

At December 31, 2015 and 2014, we had 300,000,000 shares of common stock authorized, of which 120,351,480 and 118,442,726 were issued and outstanding, respectively. As of December 31, 2015, total common shares reserved for future issuance were 18,512,177.

During the years ending December 31, 2015, 2014 and 2013, we issued 1,908,000, 1,972,000 and 5,372,000 shares of common stock, respectively, for stock option exercises, vesting of restricted stock units, and ESPP purchases. We received net proceeds from these transactions of $24.9 million, $23.1 million and $63.0 million in 2015, 2014 and 2013, respectively.

Stock Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20,000,000 shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. At December 31, 2015, a total of 3,619,716 options were outstanding, of which options to purchase 2,927,597 shares were exercisable, and 13,462 shares were available for future grant under the 1989 Plan.

2000 Broad Based Equity Incentive Plan

In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the 2000 Plan), which, as amended, provided for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis thereafter. At December 31, 2015, a total of 44,025 options were outstanding and exercisable, and no shares were available for future grant under the 2000 Plan. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

With respect to both the 1989 Plan and 2000 Plan, in the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise,

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan and the 1989 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan and the 1989 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan and the 1989 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

2011 Equity Incentive Plan

In March 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards to our employees, directors, and consultants. In June 2015, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan to increase the total number of shares reserved for issuance. We increased the shares available under our 2011 Equity Incentive Plan from 5,500,000 to 11,000,000. The plan expires in June 2021. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock unit awards to our employees, directors and consultants. Under the 2011 Plan, stock options cannot vest in a period of less than two years and restricted stock unit awards cannot vest in a period of less than three years. We have granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four-year period. At December 31, 2015, a total of 3,832,225 options were outstanding, of which 659,254 were exercisable, 712,034 restricted stock unit awards were outstanding, and 5,989,752 shares were available for future grant under the 2011 Plan.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issue to our chief executive officer and chief operating officer will accelerate upon a change of control, as defined in the 2011 Plan.

Corporate Transactions and Change in Control under 2011 Plan

In the event of certain significant corporate transactions, our Board of Directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 Plan:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan (the 2002 Plan). In June 2015, after receiving approval from our stockholders, we amended our 2002 Non-Employee Directors Stock Option Plan to increase the total number of shares reserved for issuance. We increased the shares available under our 2002 Non-Employee Directors Stock Option Plan from 1,200,000 to 2,000,000. Options under this plan expire ten years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2015, a total of 544,812 options were outstanding, of which 309,319 were exercisable, 38,621 restricted stock unit awards were outstanding, and 859,871 shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3,224,596 million shares authorized under the plan as of December 31, 2015. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each six-month purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase. During 2015, employees purchased and we issued to employees 38,372 shares under the ESPP at a weighted average price of $37.43 per share. At December 31, 2015, there were 481,764 shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity for the year ended December 31, 2015 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Exercise Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2014	7,379	$ 19.52		
Granted	2,550	$ 61.02		
Exercised	(1,674)	$ 14.07		
Cancelled/forfeited/expired	(214)	$ 42.43		
Outstanding at December 31, 2015	8,041	$ 33.21	4.57	$ 232,581
Exercisable at December 31, 2015	3,940	$ 16.43	3.32	$ 179,273

The weighted-average estimated fair values of options granted were $27.44, $17.54 and $7.10 for the years ended December 31, 2015, 2014 and 2013, respectively. The total intrinsic value of options exercised during the years ended December 31, 2015, 2014 and 2013 were $84.7 million, $62.8 million and $69.6 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $23.6 million, $22.4 million and $62.0 million for the years ended December 31, 2015, 2014 and 2013, respectively. For the year ended December 31, 2015, the weighted-average fair value of options exercised was $64.69. As of December 31, 2015, total unrecognized compensation cost related to non-vested stock-based compensation plans was $45.7 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.3 years.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2015 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2014	638	$ 30.52
Granted	348	$ 65.69
Vested	(196)	$ 27.40
Cancelled/forfeited	(39)	$ 42.87
Non-vested at December 31, 2015	751	$ 47.47

For the years ended December 31, 2015, 2014 and 2013, the weighted-average grant date fair value of RSUs granted was $65.69, $44.94 and $17.42 per RSU, respectively. As of December 31, 2015, total unrecognized compensation cost related to RSUs was $16.0 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.2 years.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2015, 2014 and 2013 (in thousands), which was allocated as follows and includes $6.5 million of stock-based compensation expense for Akcea employees in 2015:

	Year Ended December 31,		
	2015	2014	2013
Research, development and patents	$ 43,638	$ 25,843	$ 9,673
General and administrative	15,676	5,540	1,745
Total	$ 59,314	$ 31,383	$ 11,418

Determining Fair Value

Valuation. We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, and stock purchase rights under the ESPP at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period. We value RSUs based on the market price of our common stock on the date of grant.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on actual and projected exercise patterns. We recognize compensation expense for stock options granted, RSUs, and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

For the years ended December 31, 2015, 2014 and 2013, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	December 31,		
	2015	**2014**	**2013**
Risk-free interest rate	1.5 %	1.7 %	1.1 %
Dividend yield	0.0 %	0.0 %	0.0 %
Volatility	53.8 %	50.1 %	51.1 %
Expected life	4.5 years	4.7 years	5.1 years

Board of Director Stock Options:

	December 31,		
	2015	**2014**	**2013**
Risk-free interest rate	2.1 %	2.2 %	2.2 %
Dividend yield	0.0 %	0.0 %	0.0 %
Volatility	52.2 %	54.2 %	52.7 %
Expected life	6.9 years	6.9 years	7.2 years

ESPP:

	December 31,		
	2015	**2014**	**2013**
Risk-free interest rate	0.1 %	0.1 %	0.1 %
Dividend yield	0.0 %	0.0 %	0.0 %
Volatility	51.7 %	60.1 %	62.9 %
Expected life	6 months	6 months	6 months

Risk-Free Interest Rate. We base the risk-free interest rate assumption on observed interest rates appropriate for the term of our stock option plans or ESPP.

Dividend Yield. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future.

Volatility. We use an average of the historical stock price volatility of our stock for the Black-Scholes model. We computed the historical stock volatility based on the expected term of the awards.

Expected Life. The expected term of stock options we have granted represents the period of time that we expect them to be outstanding. We estimated the expected term of options we have granted based on actual and projected exercise patterns.

Forfeitures. We reduce stock-based compensation expense for estimated forfeitures. We estimate forfeitures at the time of grant and revise, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience. Our historical forfeiture estimates have not been materially different from our actual forfeitures.

5. Income Taxes

The provisions for income taxes on income from continuing operations were as follows (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Current:			
Federal	$ 379	$ 263	$ —
State	(7)	(4,295)	2
Total current	372	(4,032)	2
Deferred:			
Federal	—	(8,948)	(5,082)
State	—	(2,427)	(834)
Total deferred	—	(11,375)	(5,916)
Income tax expense (benefit)	$ 372	$ (15,407)	$ (5,914)

In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, intraperiod tax allocation rules require us to allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During 2015, we recorded unrealized losses on our investments in available-for-sale securities in other comprehensive income, therefore we did not have to allocate our tax provision to our other categories of earnings. However, during 2014 and 2013, we recorded unrealized gains on our investments in available-for-sale securities and had to allocate our tax provision between continuing operations and other comprehensive income. As a result, for the years ended December 31, 2014 and 2013, we recorded a $12.8 million and $5.9 million tax benefit, respectively, in continuing operations and a $12.8 million and $5.9 million tax expense, respectively, in other comprehensive income.

In December 2014, we reached an agreement with the State of California Franchise Tax Board with regard to California franchise tax we paid for the tax year ended December 31, 2009. As part of the agreement, we received a franchise tax refund of $4.3 million in 2015 and our research credit carry-forward to December 31, 2010 increased by $4.3 million. We recognized an income tax benefit for the refund in the fourth quarter of 2014. The increase in our research credit carry-forward increased our deferred tax assets but did not impact our consolidated balance sheet as we recorded a full valuation allowance on our deferred tax assets.

The reconciliation between our effective tax rate on income from continuing operations and the statutory U.S. tax rate is as follows (in thousands):

	Year Ended December 31,					
	2015		2014		2013	
Pre-tax loss	$ (87,906)		$ (54,391)		$ (66,558)	
Statutory rate	(30,767)	35.0%	(19,035)	35.0%	(23,295)	35.0%
State income tax net of federal benefit	1	0.0%	(3,125)	5.7%	(3,823)	5.7%
Net change in valuation allowance	69,499	(79.1)%	29,547	(54.3)%	28,850	(43.3)%
Loss on debt extinguishment	—	0.0%	2,406	(4.4)%	—	0.0%
Tax credits	(41,284)	47.0%	(23,628)	43.4%	(15,839)	23.8%
California franchise tax refund	—	0.0%	(2,795)	5.1%	—	0.0%
Deferred tax true-up	1,496	(1.7)%	977	(1.8)%	8,023	(12.1)%
Other	1,427	(1.6)%	246	(0.5)%	170	(0.2)%
Effective rate	$ 372	(0.4)%	$ (15,407)	28.2%	$ (5,914)	8.9%

Significant components of our deferred tax assets and liabilities as of December 31, 2015 and 2014 are as follows (in thousands):

	Year Ended December 31,	
	2015	2014
Deferred Tax Assets:		
Net operating loss carryovers	$ 218,493	$ 231,654
R&D credits	153,601	93,594
Deferred revenue	45,110	58,836
Stock-based compensation	31,093	21,553
Other	19,655	15,549
Total deferred tax assets	$ 467,952	$ 421,186
Deferred Tax Liabilities:		
Convertible debt	$ (55,928)	$ (73,733)
Unrealized gain in other comprehensive income	(5,288)	(27,878)
Intangible and capital assets	(2,643)	(3,641)
Net deferred tax asset	$ 404,093	$ 315,934
Valuation allowance	(404,093)	(315,934)
Net deferreds	$ —	$ —

We have net deferred tax assets relating primarily to net operating loss carryforwards, or NOL's, and research and development tax credit carryforwards. Subject to certain limitations, we may use these deferred tax assets to offset taxable income in future periods. Since we have a history of losses and the likelihood of future profitability is not assured, we have provided a full valuation allowance for the deferred tax assets in our balance sheet as of December 31, 2015. If we determine that we are able to realize a portion or all of these deferred tax assets in the future, we will record an adjustment to increase their recorded value and a corresponding adjustment to increase income or additional paid in capital, as appropriate, in that same period.

We recognize excess tax benefits associated with share-based compensation to stockholders' equity only when realized. We follow the with-and-without approach excluding any indirect effects of the excess tax deductions to determine when we should realize excess tax benefits relating to share-based compensation. Under this approach, we do not realize our excess tax benefits related to share-based compensation until after we utilize all other our tax benefits available to us. During the year ended December 31, 2015, we realized $0.4 million of such excess tax benefits, and accordingly, we recorded a corresponding credit to additional paid-in capital. As of December 31, 2015, we had $76.9 million of unrealized excess tax benefits associated with share-based compensation. We will account for the tax benefits as a credit to additional paid-in capital, if and when we realize them, rather than a reduction of the provision for income taxes.

At December 31, 2015, we had federal and California tax net operating loss carryforwards of approximately $734.7 million and $886.5 million, respectively. Our federal tax loss carryforwards will begin to expire in 2023, unless we use them before then. Our California loss carryforwards continue to expire in 2015. At December 31, 2015, we also had federal and California research and development tax credit carryforwards of approximately $146.8 million and $44.7 million, respectively. Our Federal research and development tax credit carryforwards begin to expire in 2018. Our California research and development tax credit carryforwards are available indefinitely. In 2009, we had a substantial amount of taxable income and we used a portion of our Federal NOL carryforwards to reduce our federal income taxes.

We analyze filing positions in all of the federal and state jurisdictions where we file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of the applicable tax authority sustaining our position.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Beginning balance of unrecognized tax benefits	$ 27,365	$ 23,964	$ 10,872
Decrease for prior period tax positions	—	(1,653)	—
Increase for prior period tax positions	215	—	9,821
Increase for current period tax positions	23,677	5,054	3,271
Ending balance of unrecognized tax benefits	$ 51,257	$ 27,365	$ 23,964

At December 31, 2015 we had $33.3 million of tax benefits included in our unrecognized tax benefits that, if we recognized them, would reduce our annual effective tax rate subject to the valuation allowance.

We do not foresee any material changes to our gross unrecognized tax benefits within the next twelve months. We recognize interest and/or penalties related to income tax matters in income tax expense. We did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2015.

Due to the carryforward of unutilized net operating losses and research and development credits, we are subject to taxation in the United States and various state jurisdictions. Our tax years for 1998 and forward are subject to examination by the U.S. tax authorities and our tax years for 2002 and forward are subject to examination by the California tax authorities.

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnerships

AstraZeneca

Cardiometabolic and Renal Diseases Collaboration

In July 2015, we and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases primarily focused on targets in the kidney, and renal diseases. As part of the agreement, we granted AstraZeneca an exclusive license to a preclinical program and the option to license a drug for each target advanced under this research collaboration. Upon acceptance of a drug development candidate, AstraZeneca will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received a $65 million upfront payment. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement and determined that none of the deliverables have stand-alone value because of the early stage of research for this collaboration. Therefore, we concluded there is one unit of accounting and we are amortizing the $65 million upfront payment through August 2021. We are eligible to receive license fees and substantive milestone payments of up to more than $4 billion, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for regulatory milestones. We will earn the next milestone payment of $25 million under this collaboration upon identification of the first drug candidate to move into development. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration agreement.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs for cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize IONIS-STAT3-2.5$_{Rx}$ for the treatment of cancer and an option to license up to three anti-cancer drugs under a separate research program. AstraZeneca is responsible for all global development, regulatory and commercialization activities for IONIS-STAT3-2.5$_{Rx}$. We and AstraZeneca have evaluated IONIS-STAT3-2.5$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma and advanced lymphoma. AstraZeneca is evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with MEDI4736, AstraZeneca's investigational anti-PD-L1 drug, in patients with head and neck cancer. For the research program, we are responsible for identifying a development candidate for each of the three anti-cancer research programs. AstraZeneca has the option to license drugs resulting from each of the three anti-cancer research programs, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities for such drug.

Under the terms of the agreement, we received $31 million in upfront payments. We recorded revenue of $11.5 million upon receipt of these payments and we have amortized $11.9 million into revenue as we have performed development activities under this collaboration. We are recognizing the remaining $7.6 million related to the option to license three drugs under the research program through December 2016. In January 2016, we and AstraZeneca amended the agreement for the research program. Under the amended terms of the agreement, we can earn an additional $5 million in milestone payments for advancing a drug under our research program.

We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive tiered royalties up to the low to mid-teens on sales from any drugs resulting from these programs. If AstraZeneca successfully develops IONIS-STAT3-2.5$_{Rx}$ and the three drugs under the research program, we could receive license fees and substantive milestone payments of nearly $750 million, including up to $226 million for the achievement of development milestones and up to $485 million for the achievement of regulatory milestones. From inception through December 2015, we have received $63.5 million in milestone payments and upfront fees under this oncology collaboration. We will earn the next milestone payment of $15 million if we further advance a cancer drug under our research program with AstraZeneca.

Each of our agreements with AstraZeneca will continue until the expiration of all payment obligations under the applicable agreement. In addition, the agreement, or any program under the applicable agreement, may terminate early under the following situations:

- AstraZeneca may terminate the agreement or any program at any time by providing written notice to us;
- AstraZeneca may terminate the agreement or any program by providing written notice if we undergo a change of control with a third party; and
- Either we or AstraZeneca may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2015, 2014 and 2013 we earned revenue of $6.4 million, $27.7 million and $29.1 million, respectively, from our relationship with AstraZeneca, which represented two percent, 13 percent and 20 percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2015 and 2014 included deferred revenue of $63.3 million and $4.4 million, respectively, related to our relationship with AstraZeneca.

Biogen

We have established four strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological and neuromuscular disorders. These collaborations combine our expertise in creating antisense drugs with Biogen's expertise in developing therapies for neurological disorders. We and Biogen are currently developing six drugs to treat neurological diseases under these collaborations, including nusinersen, IONIS-DMPK-2.5$_{Rx}$, IONIS-SOD1$_{Rx}$, formerly ISIS-BIIB3$_{Rx}$, and three drugs to treat undisclosed neurodegenerative diseases, IONIS-BIIB4$_{Rx}$, IONIS-BIIB5$_{Rx}$, and IONIS-BIIB6$_{Rx}$. In addition to these six drugs, we and Biogen are evaluating numerous additional targets for the development of drugs to treat neurological diseases.

Nusinersen

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize nusinersen for the treatment of SMA. We are currently conducting a Phase 3 study evaluating nusinersen in infants with SMA, which we expect to be fully enrolled in the second quarter of 2016. We are also conducting a Phase 3 study evaluating nusinersen in children with SMA, for which we have completed target enrollment. In addition, we are evaluating nusinersen in two Phase 2 open-label studies, one in children with SMA and one in infants with SMA. Patients from all of these studies continue to have access to nusinersen through open-label extension dosing. We are responsible for completing the studies we are currently conducting. Biogen has the option to license nusinersen. If Biogen exercises its option, it will pay us a license fee and will assume all other global development, regulatory and commercialization responsibilities. Biogen may exercise this option upon completion of and data review of the first successful Phase 2/3 trial or completion of both Phase 2/3 trials. An amendment in December 2014 provided for additional opt-in scenarios, based on the filing or the acceptance of a new drug application or marketing authorization application with the FDA or EMA. In June 2015, we and Biogen amended the development plan for nusinersen to include conducting the open-label extension study for the Phase 3 studies in infants and children. As a result of the change to the development plan, we earned an $11 million milestone payment when we initiated the Phase 3 open-label extension study and we are eligible to earn additional milestone and other payments.

Under the terms of the agreement, we received an upfront payment of $29 million, which we are amortizing through February 2017. We are also eligible to receive a license fee, milestone payments and tiered royalties up to the mid-teens on any sales of nusinersen. Over the term of the collaboration, we are eligible to receive up to $346 million in a license fee and payments, including up to $121 million in substantive milestone and other payments associated with the clinical development of nusinersen prior to licensing and up to $150 million in substantive milestone payments if Biogen achieves pre-specified regulatory milestones. From inception through December 2015, we have received more than $130 million in milestone payments and upfront fees for advancing nusinersen. In 2015, we earned $40 million for advancing the studies we are conducting in infants and children with SMA. In addition we earned a $2 million milestone payment in February 2016 for further advancing the Phase 3 study of nusinersen in infants. We will earn the next milestone payment of $2 million if we further advance the Phase 3 study of nusinersen in infants.

IONIS-DMPK-2.5$_{Rx}$

In June 2012, we and Biogen entered into a second and separate collaboration agreement to develop and commercialize a novel antisense drug, IONIS-DMPK-2.5$_{Rx}$, targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. We are currently evaluating IONIS-DMPK-2.5$_{Rx}$ in a Phase 1/2 clinical study in patients with DM1. Biogen has the option to license the drug through the completion of the first Phase 2 trial. If Biogen exercises its option, it will assume all other global development, regulatory and commercialization responsibilities. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through October 2018. In June 2015, we and Biogen amended the development plan for IONIS-DMPK-2.5$_{Rx}$ under which we are eligible to earn additional milestone payments of up to $4.2 million for further advancing the Phase 1/2 study of IONIS-DMPK-2.5$_{Rx}$. Over the term of the collaboration, we are eligible to receive up to $263 million in a license fee and substantive milestone payments, including up to $63 million in development milestone payments and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on any sales of IONIS-DMPK-2.5$_{Rx}$. From inception through December 2015, we have received nearly $39 million in milestone payments and upfront fees for advancing IONIS-DMPK-2.5$_{Rx}$, including a $2.8 million milestone payment we earned in November 2015. We will earn the next milestone payment of $1.4 million if we further advance the Phase 1/2 study for IONIS-DMPK-2.5$_{Rx}$ and we will earn a $35 million milestone payment if we initiate a Phase 2 study for IONIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen entered into a third and separate collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-BIIB4$_{Rx}$ under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We are eligible to receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials. We are also eligible to receive up to $130 million in milestone payments per program if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any drugs resulting from each of the three programs. In February 2015, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study of IONIS-BIIB4$_{Rx}$, a drug for an undisclosed target designed to treat a neurodegenerative disease. From inception through December 2015, we have received $40 million in milestone payments and upfront fees under this collaboration, not including the $3 million milestone payment we earned in February 2016. We will earn the next milestone payment of up to $10 million for the continued development of IONIS-BIIB4$_{Rx}$.

Strategic Neurology

In September 2013, we and Biogen entered into a fourth and separate collaboration agreement, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs being pursued under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs after Phase 2 proof of concept. We are currently advancing three drugs, IONIS-SOD1$_{Rx}$, IONIS-BIIB5$_{Rx}$, and IONIS-BIIB6$_{Rx}$ under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six-year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six-year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen could potentially require us to refund.

For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered single-digit royalties on sales from any drugs using non-antisense modalities developed under this collaboration. From inception through December 2015, we have received $135 million in milestone payments and upfront fees under this collaboration. In December 2015, we earned a $5 million milestone payment for validating a fifth target under this collaboration. We will earn the next milestone payment of up to $10 million if we choose another target to advance under this collaboration.

Each of our agreements with Biogen will continue until the earlier of the date all of Biogen's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen exercises its option, until the expiration of all payment obligations under the applicable agreement. In addition, each agreement, or any program under an agreement, may terminate early under the following situations:

- Biogen may terminate the agreement or any program at any time by providing written notice to us;
- Under specific circumstances, if we are acquired by a third party with a product that directly competes with a compound being developed under the agreement, Biogen may terminate the affected program by providing written notice to us;
- If, within a specified period of time, any required clearance of a transaction contemplated by an agreement under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, is not received, then either we or Biogen may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2015, 2014 and 2013, we earned revenue of $106.2 million, $123.2 million and $37.0 million, respectively, from our relationship with Biogen, which represented 37 percent, 58 percent and 25 percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2015 and 2014 included deferred revenue of $91.6 million and $118.1 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. We are responsible for completing our ongoing Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis. Bayer is responsible for all other development and commercialization activities for IONIS-FXI$_{Rx}$.

Under the terms of the agreement, we are eligible to receive $155 million in near-term payments, including a $100 million upfront payment we received in the second quarter of 2015 and a $55 million milestone payment that we are eligible to receive upon advancement of the program following the Phase 2 study in patients with end-stage renal disease on hemodialysis. We recorded revenue of $91.2 million related to the license for IONIS-FXI$_{Rx}$ in June 2015 and we are recognizing the remaining $8.8 million related to the ongoing development activities for IONIS-FXI$_{Rx}$ through July 2016.

Over the term of the agreement, we are eligible to receive up to $375 million in license fees, substantive milestone payments and other payments, including up to $120 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low-to-high 20 percent range on gross margins of IONIS-FXI$_{Rx}$. We will earn the next milestone payment of $55 million upon the advancement of the program following the ongoing Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis.

Our agreement with Bayer will continue until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Bayer may terminate the agreement or any program at any time by providing written notice to us;
- Either we or Bayer may terminate the agreement or any program by providing written notice to the other party upon the other party’s uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2015 we earned revenue of $93.4 million, from our relationship with Bayer, which represented 33 percent of our total revenue for the period. Our consolidated balance sheet at December 31, 2015 included deferred revenue of $6.7 million related to our relationship with Bayer.

Genzyme Corporation, a Sanofi company

In January 2008, we entered into an alliance with Genzyme focused on the licensing and co-development of Kynamro. The license and co-development agreement provided Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to Kynamro. The transaction included a $175 million licensing fee and a $150 million equity investment by Genzyme in our stock. From inception through December 2015, we have received $375 million in a license fee, milestone payments and an equity investment for advancing Kynamro in development. In January 2016, we terminated our license agreement with Genzyme.

During 2015 and 2014, we did not earn any revenue from our relationship with Genzyme. During 2013, we earned revenue of $32.5 million from our relationship with Genzyme, which represented 22 percent of our total revenue for that year.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Our alliance currently comprises five drugs in development, including our Phase 3 drug IONIS-TTR$_{Rx}$. GSK has the exclusive option to license drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee. If GSK exercises its exclusive option for any drugs resulting from this alliance, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received $38 million in upfront and expansion payments, which we are amortizing through March 2017.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for IONIS-TTR_{Rx}. We are currently evaluating IONIS-TTR_{Rx} in a broad Phase 3 development program. We have completed target enrollment in the Phase 3 study in patients with FAP. From inception through December 2015, we have earned $60 million from GSK related to the development of IONIS-TTR_{Rx}, primarily in milestone payments. We are also eligible to earn an additional $10 million pre-licensing milestone payment associated with our ongoing study of IONIS-TTR_{Rx}. In addition, under the amended agreement, we and GSK increased the regulatory and commercial milestone payments we can earn should IONIS-TTR_{Rx} receive marketing authorization and meet pre-agreed sales targets. In September 2015, we and GSK amended the development plan for IONIS-TTR_{Rx} to support the Phase 3 cardiomyopathy study, which GSK plans to conduct.

In addition to IONIS-TTR_{Rx}, we have four drugs in development with GSK. We are developing two antisense drugs we designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV, infection; IONIS-HBV_{Rx} and IONIS-HBV-L_{Rx}, a follow-on drug using our LICA technology. We are also developing IONIS-GSK4-L_{Rx} and IONIS-RHO-2.5_{Rx}, which are antisense drugs we designed to treat ocular diseases.

Under our agreement, if GSK successfully develops all five drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.0 billion, including up to $183.5 million for the achievement of development milestones, up to $363.5 million for the achievement of regulatory milestones and up to $348 million for the achievement of commercialization milestones. Through December 2015, we have received $135 million in milestone payments and upfront fees under this alliance with GSK, not including a $1.5 million payment we earned in January 2016 when GSK further advanced IONIS-HBV-L_{Rx}. We will earn the next milestone payment of up to $5 million if we further advance a program under this collaboration. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

Our alliance with GSK will continue until the earlier of the date that all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- GSK may terminate any program, other than the IONIS-TTR_{Rx} program, at any time by providing written notice to us;
- GSK may terminate the IONIS-TTR_{Rx} program by providing written notice to us after reviewing specific data from the Phase 3 study for the program; and
- Either we or GSK may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2015, 2014 and 2013, we earned revenue of $33.3 million, $37.3 million and $35.3 million, respectively, from our relationship with GSK, which represented 12 percent, 17 percent and 24 percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2015 and 2014 included deferred revenue of $4.9 million and $10.0 million, respectively, related to our relationship with GSK.

Janssen Biotech, Inc., a pharmaceutical company of Johnson & Johnson

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the gastrointestinal tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under the terms of the agreement, we received $35 million in upfront payments, which we are amortizing through December 2018. We are eligible to receive nearly $800 million in license fees and substantive milestone payments for these programs, including up to $175 million for the achievement of development milestones, up to $420 million for the achievement of regulatory milestones and up to $180 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the near teens on sales from any drugs resulting from this collaboration. We will earn the next milestone payment of $5 million if Janssen chooses another target to advance under this collaboration.

Our agreement with Janssen will continue until the earlier of the date that all of Janssen's options to obtain the exclusive licenses under the agreement expire unexercised or, if Janssen exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Janssen may terminate the agreement or any program at any time by providing written notice to us; and
- Either we or Janssen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2015 we earned revenue of $8.9 million from our relationship with Janssen. During 2014 and 2013 we did not earn any revenue from our relationship with Janssen. Our balance sheet at December 31, 2015 included deferred revenue of $26.3 million related to our relationship with Janssen.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease, or HD, based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Under the agreement, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We are currently evaluating a drug targeting HTT, IONIS-HTT_{Rx}, in a Phase 1/2 clinical study in patients with early stage HD. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through January 2017. We are eligible to receive up to $362 million in a license fee and substantive milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestone payments if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties up to the mid-teens on any product sales of drugs resulting from this alliance. Through December 2015, we have received $52 million in milestone payments and upfront fees under this alliance with Roche. We will earn the next milestone payment of $10 million if Roche initiates a Phase 2 trial for IONIS-HTT_{Rx}.

Our alliance with Roche will continue until the earlier of the date Roche's option to obtain the exclusive license under the agreement expires unexercised or, if Roche exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement may terminate early under the following situations:

- Roche may terminate the agreement at any time by providing written notice to us;
- Either we or Roche may terminate the agreement by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement or if the other party becomes insolvent; and
- Either we or Roche may terminate the brain shuttle program if at least one development candidate is not designated under such program by a mutually agreed deadline.

During 2015, 2014 and 2013, we earned revenue of $31.2 million, $8.7 million and $5.1 million, respectively from our relationship with Roche, which represented 11 percent, four percent and three percent, respectively, of our total revenue for those years. Our balance sheet at December 31, 2015 and 2014 included deferred revenue of $8.8 million and $17.0 million, respectively related to our relationship with Roche.

Satellite Company Collaborations

Achaogen, Inc.

In 2006, we exclusively licensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In exchange, Achaogen agreed to certain payment obligations related to aminoglycosides Achaogen developed. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. If Achaogen successfully develops and commercializes two drugs under our agreement, we will receive payments totaling up to $49.3 million for the achievement of key clinical, regulatory and sales events. Through December 2015, we have earned $7 million in milestone payments from Achaogen, including a $4 million milestone payment we earned in September 2014 when Achaogen initiated a Phase 3 study of plazomicin in patients with serious multi-drug resistant, gram-negative bacterial infections. We will earn the next milestone payment of $7.5 million if Achaogen obtains regulatory approval for plazomicin in a major market. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

During 2015 and 2013, we did not earn any revenue from our relationship with Achaogen. During 2014 we earned revenue of $4 million from our relationship with Achaogen and we sold all of the Achaogen stock we owned resulting in net proceeds of $1.3 million.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into an alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam’s partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. We will earn the next milestone payment of $0.4 million if Alnylam initiates a Phase 1 study for a drug in Alnylam’s pipeline. We also have the potential to earn royalties on drug sales and a portion of payments that Alnylam receives from licenses of our technology it grants to its partners plus royalties. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, ssRNAi therapeutics, and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam’s technology, we will pay Alnylam up to $3.4 million in milestone payments for specified development and regulatory events, plus royalties. To date, we do not have an RNAi-based drug in development.

In 2015, we and Alnylam entered into an alliance in which we formed an intellectual property cross-license under which we and Alnylam each obtained exclusive license rights to four therapeutic programs. Alnylam granted us an exclusive, royalty-bearing license to its chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four targets. In exchange, we granted Alnylam an exclusive, royalty-bearing license to our chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four targets. Alnylam also granted us a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, we granted Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics. Through December 2015, we have received nearly $70 million from Alnylam.

During 2015, 2014 and 2013, we earned revenue from our relationship with Alnylam totaling $1.3 million, $9.9 million and $1.5 million, respectively.

Antisense Therapeutics Limited

In 2001 we licensed ATL1102 and ATL1103 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL is currently undertaking a chronic toxicology study in primates to support a potential Phase 2b trial of ATL1102 in patients with multiple sclerosis, or MS. In addition, ATL is currently developing ATL1103 for growth and sight disorders. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103. At December 31, 2015 and 2014, we owned less than ten percent of ATL's equity. During 2015, 2014 and 2013, we did not earn any revenue from our relationship with ATL.

Atlantic Pharmaceuticals Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006. Atlantic Pharmaceuticals is developing alicaforsen for the treatment of ulcerative colitis, or UC, and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. Under the agreement, we could receive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. We will earn the next milestone payment of $0.6 million if Atlantic Pharmaceuticals submits an NDA for alicaforsen with the FDA. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international named patient supply regulations for patients with inflammatory bowel disease, or IBD, for which we receive royalties.

In 2010 and 2013, we agreed to sell Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. Additionally, in 2013 we received an advance payment in the form of equity for the initial royalties that we will earn from Atlantic Pharmaceuticals. We recorded a full valuation allowance for all of the equity we received from Atlantic Pharmaceuticals, including the upfront payment, because realization of value from the equity is uncertain. At December 31, 2015 and 2014, we owned approximately 11 percent and 12 percent, respectively, of Atlantic Pharmaceuticals' equity. We earned $0.7 million related to royalties and sales of drug substance in 2013. Because the payments were made in equity, we did not record any revenue. During 2015 and 2014, our revenue was negligible from our relationship with Atlantic Pharmaceuticals.

OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc.

Custirsen

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize custirsen, an anti-cancer antisense drug that targets clusterin. OncoGenex is currently evaluating custirsen in two Phase 3 studies. In July 2008, we and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely responsible for the costs, development and commercialization of custirsen. In exchange, OncoGenex agreed to pay us royalties on sales of custirsen and to share consideration it receives from licensing custirsen to a third party, except for consideration OncoGenex receives for the fair market value of equity and reimbursement of research and development expenses. Under the amended agreement, we assigned to OncoGenex our rights in the patents claiming the composition and therapeutic methods of using custirsen and granted OncoGenex a worldwide, nonexclusive license to our know-how and patents covering our core antisense technology and manufacturing technology solely for use with custirsen. In addition, we agreed that so long as OncoGenex or its commercialization partner is using commercially reasonable efforts to develop and commercialize custirsen, we will not research, develop or commercialize an antisense compound designed to modulate clusterin. The amended agreement will continue until OncoGenex or its commercialization partner is no longer developing or commercializing custirsen or until we terminate the agreement for OncoGenex's uncured failure to make a payment required under the agreement.

OGX-225

In August 2003, we and OncoGenex entered into a second and separate agreement for the development of an antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities. OncoGenex issued to us $0.8 million of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of key development and regulatory milestones, including up to $1.5 million for the achievement of development milestones and up to $2 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of OGX-225. As of December 31, 2015, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $0.5 million if OncoGenex initiates a Phase 2 study for OGX-225.

Apatorsen

In January 2005, we entered into a third and separate agreement with OncoGenex to allow for the development of an additional antisense anti-cancer drug, apatorsen. OncoGenex and collaborators are evaluating apatorsen in multiple Phase 2 studies in patients with cancer. OncoGenex is responsible for all development costs and activities. OncoGenex will pay us milestone payments totaling up to $5.8 million for the achievement of key development and regulatory milestones, including up to $1.3 million for the achievement of development milestones and up to $4.5 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of the drug. We will earn the next milestone payment of $1.3 million if OncoGenex initiates a Phase 3 study for apatorsen.

During 2015, 2014 and 2013, we did not earn any revenue from our relationship with OncoGenex.

Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development. MicroRNAs may also prove to be an attractive new tool for characterizing diseases. Regulus focuses its drug discovery and development efforts in numerous therapeutic areas, including cancer, fibrosis, and viral infections. Regulus currently has three drugs in clinical development. Regulus is evaluating RG-101 in a Phase 2 study in patients with HCV and in a Phase 1 study in patients with severe renal insufficiency or end-stage renal disease. Regulus is also evaluating RG-012 in a Phase 1 study to treat patients with Alport syndrome. Regulus and AstraZeneca are also evaluating RG-125 in a Phase 1 study for the treatment of NASH in patients with type 2 diabetes or pre-diabetes. We are eligible to receive royalties on any future product sales of these drugs.

During 2015, 2014 and 2013, we did not earn any revenue from our relationship with Regulus. During 2015 and 2014, we sold a portion of our Regulus stock, resulting in a gain of $20.2 million and $19.9 million, respectively, and proceeds of $25.5 million and $22.9 million, respectively. As of December 31, 2015, we owned approximately 2.8 million shares, approximately five percent of Regulus' equity, with a net carrying value of $24.8 million.

External Project Funding

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche. We made payments of $5 million and $3 million to CHDI in 2015 and 2013, respectively, associated with the progression of our Huntington's disease program. If we achieve pre-specified milestones under our collaboration with Roche, we will make additional payments to CHDI up to $4 million, upon which our obligation to CHDI will be complete.

During 2015, our revenue earned from our relationship with CHDI was negligible and during 2014, we did not earn any revenue. During 2013, we earned revenue of $0.4 million from our relationship with CHDI.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered into a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs for amyotrophic lateral sclerosis, or ALS, and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration.

Intellectual Property Sale and Licensing Agreements

Sales of Intellectual Property

Abbott Molecular Inc.

In January 2009, we sold our former subsidiary, Ibis Biosciences, to Abbott Molecular Inc., or AMI, pursuant to a stock purchase agreement for a total acquisition price of $215 million plus the earn out payments described below.

Under the stock purchase agreement, we are eligible to receive earn out payments from AMI equal to a percentage of Ibis' revenue related to sales of Ibis systems, which AMI launched in 2014 as IRIDICA, including instruments, assay kits and successor products. Once cumulative net sales reach $140 million, and through December 31, 2025, we are eligible to earn out payments in any year that net sales exceed $50 million for the applicable year. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. During 2015, 2014 and 2013, we did not earn any revenue from our relationship with AMI.

In-Licensing Arrangements

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to nusinersen. If we successfully develop and commercialize a drug incorporating the technology we licensed from the University of Massachusetts, we will pay a milestone payment to the University of Massachusetts of $0.3 million for the achievement of a key regulatory milestone. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive in consideration for sublicensing its technology, and a royalty on sales of nusinersen in the United States if our product incorporates the technology we licensed from the University of Massachusetts.

Verva Pharmaceuticals Ltd.

We have a license agreement with Verva under which we acquired an exclusive license to Verva's antisense patent rights related to IONIS-FGFR4$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology Verva licensed to us, we will pay milestone payments to Verva totaling up to $6.1 million for the achievement of key patent, clinical, and regulatory milestones. If we convert our license from an exclusive license to a nonexclusive license we could significantly reduce the milestone payments due to Verva. In addition, we will also pay royalties to Verva on sales of IONIS-FGFR4$_{Rx}$ if our product incorporates the technology we licensed from Verva.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to nusinersen. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay a portion of any sublicense revenue and post licensing milestone payments we receive in consideration for sublicensing the Cold Spring Harbor Laboratory's technology up to $11.3 million and a royalty on sales of nusinersen if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

7. Segment Information and Concentration of Business Risk

In 2015, we began reporting our financial results in two reportable segments, Ionis Core, previously referred to as Drug Discovery and Development, and Akcea Therapeutics, our wholly owned subsidiary. Segment loss from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment, we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class drugs for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

We formed Akcea to develop and commercialize drugs for cardiometabolic disorders. Moving our lipid drugs into a company that we own and control ensures that our core focus at Ionis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs. To date, Akcea has not earned any revenue.

The following is our segment information for 2015 (in thousands):

2015	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Research and development	$ 285,608	$ —	$ (4,248)	$ 281,360
Licensing and royalty	2,343	—	—	2,343
Total segment revenue	$ 287,951	$ —	$ (4,248)	$ 283,703
Loss from operations	$ (21,378)	$ (54,384)	$ —	$ (75,762)
Total assets	$ 1,004,150	$ 55,354	$ (103,399)	$ 956,105

The following is our segment information for 2014 and 2013 (in thousands) revised for comparative purposes to show operating expense for Akcea-related projects in 2014 and 2013:

2014	Ionis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 202,514	$ —	$ 202,514
Licensing and royalty	11,647	—	11,647
Total segment revenue	$ 214,161	$ —	$ 214,161
Loss from operations	$ (26,033)	$ (21,697)	$ (47,730)

2013	Ionis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 147,380	$ —	$ 144,194
Licensing and royalty	3,091	—	3,091
Total segment revenue	$ 150,471	$ —	$ 147,285
Loss from operations	$ (38,764)	$ (12,902)	$ (51,666)

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10 percent or more of our total revenue, was as follows:

	2015	2014	2013
Partner A	37 %	58 %	25 %
Partner B	33 %	0 %	0 %
Partner C	12 %	17 %	24 %
Partner D	11 %	4 %	3 %
Partner E	2 %	13 %	20 %
Partner F	0 %	0 %	22 %

Contracts receivables at December 31, 2015 and December 31, 2014 were comprised of approximately 99 percent for each year from two and three significant partners, respectively.

8. Employment Benefits

We have an employee 401(k) salary deferral plan, covering all employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($18,000 and $24,000 in 2015 for employees under 50 years old and employees 50 years old or over, respectively). We made approximately $1.5 million, $1.0 million and $0.6 million in matching contributions for the years ended December 31, 2015, 2014 and 2013, respectively.

9. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding, and may revise our estimates. We do not believe, relative to our current legal proceedings, that a loss is both probable and estimable. As such, as of December 31, 2015, we did not have a liability related to any of our current legal proceedings, including the following matters.

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of the Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712 that are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead is asking the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents infringes those patents, and requesting monetary damages to compensate for such infringement. Under our agreement with Merck, Merck is responsible for the costs of this suit. Gilead filed a motion for summary judgment alleging invalidity of the asserted patents. In February 2016, the court denied the motion. In the same order, the court granted our motion for summary judgement for a finding of infringement, but noted that Gilead may still pursue its invalidity defenses at trial. The trial for this case is scheduled to begin March 7, 2016.

10. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2015 and 2014 are as follows (in thousands, except per share data).

2015 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 62,583	$ 120,428	$ 49,121	$ 51,571
Operating expenses	$ 71,913	$ 75,782	$ 97,259	$ 114,511
Income (loss) from operations	$ (9,330)	$ 44,646	$ (48,138)	$ (62,940)
Net income (loss)	$ (16,717)	$ 35,648	$ (35,776)	$ (71,433)
Basic net income (loss) per share (1)	$ (0.14)	$ 0.30	$ (0.30)	$ (0.59)
Diluted net income (loss) per share (1) (2)	$ (0.14)	$ 0.29	$ (0.30)	$ (0.59)

2014 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 28,161	$ 57,076	$ 44,063	$ 84,861
Operating expenses	$ 57,828	$ 63,726	$ 65,556	$ 74,781
Income (loss) from operations	$ (29,667)	$ (6,650)	$ (21,493)	$ 10,080
Net income (loss)	$ (31,280)	$ (12,081)	$ (26,676)	$ 31,053
Basic net income (loss) per share (1)	$ (0.27)	$ (0.10)	$ (0.23)	$ 0.26
Diluted net income (loss) per share (1) (3)	$ (0.27)	$ (0.10)	$ (0.23)	$ 0.25

(1) We computed net income (loss) per share independently for each of the quarters presented. Therefore, the sum of the quarterly net income (loss) per share will not necessarily equal the total for the year.

(2) For the three months ended June 30, 2015, we had net income. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period. Diluted common equivalent shares for the three months ended June 30, 2015 consisted of the following (in thousands):

Three Months Ended June 30, 2015	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 35,648	119,742	$ 0.30
Effect of diluted securities:			
Shares issuable upon exercise of stock options		3,974	
Shares issuable upon restricted stock award issuance		376	
Shares issuable related to our ESPP		4	
Shares issuable related to our 2¾ percent notes	1,047	3,683	
Income available to common shareholders, plus assumed conversions	$ 36,695	127,779	$ 0.29

For the three months ended June 30, 2015, the calculation excludes the 1 percent notes because the effect on diluted earnings per share was anti-dilutive.

(3) For the three months ended December 31, 2014, we had net income. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period. Diluted common equivalent shares for the three months ended December 31, 2014 consisted of the following (in thousands):

Three Months Ended December 31, 2014	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 31,053	118,223	$ 0.26
Effect of diluted securities:			
Shares issuable upon exercise of stock options		4,189	
Shares issuable upon restricted stock award issuance		418	
Shares issuable related to our ESPP		9	
Income available to common shareholders, plus assumed conversions	$ 31,053	122,839	$ 0.25

For the three months ended December 31, 2014, the calculation excludes the 1 percent and 2¾ percent convertible senior notes because the effect on diluted earnings per share was anti-dilutive.

Exhibit 10.64

AMENDMENT NO. 2 TO LINE OF CREDIT AGREEMENT

This Amendment No. 2 to Line of Credit Agreement (the "Amendment"), dated as of February 24, 2016, is made by and between IONIS PHARMACEUTICALS, INC., f/k/a ISIS PHARMACEUTICALS, INC. (the "Borrower"), and MORGAN STANLEY PRIVATE BANK, NATIONAL ASSOCIATION, a national banking association (the "Lender").

RECITALS

A. The Lender and the Borrower entered into that certain Line of Credit Agreement dated as of June 16, 2015 (as amended, restated, supplemented or otherwise modified on or prior to the date hereof, the "Agreement").

B. The Lender and the Borrower desire to amend the Loan Documents as set forth in this Amendment.

AGREEMENT

1. Definitions. Capitalized terms used but not defined in this Amendment shall have the meaning given to them in the Agreement.

2. Amendments to Agreement.

(a) The Line of Credit Commitment section in the Basic Terms of the Agreement is hereby amended and restated as follows:

"A maximum amount of $30,000,000.00, subject to adjustment as set forth under the definition of "Commitment" on Schedule I hereto."

(b) Section 5.03(a) of the Agreement is hereby amended and restated as follows:

"(a) Leverage Ratio. Not permit the ratio of Funded Debt to Tangible Net Worth to exceed 5.00 to 1.00 at any time, measured on a quarterly basis."

(c) Section 5.03(c) of the Agreement is hereby amended and restated as follows:

"(c) Unencumbered Liquid Assets. Maintain at all times in an account at Lender or its Affiliates a minimum of $30,000,000.00 of Unencumbered Liquid Assets."

(d) The defined term "Commitment" in Schedule I of the Agreement is hereby amended and restated as follows:

""Commitment" means the obligation of the Lender to make Advances to the Borrower in an amount up to the lesser of (i) $30,000,000.00 or (ii) an amount equal to the sum of the amounts obtained by multiplying the aggregate Market Value of each type of Collateral in the Securities Account set forth in Column A of Exhibit A hereto times the corresponding percentage specified in Column B of Exhibit A hereto with respect to each such type of Collateral in the Securities Account, all on the terms and conditions set forth in this Agreement."

(e) The defined term "Total Unsubordinated Liabilities" is deleted in its entirety from Schedule I of the Agreement.

(f) The following defined term is added to Schedule I of the Agreement in the appropriate alphabetical order:

""Funded Debt" means all Debt, excluding (a) accounts payable, (b) accrued compensation incurred in the ordinary course of business, (c) accrued trade (or similar) liabilities incurred in the ordinary course of business, (d) other accruals incurred in the ordinary course of business, and (e) deferred revenues."

3. Representations and Warranties. When the Borrower signs this Amendment, the Borrower represents and warrants to the Lender that: (a) no event has occurred and is continuing that constitutes a Default under the Agreement except those events, if any, that have been disclosed in writing to the Lender or waived in writing by the Lender, (b) the representations and warranties in the Agreement are correct in all material respects as of the date of this Amendment as if made on the date of this Amendment, (c) this Amendment does not conflict with any law, agreement, or obligation by which the Borrower is bound, and (d) if the Borrower is a business entity or a trust, this Amendment is within the Borrower's powers, has been duly authorized, and does not conflict with any of the Borrower's organizational papers.

4. Effect of Amendment. Except as provided in this Amendment, all of the terms and conditions of the Agreement shall remain in full force and effect.

5. Electronic Signature; Counterparts. This Amendment may be executed and delivered by electronic signature and in counterparts, each of which when so executed shall be deemed an original, but all such counterparts together shall constitute one and the same instrument.

[Remainder of Page Intentionally Left Blank]

The parties executed this Amendment as of the date stated at the beginning of this Amendment, intending to create an instrument executed under seal.

LENDER:	BORROWER:
MORGAN STANLEY PRIVATE BANK, NATIONAL ASSOCIATION	IONIS PHARMACEUTICALS, INC.
By: */s/ Mark Reardon*	By: */s/ Elizabeth L. Hougen*
Name: Mark Reardon	Name: Elizabeth L. Hougen
Title: Authorized Signatory	Title: SVP, Finance and CFO

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Akcea Therapeutics, Inc., a Delaware Corporation

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements on Form S-3 (Nos. 33-55790, 33-72124, 33-75068, 33-96138 , 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076 and 333-188407) and in the related Prospectuses, as applicable, and in the Registration Statements on Form S-8 (Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780 , 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788, 333-190408 and 333-207900) of Ionis Pharmaceuticals, Inc. of our reports dated February 25, 2016, with respect to the consolidated financial statements of Ionis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Ionis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2015.

/s/ ERNST & YOUNG LLP

San Diego, California
February 25, 2016

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ionis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: February 25, 2016

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ionis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: February 25, 2016

/s/ ELIZABETH L. HOUGEN

Elizabeth L. Hougen
Chief Financial Officer

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Stanley T. Crooke, the Chief Executive Officer of Ionis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the year ended December 31, 2015, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Annual Report and the results of operations of the Company for the period covered by the Annual Report.

Dated: February 25, 2016

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	*Chief Financial Officer*

A signed original of this written statement required by Section 906 has been provided to Ionis Pharmaceuticals, Inc. and will be retained by Ionis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Ionis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.