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, 2016

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 $2,337,558,702 as of June 30, 2016.*

The number of shares of voting common stock outstanding as of February 21, 2017 was 123,749,472.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 5, 2017 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on May 24, 2017 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 70 to 76 incorporates several documents by reference as indicated therein.

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* Excludes 20,485,236 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, 2016. 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 SPINRAZA (nusinersen), volanesorsen and IONIS-TTR$_{Rx}$ and other of our drugs in development. 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.

SPINRAZA™ is a trademark of Biogen, Inc.

KYNAMRO® is a registered trademark of Kastle Therapeutics LLC

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 to treat patients with serious cardiometabolic diseases caused by lipid disorders.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2016
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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 we are fundamentally changing medicine with the goal to transform the lives of those suffering from severe, often life-threatening, diseases. The recent U.S. approval of SPINRAZA for pediatric and adult patients with spinal muscular atrophy, or SMA, highlights our progress toward this goal. Our pipeline also contains two near-term potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential. We plan to report data from our Phase 3 study of volanesorsen in patients with familial chylomicronemia, or FCS in the first quarter of 2017. We also plan to report data from our Phase 3 study of IONIS-TTR_{Rx} in patients with familial amyloid polyneuropathy, or FAP, in the second quarter of 2017.

With FDA approval in December 2016, SPINRAZA™ (nusinersen) injection became the first and only approved drug to treat pediatric and adult patients with SMA. SMA is a leading genetic cause of death in infants and toddlers that is marked by progressive, debilitating muscle weakness. We and Biogen conducted a broad, innovative clinical development program that moved SPINRAZA from its first dose in humans in 2011 to its first regulatory approval five years later. We conducted two sham-controlled Phase 3 studies, one in babies with infantile-onset SMA called ENDEAR and one in children with later-onset SMA called CHERISH. Both of these studies achieved statistically significant improvements in their primary endpoints and the drug demonstrated a favorable safety profile. Biogen has filed for marketing authorization in the EU, Japan, Australia and Canada, and plans to file in other countries this year. The European Medicines Agency, or EMA, is reviewing the SPINRAZA marketing application under accelerated assessment. Biogen estimates that there are approximately 20,000 patients with SMA in the U.S., EU and Japan, with a large percentage in the United States.

Akcea Therapeutics, Inc. is our wholly owned subsidiary focused on developing and commercializing volanesorsen and three other clinical-stage drugs for serious cardiometabolic diseases caused by lipid disorders, AKCEA-APO(a)-L_{Rx}, AKCEA- AKCEA-APOCIII-L_{Rx} and ANGPTL3-L_{Rx}. Each of these four drugs could potentially treat multiple patient populations. Moving these drugs into a company that we own allows us to retain substantial value from them and ensures Ionis' core focus remains on innovation. Akcea is assembling the global infrastructure to continue developing the drugs in its pipeline, to commercialize them with a focus on lipid specialists as the primary call point and to provide the specialized patient and physician support required to address rare disease patient populations.

We and Akcea are developing volanesorsen to treat two severe and rare, genetically defined diseases, FCS and familial partial lipodystrophy, or FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. Volanesorsen acts to reduce triglyceride levels by inhibiting the production of ApoC-III, a protein that is a key regulator of triglyceride clearance. The clinical development program for volanesorsen consists of three Phase 3 studies called APPROACH, BROADEN and COMPASS. The APPROACH study is in patients with FCS. It is fully enrolled and we plan to report data from it in the first quarter of 2017. We plan to file for marketing authorization in the U.S., Europe and Canada in 2017 if the data are positive. The BROADEN study is in patients with FPL. The study is currently enrolling patients and we plan to have data from this study in 2019. We also recently completed the COMPASS study in patients with triglycerides above 500 mg/dL to expand the exposure database for volanesorsen to support global regulatory filings. In December 2016, we reported that the COMPASS study met its primary endpoint of a statistically significant 71% mean reduction in triglycerides in volanesorsen-treated patients. In a small subset of patients with FCS, volanesorsen-treated patients achieved a mean reduction in triglycerides of 73% from baseline. Safety in this study was supportive of continuing development. We estimate that FCS and FPL each affect 3,000 to 5,000 patients globally. If approved, we plan to commercialize volanesorsen for both FCS and FPL through Akcea.

IONIS-TTR_{Rx} is potentially a first-in-class and best-in-class drug for the treatment of all forms of transthyretin, or TTR, amyloidosis, a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body, including peripheral nerves, heart, intestinal tract, kidney and bladder. IONIS-TTR_{Rx} is given as one subcutaneous injection, once a week. We are evaluating IONIS-TTR_{Rx} in an ongoing Phase 3 study, NEURO-TTR, in patients with FAP. More than half of these patients also have TTR amyloid cardiomyopathy. As part of our Phase 3 study, we are evaluating cardiomyopathy in this subset of patients by cardiac imaging and biomarkers which will provide data on cardiovascular endpoints. Together the polyneuropathy and cardiomyopathy forms of TTR amyloidosis represent a large commercial opportunity for IONIS-TTR_{Rx}. We plan to have data from the NEURO-TTR study in the second quarter of 2017. We and GSK, our partner for IONIS-TTR_{Rx}, are preparing to file for marketing authorization if these data are positive. 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. GSK is preparing to commercialize IONIS-TTR_{Rx}.

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 diseases that have inadequate treatment options. We are addressing a broad spectrum of diseases from common diseases affecting millions, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease, to rare diseases, such as amyotrophic lateral sclerosis and Huntington's disease. 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 AKCEA-APO(a)-L$_{Rx}$ represent 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. AKCEA-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.

The depth of our knowledge and expertise with antisense technology, together with our strong financial position, provides us the flexibility to determine the optimal development and commercialization strategy to maximize the near- and longer-term value of our drugs. We have distinct partnering strategies that we employ based on the specific drug, therapeutic area and expertise and resources our potential partners may bring to the collaboration. For some drugs, we may choose to develop and commercialize them through wholly owned subsidiaries like Akcea. In general, these are drugs, such as volanesorsen, that we have the internal expertise to advance, that have a clear development path with manageable costs and that have the potential for initial rare disease indications. For other drugs, we may form partnerships that enable us to leverage our partner's global expertise and resources needed to support large commercial opportunities, as we did with Bayer and Novartis.

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 substantial resources and expertise that augment and build upon our internal capabilities. 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 for which our partners can provide expertise, tools and resources to complement our drug discovery efforts. We also have partnerships with Bayer, GSK, Janssen, Novartis and Roche. Each of these companies brings significant expertise and global resources to develop and potentially commercialize the drugs under each partnership. Most recently, in January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. As a leader in the cardiovascular disease space, Novartis brings significant resources and expertise that should support the development and commercialization of these two drugs for significant high-risk patient populations. The collaboration with Novartis should enable us to accelerate the development of these drugs for broader patient populations as Novartis plans to conduct a cardiovascular outcomes study for each of these drugs. In addition, Akcea has the right to co-commercialize these drugs using its specialized sales force focused on lipid specialists in select markets. 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. 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 research and development, or R&D, revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Our R&D revenue has consistently grown year over year since 2011. In 2016, we earned more than $345 million in R&D revenue. Moreover, we have the potential to earn nearly $13 billion in future milestone payments and licensing fees from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out or royalty arrangements. With the approval of SPINRAZA in the U.S., we are adding commercial revenue from SPINRAZA royalties to our existing R&D revenue base. Looking forward, we have the potential to increase our commercial revenue from SPINRAZA royalties if Biogen achieves marking authorization in additional countries. We also have the potential to further increase our commercial revenue with volanesorsen product sales and IONIS-TTR$_{Rx}$ royalties. We believe we have the key elements in place to achieve sustained long-term financial growth, including multiple drivers of revenue; a mature, broad and rapidly-advancing clinical pipeline; a partnership strategy that leverages our partner resources; and an innovative drug technology that we continue to deploy across a range of therapeutic areas to address both rare and large patient populations.

2016 and Recent SPINRAZA Accomplishments

- We and Biogen achieved FDA approval of SPINRAZA in three months under Priority Review for the treatment of SMA in pediatric and adult patients.
- Biogen filed for marketing authorization in the EU and was granted Accelerated Assessment.
- Biogen filed for marketing authorization in Canada, Japan, and Australia.
- Biogen reported positive data from an end of study analysis of the ENDEAR Phase 3 study in patients with infantile-onset (consistent with type 1) SMA at the British Pediatric Neurology Association annual conference. We previously reported data from an interim analysis of ENDEAR, which along with several other studies, formed the basis for the marketing application for SPINRAZA in the U.S.
- We and Biogen reported positive data from an interim analysis of the Phase 3 CHERISH study in patients with later-onset (consistent with Type 2) SMA.
- We and Biogen presented new positive clinical data with SPINRAZA at the World Muscle Society Congress supporting the companies' efforts to rapidly make SPINRAZA available to patients with SMA, including:
    - Safety results from the interim analysis of the Phase 3 ENDEAR study in patients with infantile-onset (consistent with Type 1) SMA;
    - Encouraging preliminary results from NURTURE, a Phase 2 open-label study in pre-symptomatic infants; and
    - A recent analysis of the ongoing Phase 2 open-label study in patients with later-onset SMA.
- We and Biogen reported positive data from an interim analysis of the ENDEAR Phase 3 study in patients with infantile-onset (consistent with Type 1) SMA. Biogen paid us $75 million to license the drug.

Corporate Highlights

- We earned more than $200 million from Biogen in 2016, including payments related to SPINRAZA.
- We and Akcea formed a strategic collaboration with Novartis to develop and co-commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} for the treatment of lipid disorders, for which Ionis and Akcea are eligible to receive $225 million in near-term payments, including $100 million we have received and $75 million we expect to receive in the first quarter of 2017. The transaction has a potential value of up to over $1 billion.
- We earned $75 million from Bayer to advance both IONIS-FXI$_{Rx}$ and its LICA follow on, IONIS-FXI-L_{Rx}.
- We sold the global rights to develop and commercialize Kynamro to Kastle Therapeutics and earned a $15 million upfront payment.
- We and MD Anderson Cancer Center formed a strategic alliance to advance novel cancer therapies.
- We added to our pipeline our first oral locally acting drug for gastrointestinal autoimmune diseases for which Ionis earned a $10 million license fee from Janssen.
- We advanced IONIS-KRAS-2.5$_{Rx}$ into development and earned $28 million from AstraZeneca.
- We advanced IONIS-AZ4-2.5-L_{Rx}, our first Generation 2.5 LICA drug, into development and earned $25 million from AstraZeneca.
- Our CEO, Dr. Stanley Crooke, received two awards, the E. B. Hershberg Award from the American Chemical Society and the Lifetime Achievement Award from the Oligonucleotide Therapeutics Society, recognizing his achievements in the field of oligonucleotide therapeutics.

Drug Development and Technology Highlights

- We continued to advance our pipeline of innovative first-in-class or best-in-class drugs, reported positive data from 11 clinical studies with six drugs. These data and clinical advancements represent the broad applicability of our technology to address unmet medical needs across multiple disease targets.
- The FDA and EMA granted orphan drug designation to IONIS-HTT$_{Rx}$ for the treatment of patients with Huntington's disease.
- Akcea launched IN-FOCUS, a research study to assess the impact of FCS.
- Akcea published positive clinical data from a Phase 2 study of volanesorsen in patients with high plasma triglyceride levels and type 2 diabetes in *Diabetes Care*.
- We published a paper in *Nature Biotechnology* on the novel mechanism of action for antisense drugs that significantly expands therapeutic opportunities for the technology.
- We published a paper in *Nucleic Acid Therapeutics* on the analysis of its Integrated Safety Database, which demonstrated no class generic effect of 2'-O-methoxyethyl (2'MOE)-modified antisense oligonucleotides (ASOs) on platelet numbers and function.

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 severe and rare diseases, including neurodegenerative diseases, cardiovascular, metabolic 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 six 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 Generation 2.0+ and our Generation 2.5 drugs. Our LICA technology conjugates specific chemical structures or molecules to antisense drugs and has shown to increase the efficiency of drug uptake in a particular tissue and increase drug potency from 20 to over 30 fold compared to non-conjugated antisense drugs. We currently have ten Generation 2.0+ LICA drugs in our pipeline, all of which we designed to inhibit targets in the liver. We also recently added IONIS-AZ4-2.5-L_{Rx} a drug that combines our Generation 2.5 and LICA technology, to our preclinical pipeline.

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 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 drugs that Akcea is developing by starting the drug name with AKCEA, instead of IONIS, such as AKCEA-ANGPTL3-L_{Rx}. We differentiate our Generation 2.5 drugs by adding a 2.5 notation at the end of the drug name, such as IONIS-STAT3-2.5_{Rx}. We differentiate our LICA drugs by adding an L at the end of the drug name, such as AKCEA-APO(a)-L_{Rx}. We also recently added IONIS-AZ4-2.5-L_{Rx}, a drug that combines our Generation 2.5 and LICA technology, to our preclinical pipeline. 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, volanesorsen is a nonproprietary name that we obtained for ISIS-$APOCIII_{Rx}$. Once we or our partners establish a brand name, we will adopt the brand name. For example, SPINRAZA is the brand name for nusinersen, which was formerly ISIS-SMN_{Rx}.

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 2017, we plan to initiate multiple clinical studies, report data on multiple drugs and add three to five new drugs into development.

Our Newly Marketed Drug

SPINRAZA – SPINRAZA is a Generation 2.0+ antisense drug and is the first and only approved treatment for SMA in pediatric and adult patients in the U.S.

SMA is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Ultimately, individuals with the most severe type of SMA, infantile-onset SMA, can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing. Due to a loss of, or defect in, the SMN1 gene, people with SMA do not produce enough survival motor neuron, or SMN, protein, which is critical for the maintenance of motor neurons. The severity of SMA correlates with the amount of SMN protein a patient can produce on his/her own. Patients with infantile-onset, consistent with Type 1, SMA, the most severe life-threatening form, produce very little SMN protein and do not achieve the ability to sit without support or live beyond two years without respiratory support. Patients with later-onset, consistent with Type 2 or Type 3 SMA, produce greater amounts of SMN protein and have less severe, but still life-altering, forms of SMA.

SPINRAZA is administered via intrathecal injection, which delivers therapies directly to the cerebrospinal fluid, or CSF, around the spinal cord, where motor neurons degenerate in patients with SMA due to insufficient levels of SMN protein.

In December 2016, the FDA approved SPINRAZA for the treatment of pediatric and adult patients with SMA. The European Medicines Agency, or EMA, has validated the Marketing Authorization Application, or MAA, for SPINRAZA for the treatment of SMA and the Committee for Medicinal Products for Human Use, or CHMP, has granted SPINRAZA Accelerated Assessment. The Accelerated Assessment designation can reduce the standard review time. The EMA has granted Orphan Drug Designation to SPINRAZA for the treatment of patients with SMA. Biogen has also submitted regulatory filings in Japan, Canada and Australia and will be initiating regulatory filings in additional countries in 2017.

We and Biogen submitted marketing applications for SPINRAZA in the U.S. and EU in less than two months after announcing positive results from the ENDEAR interim analysis. ENDEAR was a pivotal Phase 3 controlled study evaluating SPINRAZA in patients with infantile-onset SMA. The data package included the interim analysis of ENDEAR, as well as open-label data in pre-symptomatic and symptomatic patients with SMA, or likely to develop, Types 1, 2 and 3 SMA.

In ENDEAR, infantile-onset SMA patients treated with SPINRAZA achieved and sustained clinically meaningful improvement in motor function compared to untreated study participants. In addition, a greater percentage of patients on SPINRAZA survived compared to untreated patients. In January 2017, Biogen presented the ENDEAR pre-specified primary endpoint, time to death or permanent ventilation, from the end of study, or EOS, analysis, which includes data from patients' final study visit, which occurred after the announcement that the study was being stopped and was not part of the interim analysis. SPINRAZA met the pre-specified primary endpoint at the ENDEAR EOS, demonstrating a statistically significant 47% reduction in the risk of death or permanent ventilation ($p<0.01$). SPINRAZA demonstrated a favorable safety profile, with commonly reported adverse events including respiratory events and constipation, consistent with those expected in the general population of infants with SMA.

We also conducted CHERISH, our Phase 3 study in patients with later-onset SMA. CHERISH also met the primary endpoint for the pre-specified interim analysis. The analysis found that children receiving SPINRAZA experienced a highly statistically significant improvement in motor function compared to those who did not receive treatment. SPINRAZA demonstrated a favorable safety profile in the study.

Additionally, Biogen conducted NURTURE, a Phase 2 open-label study in pre-symptomatic infants. At the 2016 World Muscle Society Congress in October 2016, encouraging preliminary results from NURTURE were presented in addition to an analysis of the then ongoing Phase 2 open-label study in patients with later-onset SMA. The interim analysis of the ongoing, open-label, 30-month, Phase 2 NURTURE study showed that SPINRAZA-treated pre-symptomatic infants exhibited improvements in motor function and motor milestones such as full head control, independent sitting, standing with support, standing unaided, and walking with support, as measured by validated scales. At the time of the interim analysis all patients were alive and did not require respiratory intervention. Three infants experienced AEs considered possibly related to SPINRAZA, all of which were resolved.

Further, in open-label studies, some patients achieved milestones that they would not be expected to achieve, such as the ability to sit unassisted, stand or walk, and maintained milestones at ages that they would expect to lose. The overall findings of these studies support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment.

The most common adverse reactions reported for SPINRAZA were upper respiratory infection, lower respiratory infection and constipation. Serious adverse reactions of partial or complete lung collapse were more frequent in SPINRAZA-treated patients.

We and Biogen entered into an alliance to develop and commercialize SPINRAZA in January 2012. In July 2016, Biogen licensed SPINRAZA from us and paid us a $75 million license fee. We have transitioned all SPINRAZA development activities to Biogen as they are now responsible for all global development, regulatory and commercialization activities and costs.

Our Phase 3 Drugs

We have two drugs for which we are conducting pivotal Phase 3 studies: volanesorsen and IONIS-TTR_{Rx}. Both of these drugs have the potential to transform the treatment of patients with an orphan disease, and we believe these drugs are close to commercialization. In 2015, we completed target enrollment in a Phase 3 study for each of these drugs.

Volanesorsen – Volanesorsen is a Generation 2.0+ antisense drug we and Akcea are developing to treat patients with FCS and FPL, orphan diseases characterized by extremely elevated triglyceride levels and a high risk of life-threatening pancreatitis.

Due to the high levels of triglycerides in their blood, patients with FCS and FPL experience a variety of debilitating and potentially life-threatening conditions, including pancreatitis, persistent and often severe abdominal pain and abnormal enlargement of the liver or spleen. In addition, patients with FCS or FPL have to adhere to a very low fat diet. As a result of these factors, patients with FCS and FPL are often unable to work, adding to the burden of the disease. While all the complications of FCS or FPL cause patients to have a lower quality of life, pancreatitis is the most serious consequence of the disease. Patients with FCS and FPL suffer from acute pancreatitis, a sudden inflammation of the pancreas that may be fatal. The symptoms of an acute pancreatitis episode are severe, debilitating upper abdominal pain that radiates into the back, fever and nausea and vomiting. In severe cases, patients can have bleeding into the pancreas, serious tissue damage, infection and cyst formation, as well as damage to other vital organs such as the heart, lungs and kidneys. We estimate there are 3,000 to 5,000 FCS patients and an additional 3,000 to 5,000 FPL patients globally.

Volanesorsen acts to reduce triglyceride levels by inhibiting the production of ApoC-III, a protein that is a key regulator of triglyceride clearance. People who have low levels of ApoC-III or reduced ApoC-III function have lower levels of triglycerides and a lower incidence of cardiovascular disease, or CVD. By inhibiting the production of ApoC-III, volanesorsen is able to increase triglyceride clearance in FCS patients, reducing their triglyceride levels.

We demonstrated in Phase 2 studies that volanesorsen robustly reduced ApoC-III and triglycerides in patients, including in patients with FCS, and also had a beneficial impact on insulin sensitivity. We published our findings from the Phase 2 studies with volanesorsen in two publications in the New England Journal of Medicine.

We and Akcea are currently conducting two Phase 3 studies of volanesorsen. The study in patients with FCS, called APPROACH, is fully enrolled and we and Akcea plan to report data from this study in the first quarter of 2017. The study in patients with FPL, called BROADEN, is currently enrolling and we and Akcea plan to report data from this study in 2019. We and Akcea also conducted an additional Phase 3 study, called COMPASS, in patients with triglycerides above 500 mg/dL to expand the exposure database for volanesorsen to support global regulatory filings.
In December 2016, we and Akcea announced that the COMPASS study met its primary endpoint. The treatment effect observed was sustained through the end of the 26 week treatment period for both the full study population and the subset of patients with FCS.

Volanesorsen has been granted orphan drug status in both the U.S. and EU for the treatment of FCS. Further, volanesorsen has been granted orphan drug status in the EU for the treatment of FPL, and we are in the process of applying for this status for this indication in the U.S. Akcea plans to globally commercialize volanesorsen for both FCS and FPL if approved.

See our separate section below where we further discuss our subsidiary, Akcea.

IONIS-TTR$_{Rx}$ – IONIS-TTR$_{Rx}$ is a Generation 2.0+ antisense drug we 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. 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 and is a painful, fatal disease that ultimately leads to multi-organ failure and death within five to 15 years after symptom onset and diagnosis. FAP patients primarily have TTR build up in the peripheral nervous system, but can also have significant TTR build up in multiple organs. 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 NEURO-TTR, a randomized, double-blinded, placebo-controlled, international Phase 3 study for FAP patients. We have completed target enrollment. We plan to report data from this study in the second quarter of 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.

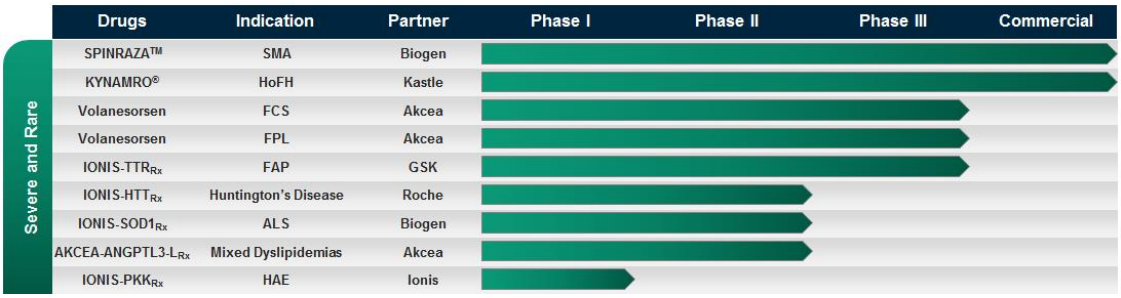
The FDA has granted Orphan Drug Designation and Fast Track Status to IONIS-TTR$_{Rx}$ for the treatment of patients with FAP. The EMA has granted Orphan Drug Designation to IONIS-TTR$_{Rx}$ for the treatment of patients with TTR amyloidosis.

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 neurodegenerative 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 resulting in profound effects on the family.

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. For example, SPINRAZA was approved five years after we began the Phase 1 study for it.

IONIS' Severe and Rare Disease Pipeline



SPINRAZA – SPINRAZA is our recently marketed Generation 2.0+ antisense drug to treat patients with SMA. SMA is a severe motor neuron disease that is the leading genetic cause of infant mortality. For more information on SPINRAZA, see the drug description under Our Newly Marketed Drug.

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 U.S. and several other countries. In 2016 Kastle acquired the global rights to develop and commercialize Kynamro and also began marketing and selling Kynamro.

Volanesorsen – Volanesorsen is a Generation 2.0+ antisense drug we and Akcea are developing to treat patients with FCS and FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. For more information on the development plan for volanesorsen see the drug description under Our Phase 3 Drugs.

IONIS-TTR$_{Rx}$ – IONIS-TTR$_{Rx}$ is a Generation 2.0+ 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.

IONIS-HTT$_{Rx}$ – IONIS-HTT$_{Rx}$ is a Generation 2.0+ antisense drug we designed to reduce the production of the huntingtin, or HTT, protein, 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 an inherited genetic brain disorder that results in the progressive loss of both mental faculties 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 is toxic and gradually destroys neurons. 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 a Generation 2.0+ 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.

AKCEA-ANGPTL3-L$_{Rx}$ – AKCEA-ANGPTL3-L$_{Rx}$ is a LICA drug we designed to reduce angiopoietin-like 3 protein, or ANGPTL3, an independent risk factor for cardiovascular disease. We and Akcea are developing AKCEA-ANGPTL3-L$_{Rx}$ to treat multiple lipid disorders, or mixed dyslipidemias. For more information on the development plan for AKCEA-ANGPTL3-L$_{Rx}$, see the drug description under the Akcea Therapeutics section below.

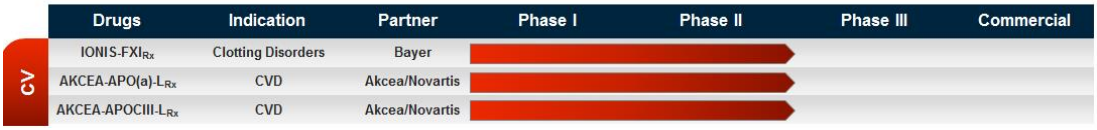
IONIS-PKK$_{Rx}$ – IONIS-PKK$_{Rx}$ is a Generation 2.0+ antisense drug we designed to reduce the production of prekallikrein, or PKK, to treat patients with hereditary angioedema, or HAE. HAE is a rare genetic disease that is characterized by rapid and painful attacks of inflammation in the hands, feet, limbs, face, abdomen, larynx and trachea and can be fatal if swelling occurs in the larynx. PKK plays an important role in the activation of inflammatory mediators associated with 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 or reduce the severity of HAE attacks. However, current prophylactic treatment approaches are very limited and have major tolerability issues due to challenging administration requirements leaving patients with few therapeutic options.

We have completed a Phase 1 study evaluating IONIS-PKK$_{Rx}$ in healthy volunteers and we are exploring potential development options.

Cardiovascular Franchise

Cardiovascular disease is an important area of focus for us. Our cardiovascular franchise includes the drugs Akcea is developing that we describe below and IONIS-FXI$_{Rx}$, which we are developing and have licensed to Bayer. The drugs in our cardiovascular franchise target all the key components of cardiovascular disease, including various atherogenic lipids, inflammation and thrombosis.

IONIS' Cardiovascular Disease Pipeline



IONIS-FXI$_{Rx}$ – IONIS-FXI$_{Rx}$ is a Generation 2.0+ antisense drug we designed to reduce the production of Factor XI. Factor XI is a clotting factor produced in the liver that 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 thromboembolic 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, we believe that our drug has the potential to be used broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic drugs are needed.

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 were published in the New England Journal of Medicine in December 2014. In May 2015, we exclusively licensed IONIS-FXI$_{Rx}$ to Bayer.

In November 2016, we completed a Phase 2 double-blinded, randomized, placebo-controlled study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis. In this Phase 2 study, patients treated with IONIS-FXI$_{Rx}$ achieved statistically significant, dose-dependent reductions in Factor XI activity. There were no clinically meaningful reductions in platelets and no treatment-related major or clinically relevant non-major bleeding events.

In February 2017 we announced the advancement of IONIS-FXI$_{Rx}$ in clinical development under the existing exclusive license agreement with Bayer. We plan to conduct a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in approximately 200 patients with end-stage renal disease on hemodialysis to finalize dose selection. We will also initiate development of IONIS-FXI-L$_{Rx}$ which is currently in preclinical development and is shown in our Preclinical Pipeline section below.

AKCEA-APO(a)-L$_{Rx}$ – AKCEA-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 CVD. We believe addressing Lp(a) is the next important horizon in lipid focused CVD treatment. For more information on the development plan for AKCEA-APO(a)-L$_{Rx}$, see the drug description under the Akcea Therapeutics section below.

AKCEA-APOCIII-L$_{Rx}$ – AKCEA-APOCIII-L$_{Rx}$ is a LICA-conjugated Generation 2.0+ antisense drug designed to inhibit the production of apoC-III, the same protein inhibited by volanesorsen, for the broad population of patients who are at risk for cardiometabolic disease due to their elevated triglyceride levels. For more information on the development plan for AKCEA-APOCIII-L$_{Rx}$, see the drug description under the Akcea Therapeutics section below.

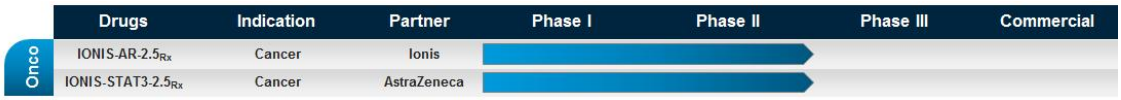
Cancer Franchise

Cancer is an area of significant unmet medical need. Cancer is an extremely complex disease that involves a large number of targets. Using our antisense technology, we can validate multiple potential cancer targets from a variety of different cancers, and rapidly identify anti-cancer drugs, which in many cases are the same or similar sequences to those used to validate the target. 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 a robust 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. In December 2016 we expanded our cancer franchise when AstraZeneca licensed our preclinical drug, IONIS-KRAS-2.5$_{Rx}$. IONIS-KRAS-2.5$_{Rx}$ is an antisense drug we discovered and designed to directly target *KRAS*, one of the most frequently mutated genes in cancer. We also have a collaboration agreement with University of Texas MD Anderson Cancer Center to identify cancer targets and create novel antisense drugs to treat cancer together.

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, STAT3 is a protein known to be important in carcinogenesis, however, it has been difficult to approach with traditional drug modalities. 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 a Generation 2.5 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. The drug exhibited a good safety and tolerability profile supportive of continued development. 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 a Generation 2.5 antisense drug we designed to reduce the production of signal transducer and activator of transcription 3, or STAT3, to treat patients with cancer. 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. 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 in which STAT3 is implicated.

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 and in patients with diffuse large B cell lymphoma.

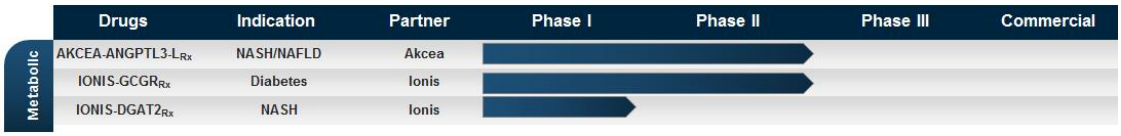
Metabolic Franchise

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 U.S., 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 franchise to be effective alone or when added to existing therapies to treat metabolic diseases, such as diabetes.

We have reported positive Phase 2 data from IONIS-GCGR$_{Rx}$, the most advanced drug in our metabolic franchise. We designed this drug 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 nonalcoholic steatohepatitis, or NASH. NASH is a common liver disease characterized by excessive triglycerides in the liver with concurrent inflammation and cellular damage. 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 have a liver that does not function properly due to long-term damage, known as 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 Pipeline



AKCEA-ANGPTL3-L$_{Rx}$ – AKCEA-ANGPTL3-L$_{Rx}$ is a LICA drug we designed to reduce angiopoietin-like 3 protein, or ANGPTL3, an independent risk factor for cardiovascular disease. We and Akcea are developing AKCEA-ANGPTL3-L$_{Rx}$ to treat multiple lipid disorders, or mixed dyslipidemias. For more information on the development plan for AKCEA-ANGPTL3-L$_{Rx}$, see the drug description under the Akcea Therapeutics section below.

IONIS-GCGR$_{Rx}$ – IONIS-GCGR$_{Rx}$ is a Generation 2.0+ 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. In patients with advanced diabetes, uncontrolled glucagon action can lead to significant increases in blood glucose level. In addition, reducing GCGR produces more active glucagon-like peptide-1, or GLP-1, a hormone that preserves pancreatic function and enhances insulin secretion.

We have completed two Phase 2 studies with IONIS-GCGR$_{Rx}$: 1) a 13-week study in patients with type 2 diabetes who are poorly controlled on stable metformin therapy and 2) a 26-week study to identify the optimal dose and schedule to achieve glucose control with manageable glucagon receptor-related liver enzyme elevations. In January 2017, we reported results from the Phase 2 dose optimization study in which patients treated with IONIS-GCGR$_{Rx}$ achieved robust and sustained, statistically significant improvements in hemoglobin A1c, or HbA1c, and other measures of glucose control after 26 weeks of treatment. Additionally, IONIS-GCGR$_{Rx}$-treated patients experienced a mean increase in total GLP-1 from baseline compared to a decline in placebo-treated patients. The safety and tolerability profile of IONIS-GCGR$_{Rx}$ in the Phase 2 studies supports continued development.

We are now evaluating partnership opportunities for IONIS-GCGR$_{Rx}$.

IONIS-DGAT2$_{Rx}$ – IONIS-DGAT2$_{Rx}$ is a Generation 2.0+ antisense drug we designed to reduce the production of DGAT2, or diacylglycerol acyltransferase 2, to treat patients with NASH, a common liver disease. 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 U.S.

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 non-alcoholic fatty liver disease, or NAFLD, lowered blood lipid levels and reversed diet-induced insulin resistance.

We completed a Phase 1 randomized, placebo-controlled, dose-escalation study of IONIS-DGAT2$_{Rx}$ 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. We are developing IONIS-GSK4-L_{Rx} with GSK.

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 our first anti-infective drug in development that incorporates our LICA technology. 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, including cirrhosis, liver failure and liver cancer. Chronic HBV infection is one of the most common persistent viral infections in the world. Currently available therapies, although effective in reducing circulating HBV in the blood, do not effectively inhibit HBV antigen production and secretion, which are associated with poor prognosis and increased risk of liver cancer.

We have completed a randomized, placebo-controlled, dose-escalation, Phase 1 study of IONIS-HBV_{Rx} in healthy volunteers. The safety and tolerability profile of IONIS-HBV_{Rx} in the Phase 1 study supports continued development. 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. GSK is planning to initiate Phase 2 studies for both IONIS-HBV_{Rx} and IONIS-HBV-L_{Rx} in the first quarter of 2017.

Preclinical Drugs in Development

The efficiency and broad applicability of our technology provides us with nearly unlimited targets against which to develop drugs. On average, it takes 12 to 18 months to complete the preclinical studies necessary to support clinical development. Over the last year we added six new drugs to our preclinical pipeline, IONIS-PKK-L_{Rx}, IONIS-ENAC-2.5$_{Rx}$, IONIS-KRAS-2.5$_{Rx}$, IONIS-JBI1-2.5$_{Rx}$, IONIS-FXI-L_{Rx} and IONIS-AZ4-2.5-L_{Rx}, our first drug that combines our Generation 2.5 and LICA technology.

IONIS' Preclinical Pipeline

Severe and Rare

Drugs	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	Ionis
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia	Ionis
IONIS-PKK-L_{Rx}	HAE	Ionis
IONIS-ENAC-2.5$_{Rx}$	Cystic Fibrosis	Ionis

Cardiovascular

Drugs	Indication	Partner
IONIS-AGT-L_{Rx}	Treatment-Resistant Hypertension	Ionis
IONIS-AZ4-2.5-L_{Rx}	CVD	AstraZeneca
IONIS-FXI-L_{Rx}	Clotting Disorders	Bayer

Oncology

Drugs	Indication	Partner
IONIS-KRAS-2.5$_{Rx}$	Cancer	AstraZeneca

Other

Drugs	Indication	Partner
IONIS-JBI1-2.5$_{Rx}$	GI Autoimmune Disease	Janssen

Akcea Therapeutics: Our Wholly Owned Subsidiary to Develop and Commercialize Drugs for Cardiometabolic Diseases Caused by Lipid Disorders

Akcea Therapeutics is our wholly owned subsidiary that we formed in late 2014. We formed Akcea to focus on developing and commercializing our drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. As part of its formation, we granted Akcea exclusive rights to develop and commercialize volanesorsen, AKCEA-APO(a)-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx}. These four novel drugs are based on our antisense technology and have the potential to treat multiple indications. We describe each of these drugs in more detail below.

Akcea is assembling the global infrastructure to develop the drugs in its pipeline, to commercialize them with a focus on lipid specialists as the primary call point and to create the specialized support required to address rare disease patient populations. We and Akcea entered into a collaboration, option and license agreement with Novartis. Akcea granted Novartis an exclusive option to license AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, which have the potential to treat patients who are at high cardiovascular risk due to inadequately treated lipid disorders. After Akcea completes its Phase 2 development of each of these drugs, if Novartis exercises its option, it plans to use commercially reasonable efforts to conduct, at its expense, a Phase 3 cardiovascular outcome study in a high-risk patient population and will be responsible for the worldwide development and commercialization activities for each licensed drug. Novartis brings significant resources and expertise that should support the development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} for significant high-risk patient populations. Akcea also plans to co-commercialize any such drug through its specialized sales force focused on lipid specialists in selected markets.

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.

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 above.

AKCEA-APO(a)-L_{Rx} – AKCEA-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 CVD. We and Akcea initiated a collaboration with Novartis in January 2017 to advance AKCEA-APO(a)-L_{Rx}.

Akcea is developing AKCEA-APO(a)-L_{Rx} for patients who are at significant risk of CVD because of their elevated levels of Lp(a). AKCEA-APO(a)-L_{Rx} inhibits the production of the apolipoprotein(a), or Apo(a), protein, thereby reducing Lp(a), a very atherogenic (promoting the formation of plaques in the arteries) and thrombogenic (promoting the formation of blood clots) form of low density lipoprotein, or LDL. Elevated Lp(a) is recognized as an independent, genetic cause of coronary artery disease, heart attack, stroke and peripheral arterial disease. Inhibiting the production of Apo(a) in the liver reduces the level of Lp(a) in blood, potentially slowing down or reversing cardiovascular disease in patients with hyperlipoproteinemia(a), a condition in which individuals have elevated levels of Lp(a), which we define as levels greater than 60 mg/dL. Lp(a) is difficult to target using other technologies, like small molecules and antibodies, because there are multiple forms of the Apo(a) molecule that are determined by genetic variation. We believe addressing Lp(a) is the next important horizon in lipid focused CVD treatment and, through Akcea's collaboration with Novartis, Akcea plans to develop AKCEA-APO(a)-L_{Rx} to treat patients with CVD in whom hyperlipoproteinemia(a) plays a causal role.

We and Akcea completed a Phase 1/2a study with AKCEA-APO(a)-L_{Rx} in patients with hyperlipoproteinemia(a)and reported results at the AHA meeting in November 2015. In this clinical study, Akcea observed significant and sustained reductions in Lp(a) after only a single, small volume dose of AKCEA-APO(a)-L_{Rx}. With multiple doses of AKCEA-APO(a)-L_{Rx}, we and Akcea observed even greater reductions of Lp(a). Based on these results, Akcea is planning to start a dose range finding Phase 2 study of AKCEA-APO(a)-L_{Rx} in patients with hyperlipoproteinemia(a) and established CVD in the first half of 2017.

AKCEA-ANGPTL3-L_{Rx} – AKCEA-ANGPTL3-L_{Rx} is a LICA drug we designed to reduce angiopoietin-like 3 protein, or ANGPTL3, an independent risk factor for cardiovascular disease. We and Akcea are developing AKCEA-ANGPTL3-L_{Rx} to treat multiple lipid disorders, or mixed dyslipidemias.

People with elevated levels of the angiopoietin-like 3, or ANGPTL3, protein have high LDL-C and triglyceride levels. Studies show this elevation is associated with an increased risk of premature heart attacks, increased arterial wall thickness and multiple metabolic disorders, such as insulin resistance. In contrast, people with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels and thus lower risk of heart attacks and multiple metabolic disorders. In preclinical studies, an analog of AKCEA-ANGPTL3-L_{Rx} inhibited the production of the ANGPTL3 protein in the liver, inhibiting liver fat accumulation and lowering blood levels of LDL-C and very low density lipoprotein cholesterol, or VLDL-C. In addition, our preclinical data and initial Phase 1 data suggest that inhibiting the production of ANGPTL3 could improve other lipid parameters, including triglyceride levels and total cholesterol, as well as metabolic parameters, such as insulin sensitivity.

We and Akcea are conducting a Phase 1/2 program for AKCEA-ANGPTL3-L_{Rx} in people with elevated triglycerides and in patients with FCS. If we find that AKCEA-ANGPTL3-L_{Rx} can effectively lower triglyceride levels in FCS patients by using a different mechanism of action than volanesorsen, it may represent an opportunity to expand Akcea's FCS franchise in the future. We and Akcea reported initial results for the initial group of people with elevated triglycerides from this study at the AHA meeting in November 2016. These people achieved dose-dependent, statistically significant mean reductions in ANGPTL3 of up to 83% and also experienced statistically significant mean reductions in triglycerides of up to 66% and in total cholesterol of up to 36%. In this study, AKCEA-ANGPTL3-L_{Rx} displayed a favorable safety and tolerability profile. We plan to report the data from patients with FCS in the first half of 2018. We plan to begin a study of AKCEA-ANGPTL3-L_{Rx} in patients with fatty liver disease, which may include patients with nonalcoholic fatty liver disease, or NAFLD, or nonalcoholic steatohepatitis, or NASH, in the second half of 2017. Additional potential indications for which we may consider developing AKCEA-ANGPTL3-L_{Rx} include mixed dyslipidemias and numerous lipodystrophies.

AKCEA-APOCIII-L_{Rx} – AKCEA-APOCIII-L_{Rx} is a LICA-conjugated Generation 2.0+ antisense drug we designed to inhibit the production of apoC-III, the same protein inhibited by volanesorsen, for the broad population of patients who are at risk for cardiometabolic disease due to their elevated triglyceride levels. We and Akcea initiated a collaboration with Novartis in January 2017 to advance AKCEA-APOCIII-L_{Rx}.

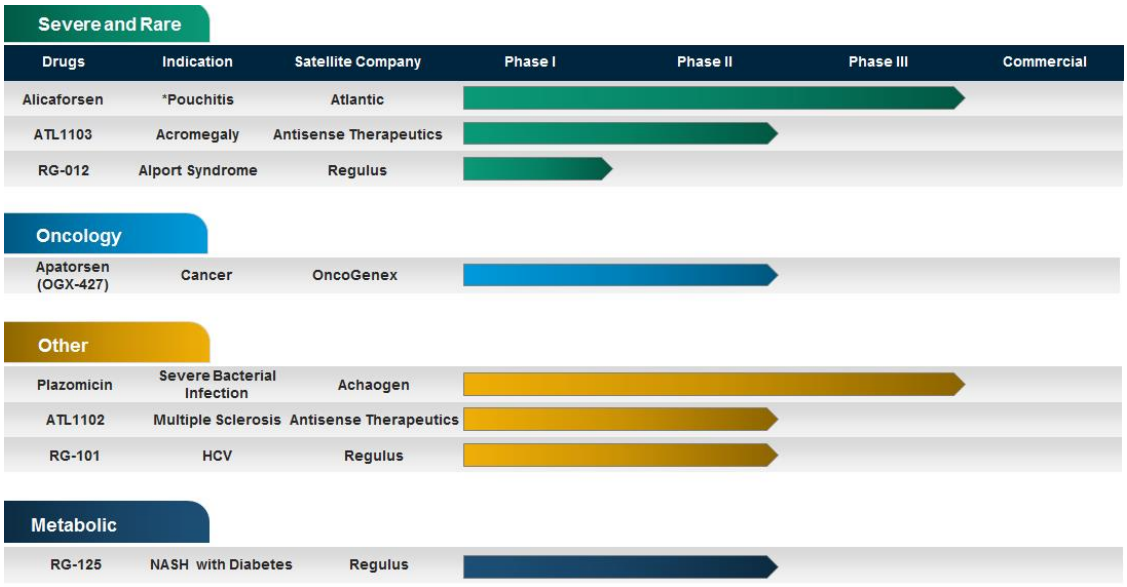
ApoC-III impacts triglyceride levels and may also increase inflammatory processes. This combination of effects makes ApoC-III a valuable target for reducing the residual cardiovascular risk in patients already on statin therapy, or for whom triglycerides are poorly controlled. We believe that the enhancements offered by our LICA technology will provide greater patient convenience by allowing for much lower and less frequent dose administration, compared to volanesorsen.

We and Akcea are conducting a Phase 1/2 study of AKCEA-APOCIII-L_{Rx} in people with elevated triglycerides and plan to report results from this study in 2017.

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



* 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. In January 2017, Atlantic announced that it received agreement from the FDA to initiate a rolling submission of its NDA for alicaforsen to treat pouchitis ahead of its Phase 3 data expected in the second half of 2017.

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.

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 December 2015, Regulus completed a Phase 1 randomized, double-blind, placebo-controlled, single ascending dose study showing the drug was well-tolerated.

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 conducted two Phase 3 studies for plazomicin, CARE and EPIC. The CARE Phase 3 study was designed to evaluate the efficacy of plazomicin in patients with infections caused by carbapenem-resistant Enterobacteriaceae, or CRE. In December 2016, Achaogen announced that a lower rate of mortality or serious disease-related complications were observed in its CARE Phase 3 study in patients receiving plazomicin compared with colistin therapy, one of the few remaining antibiotics for treatment of infections due to CRE. Also in December 2016, Achaogen announced that the EPIC Phase 3 study to evaluate the efficacy of plazomicin in patients with complicated urinary tract infections, met its primary endpoints.

Achaogen plans to submit an NDA, which will include EPIC and CARE data, to the FDA in the second half of 2017 and also plans to submit an MAA to the EMA in 2018.

The FDA has granted Fast Track Status for the development and regulatory review of plazomicin to treat serious and life-threatening CRE infections. In addition, plazomicin has received Qualified Infectious Disease Product, or QIDP, designation from the FDA. The QIDP designation was created by the Generating Antibiotic Incentives Now, or GAIN, Act, which was part of the FDA Safety and Innovation Act and provides certain incentives for the development of new antibiotics, including priority review and an additional five years of market exclusivity.

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 demonstrated that inhibition of VLA-4 could positively affect a number of inflammatory diseases, including MS. In 2001, we licensed ATL1102 to ATL. ATL completed a chronic toxicology study in primates and a Phase 2a efficacy and safety trial. ATL1102 was shown by ATL to reduce MS lesions in the Phase 2a clinical trial. ATL plans to submit an IND application for its Phase 2b study in early 2017.

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. The FDA initiated a clinical hold after Regulus reported a second serious adverse event, or SAE, of jaundice in June 2016. Subsequently, the FDA requested the final safety and efficacy data from on-going RG-101 clinical and pre-clinical studies before reconsidering the clinical hold. Regulus anticipates that data will be available in the fourth quarter of 2017.

RG-125 – RG-125, also referred to as AZD4076, is a GalNAc-conjugated 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. In December 2015, Regulus transferred all future development of RG-125 to AstraZeneca. In December 2015, AstraZeneca initiated a Phase 1 study evaluating RG-125 in healthy volunteers and in the third quarter of 2016, AstraZeneca initiated a Phase 1/2a study in patients with type 2 diabetes and NAFLD.

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.

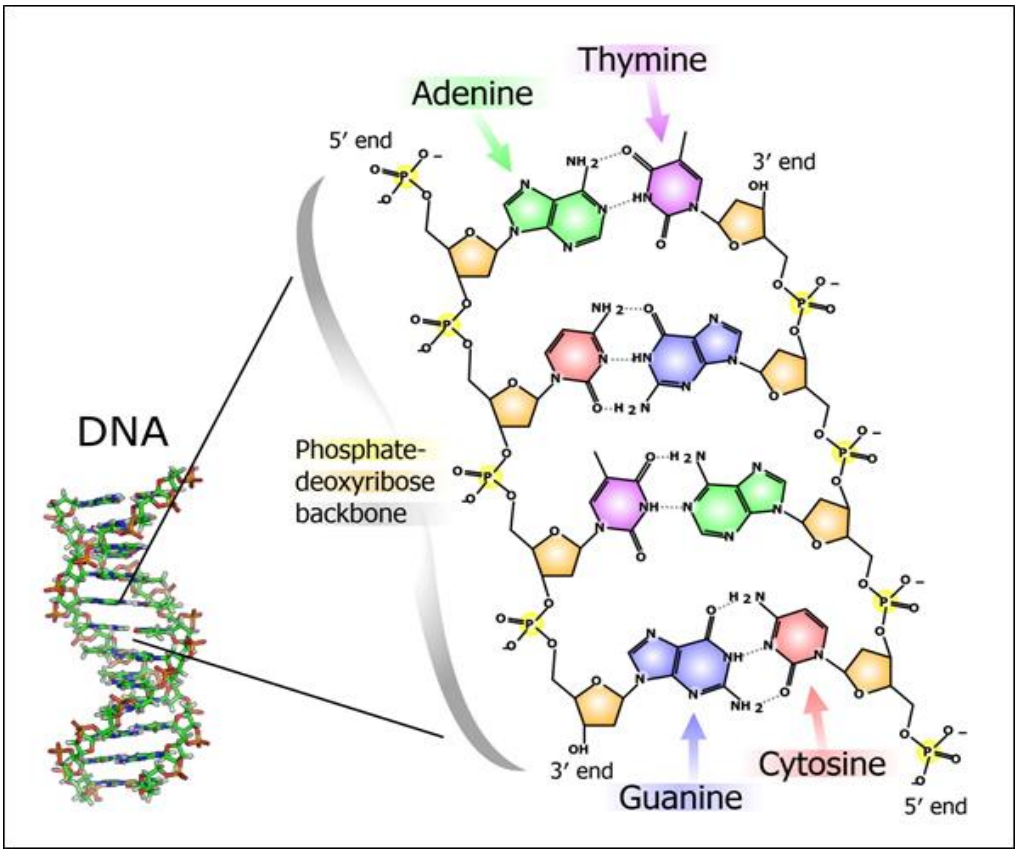


Figure 1: Illustration of DNA.

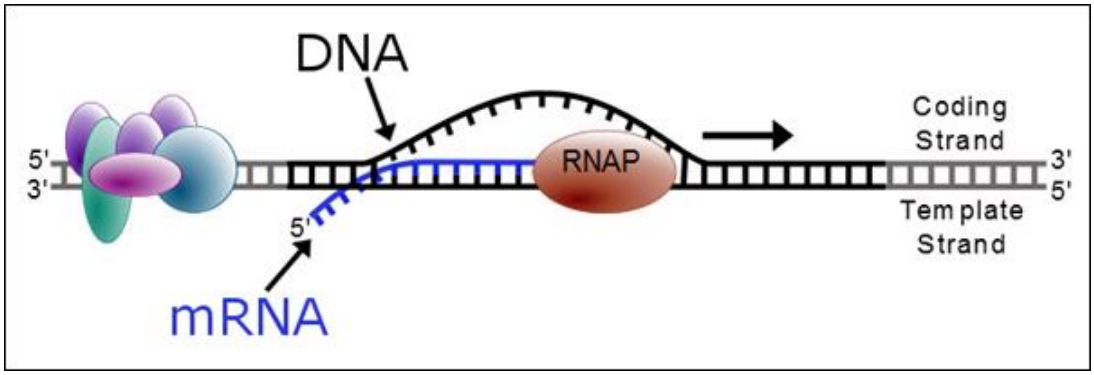


Figure 2: Transcription of information contained in a gene, or DNA, to mRNA.

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).

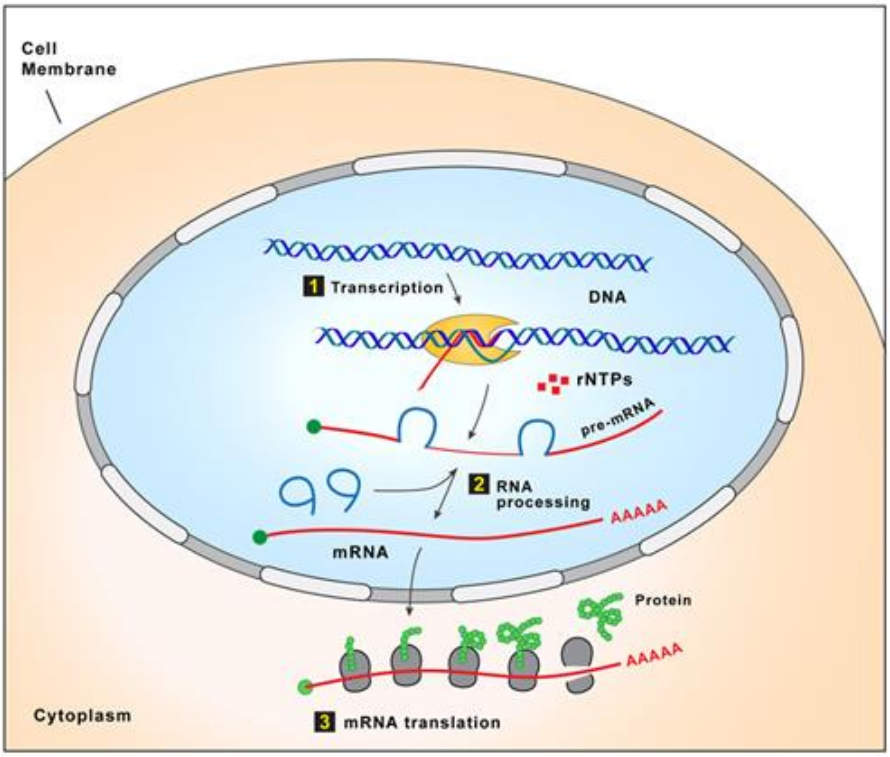


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

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 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 2.0+ 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 AKCEA-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 proprietary oligonucleotide 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, volanesorsen, IONIS-TTR$_{Rx}$, IONIS-FXI$_{Rx}$, AKCEA-APO(a)-L$_{Rx}$ and others.

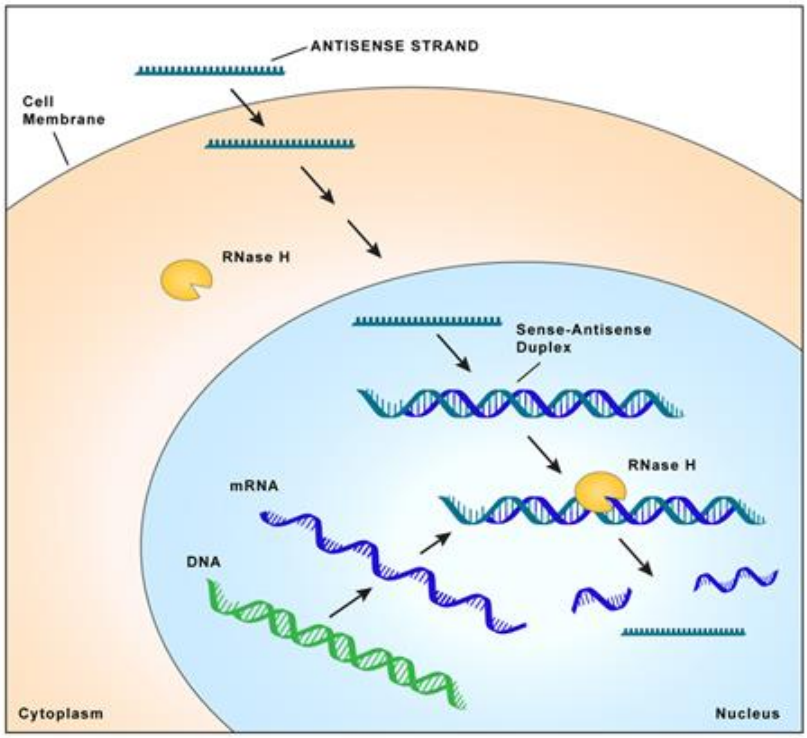


Figure 4: Antisense drug using the RNase H mechanism of action.

SPINRAZA 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.

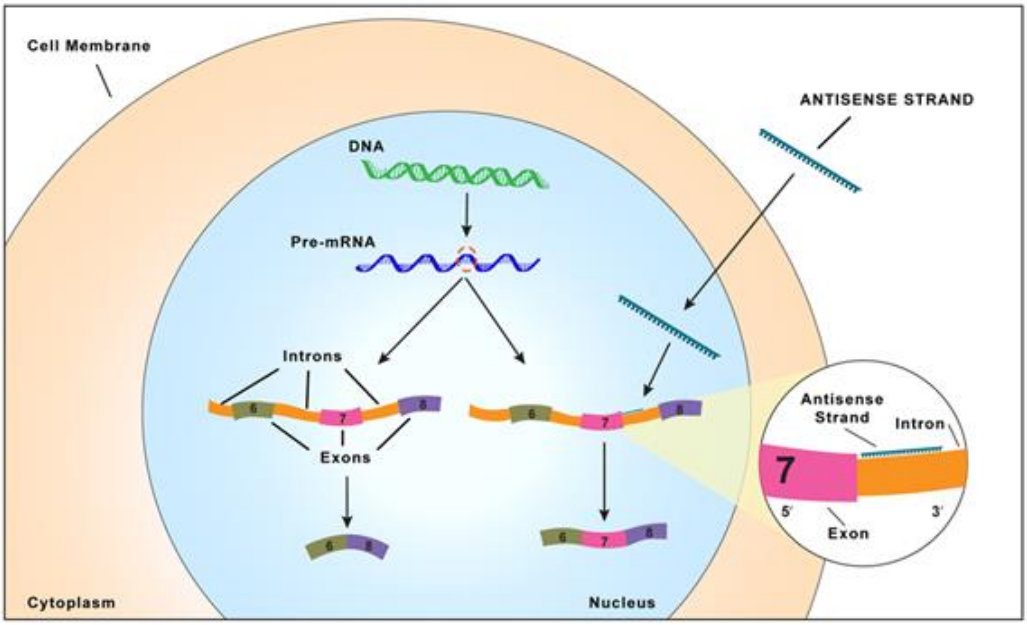


Figure 5: Antisense drug altering splicing of the SMN2 mRNA.

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

Partnering Strategy

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology, preparing to commercialize our drugs and selling our drugs. Our partners include the following companies, among others: AstraZeneca, Biogen, Bayer, GSK, Janssen, Novartis and Roche. Our partners bring resources and expertise that augment and build upon our internal capabilities. The depth of our knowledge and expertise with antisense technology together with our strong financial position 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 through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas. Our partners provide expertise, 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 neurodegenerative diseases with our antisense technology. Together we are creating a franchise of novel potential drugs for neurodegenerative diseases that we believe will expand both our pipeline and Biogen's pipeline with promising new drugs. Most recently, we licensed SPINRAZA to Biogen and began receiving commercial revenue from SPINRAZA royalties in December 2016 after SPINRAZA's approval by the FDA.

- We have partnerships with companies that bring significant expertise and global resources to develop and potentially commercialize drugs for a particular therapeutic area. In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. As a leader in the cardiovascular disease space, Novartis brings significant resources and expertise that should support the development and commercialization of these two drugs for significant high-risk patient populations. The collaboration with Novartis should enable us to accelerate the development of these drugs for broader patient populations as Novartis plans to conduct a cardiovascular outcomes study for each of these drugs.

- 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.

- 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.

Financial Impact of Our Partnerships

Through our partnerships, we have created a broad and sustaining base of potential R&D revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Since 2007, we have received more than $1.9 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 $13 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. For example, with the approval of SPINRAZA in the U.S., we are adding commercial revenue from SPINRAZA royalties to our broad base of R&D revenue.

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 milestone payments of up to more than $4 billion as drugs under this collaboration advance. 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. From inception through February 2017, we have generated $90 million in payments under this collaboration, including $25 million when we moved the first development candidate, IONIS-AZ4-2.5-L_{Rx}, our first Generation 2.5+ LICA drug, into preclinical development in December 2016.

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 and in patients with diffuse large B cell lymphoma. 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. The first development candidate identified under the anti-cancer research program was IONIS-KRAS-2.5$_{Rx}$, which AstraZeneca licensed from us in December 2016. IONIS-KRAS-2.5$_{Rx}$ is a Generation 2.5 antisense drug we designed to directly target KRAS, one of the most frequently mutated genes in cancer.

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}$, IONIS-KRAS-2.5$_{Rx}$ and two other drugs under the research program, we could receive license fees and milestone payments of up to more than $750 million. From inception through February 2017, we have generated more than $95 million in payments under this collaboration, including $28 million we earned in December 2016 following the completion of IND-supporting studies and AstraZeneca's license of IONIS-KRAS-2.5$_{Rx}$.

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 four strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our recently approved drug to treat pediatric and adult patients with SMA. Additionally, we and Biogen are currently developing four other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$, and three drugs to treat undisclosed neurodegenerative diseases, IONIS-BIIB4$_{Rx}$, IONIS-BIIB5$_{Rx}$ and IONIS-BIIB6$_{Rx}$. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. From inception through February 2017, we have generated over $550 million from our Biogen collaborations.

SPINRAZA (nusinersen)

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. In December 2016, the FDA approved SPINRAZA for the treatment of SMA in pediatric and adult patients. SPINRAZA is currently under Accelerated Assessment with the EMA for marketing authorization. Biogen has also submitted regulatory filings in Japan, Canada and Australia and will be initiating regulatory filings in additional countries in 2017. Under our collaboration agreement, we received an upfront payment of $29 million in January 2012 and we are eligible to receive up to an additional $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 SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We are obligated to pay Cold Spring Harbor Laboratory and the University of Massachusetts nominal amounts for license fees and milestone payments we receive and a low single digit royalty on sales of SPINRAZA. From inception through February 2017, we have generated nearly $320 million in payments for advancing SPINRAZA, including a $75 million license fee we received from Biogen when Biogen licensed SPINRAZA and a $60 million milestone payment we earned from Biogen upon receiving FDA approval, both in 2016. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

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 completed a Phase 1/2 clinical study in patients with DM1. Based on the data reported in December 2016, we plan to pursue a more potent drug using our LICA technology. From inception through February 2017, we have generated nearly $39 million in payments for advancing IONIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen entered into a separate collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurodegenerative 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 an additional $259 million in a license fee and 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 2017, we have generated $43 million in payments under this collaboration.

Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative 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 Biogen is pursuing 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. In October 2016, we expanded our collaboration to include the additional research activities we will perform. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. We are currently advancing three drugs, IONIS-SOD1$_{Rx}$, IONIS-BIIB5$_{Rx}$, and IONIS-BIIB6$_{Rx}$ under this collaboration. 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 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 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 2017, we have generated nearly $150 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 were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis. Under the terms of the agreement, we received a $100 million upfront payment in the second quarter of 2015. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate the development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. In conjunction with the decision to advance these programs, we will receive a $75 million payment from Bayer. We plan to conduct a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to rapidly develop IONIS-FXI-L$_{Rx}$ through Phase 1. Following these studies and Bayer's decision to further advance these programs, Bayer will be responsible for all global development, regulatory and commercialization activities for both drugs. We are eligible to receive additional milestone payments as each drug advances toward the market. In total over the term of our collaboration, we are eligible to receive up to $385 million in license fees, milestone payments and other payments. In addition, we are eligible to receive tiered royalties in the low to high twenty percent range on gross margins of both drugs combined. From inception through February 2017, we have generated over $175 million in payments under this collaboration.

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.

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 four drugs in development, including our Phase 3 drug IONIS-TTR$_{Rx}$. We are currently conducting a Phase 3 study for IONIS-TTR$_{Rx}$ and we plan to report data from this study in the second quarter of 2017. GSK has the exclusive option to license drugs resulting from this alliance after Phase 2 proof-of-concept for a license fee, including IONIS-TTR$_{Rx}$. 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.

In addition to IONIS-TTR$_{Rx}$, we have three drugs in development with GSK, including 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. GSK is currently developing IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$, and if GSK exercises its exclusive option for either of these drugs, it will be responsible for all further global development, regulatory and commercialization activities. We are also developing IONIS-GSK4-L$_{Rx}$ which is an antisense drug we designed to treat an ocular disease.

Under our agreement, if GSK successfully develops all four drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and milestone payments of up to nearly $900 million. From inception through February 2017, we have generated more than $155 million in payments under this alliance with GSK. 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 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. We are eligible to receive up to nearly $800 million in milestone payments and license fees for these programs. From inception through February 2017, we generated more than $50 million in payments under this collaboration, including the $10 million license fee we earned in July 2016 when Janssen licensed IONIS-JBI1-2.5$_{Rx}$ from us and a $5 million milestone payment when Janssen selected a development candidate for a second program in December 2016. 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.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration, option and license agreement, Novartis has an exclusive option to develop and commercialize these drugs. Akcea is responsible for completing a Phase 2 dose ranging study and conducting an end-of-Phase 2 meeting with the FDA for each drug. If Novartis exercises an option for one of these drugs, Novartis will be responsible for all further global development, regulatory and commercialization activities for each drug.

Akcea will receive a $75 million upfront payment, of which Akcea will retain $60 million and will pay us $15 million as a sublicense fee under our license agreement with Akcea. Beginning in 2017, we and Akcea will recognize revenue from this collaboration with Novartis. If Novartis exercises its option for a drug, Novartis will pay Akcea a license fee equal to $150 million for each drug it licenses. In addition, Akcea is eligible to receive up to $600 million and $530 million in milestone payments related to AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, respectively. Akcea retains the right to co-commercialize any such drug through its specialized sales force focused on lipid specialists in selected markets. Akcea is also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee.

Additionally, in January 2017, we and Akcea entered into a stock purchase agreement, or SPA, with Novartis. Under the SPA, Novartis purchased 1,631,435 shares of our common stock for $100 million. Additionally, Novartis has an obligation to make a further equity investment of $50 million on or before July 2018 in either our stock at the same premium as its initial investment or in Akcea's stock.

For additional details about our and Akcea's collaboration agreement with Novartis, 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. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013. We are eligible to receive up to $365 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. We are also eligible to receive tiered royalties up to the mid-teens on sales from any product resulting from this alliance. From inception through February 2017, 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 Partnerships

Achaogen, Inc.

In 2006, we exclusively licensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In connection with the license, Achaogen issued to us $1.5 million of Achaogen stock. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. 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. In December 2016, Achaogen announced positive data for its CARE Phase 3 study for plazomicin and that its EPIC Phase 3 study met its primary endpoints. Achaogen plans to submit an NDA, which will include EPIC and CARE data, to the FDA in the second half of 2017 and also plans to submit an MAA to the EMA in 2018. Through February 2017, 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 We are also eligible to receive low single digit royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development and commercialization 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, including FXI and Apo(a) and two other 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 other 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 2017, we have generated over $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 completed a Phase 2a efficacy and safety trial and has also completed 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 January 2017, Atlantic announced that it received agreement from the FDA to initiate a rolling submission of its NDA for alicaforsen. 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. Under the agreement, we could receive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications.

Dynacure, SAS

In October 2016, we entered into a collaboration with Dynacure to discover, develop and commercialize an antisense drug for the treatment of neuromuscular diseases. We and Dynacure will share research responsibilities to identify a drug development candidate. Upon exercising its option to license the drug, Dynacure will assume all responsibility for development and commercialization. Under the terms of the agreement, we obtained a 15 percent equity ownership in Dynacure. If Dynacure advances a target under this collaboration, we could receive cash or equity up to more than $210 million in a license fee and milestone payments for specified development, regulatory and sales events. In addition, we are eligible to receive royalties on future product sales of the drug under this collaboration.

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

In January 2005, we entered into an agreement with OncoGenex to allow for the development of an 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. We are eligible to receive royalties on future product sales of apatorsen. In 2016, we received $1.4 million from OncoGenex related to custirsen, another drug OncoGenex was developing under a collaboration agreement with us. In early 2017, OncoGenex Pharmaceuticals, Inc. entered into a definitive merger agreement under which OncoGenex will acquire Achieve Life Sciences in an all-stock transaction. The merger is expected to close mid-2017. Upon closing OncoGenex Pharmaceuticals, Inc. will be renamed Achieve Life Sciences, Inc.

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 completed a Phase 1 study of RG-012, a drug 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.

The University of Texas MD Anderson Cancer Center

In May 2016, we entered into a collaboration agreement with the University of Texas MD Anderson Cancer Center to identify cancer targets and create novel antisense drugs to treat cancer together. In the collaboration, we and MD Anderson will work together to validate novel "undruggable" cancer targets selected based on human genomic data. We will lead the drug discovery efforts against mutually agreed upon novel targets and MD Anderson will lead development activities through clinical proof of concept. Following clinical proof of concept, we and MD Anderson plan to identify a partner to complete development and to commercialize each drug with us leading business development efforts. Under the five year collaboration, we and MD Anderson will evenly share costs specific to our collaboration.

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.

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 research related payments to CHDI up to $4 million, upon completion of our Phase 1/2 study of IONIS-HTT_{Rx}. If Roche licenses IONIS-HTT_{Rx}, we will make an additional payment to CHDI.

Cystic Fibrosis Foundation

In August 2016, we entered into a collaboration agreement with the Cystic Fibrosis Foundation to discover and advance a drug for the treatment of Cystic Fibrosis. Under this agreement, we received upfront payments of $1 million and we are eligible to receive additional milestone payments up to $2 million. Under the agreement, we and the Cystic Fibrosis Foundation will evenly share the first $3 million of costs specific to our collaboration. We are obligated to pay the Cystic Fibrosis Foundation up to $18 million upon achieving specific regulatory and sales events if we advance a drug under our collaboration.

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.

For additional details about our external project funding collaborations, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

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 over $440 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.

Kastle Therapeutics

In May 2016, we entered into an agreement with Kastle under which Kastle acquired the global rights to develop and commercialize Kynamro. Kynamro is approved in the U.S. for use in patients with homozygous familial hypercholesterolemia to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol and non-high density lipoprotein-cholesterol as an adjunct to lipid lowering medications and diet. We previously licensed Kynamro to Sanofi Genzyme. As a result, Sanofi Genzyme earns a three percent royalty on sales of Kynamro and three percent of non-royalty cash payments we receive from Kastle. Under the terms of our agreement with Kastle, we are eligible to receive up to $95 million, which includes a $15 million up-front payment we received in May 2016, a $10 million payment we are entitled to receive in May 2019 and up to $70 million in sales milestones. In December 2016, we amended our agreement with Kastle. As a result of the amendment, through 2017, Kastle will only pay us the three percent royalty we owe Sanofi Genzyme on sales of Kynamro. Beginning in 2018, we will be eligible to earn tiered royalties on global sales of Kynamro that average in the mid to low teens, increasing slightly in years 2020 and 2021. In addition in May 2016, we received a 10 percent common equity position in Kastle. Because realization of our equity position is uncertain, we recorded a full valuation allowance. Through February 2017, we have generated over $15 million from Kastle.

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 SPINRAZA. We are obligated to pay the University of Massachusetts nominal amounts for license fees and milestone payments we receive and a low single digit royalty on sales of SPINRAZA.

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 SPINRAZA. We will pay a portion of any sublicense revenue and post licensing milestone payments we receive from Biogen under our SPINRAZA collaboration up to $11.3 million and a low single digit royalty on sales of SPINRAZA. In 2016, we paid Cold Spring Harbor Laboratory $3.4 million under our agreement.

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

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.

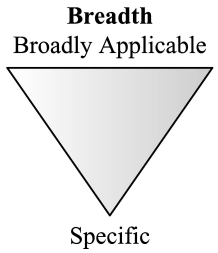
We believe we have sufficient manufacturing capacity to meet our current internal research and development needs, including the Phase 3 clinical trials we have for volanesorsen and IONIS-TTR$_{Rx}$, as well as our current and future obligations under existing agreements with our partners for commercial, research and development needs. We produced the launch supply for SPINRAZA and Biogen is responsible for additional supply. Additionally, we believe we have sufficient manufacturing capacity to supply Akcea with the API and finished drug product for at least the first two years of volanesorsen's commercial launch. 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.

For LICA conjugated drugs, to date, we have manufactured ourselves or through a contract manufacturing organization only limited supplies of LICA for our own preclinical and clinical studies. LICA enables lower doses than unconjugated oligonucleotides. With our expertise in optimizing manufacturing of oligonucleotides, we believe we will develop new processes to scale up manufacturing of these LICA conjugated 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. We own or have exclusively licensed a substantial patent estate with numerous issued patents worldwide protecting our products and, more generally, our platform for development and commercialization of oligonucleotide therapeutics. 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		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, or MOE, modified nucleosides, incorporated into many of our second generation development compounds, as well as our constrained-ethyl nucleosides, or cEt nucleosides incorporated into our Generation 2.5 compounds.

The following are some of our patents in this category in key jurisdictions (US, Europe and Japan):

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.
Europe	EP2314594	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt oligonucleotides and methods of use.
Japan	JP5342881	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.

Antisense Drug Design Motifs

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}, but excluding SPINRAZA, contain this gapmer antisense drug design motif. We own a U.S. patent that covers each of our second generation MOE gapmer antisense drugs until March of 2023.

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 our Generation 2.5 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 vigorously defended EP2410053 and in January 2017, it was upheld with only minor an amendment. The following patents are some examples of our issued patents in this category in key jurisdictions:

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.
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	5’-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers 5’-Methy BNA 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
Japan	JP 5665317	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2’-MOE and bicyclic nucleosides
Europe	EP2673361	OLIGOMERIC COMPOUNDS COMPRISING BICYCLIC NUCLEOTIDES AND USES THEREOF	2032	Gapmer having at least one bicyclic nucleoside, 2’-modified nucleoside, and 2’-deoxynucleoside in either the 5’- or 3’-wing.

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 SPINRAZA

SPINRAZA 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 SPINRAZA, 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 SPINRAZA. Those patents should protect SPINRAZA from generic and antisense innovator competition in the United States until at least 2030 without patent term extension. With Biogen's license of SPINRAZA, we assigned our interest in these patents to Biogen. The table below lists the key U.S. and European issued patents protecting SPINRAZA:

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 SPINRAZA
Europe	1910395	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Sequence and chemistry (full 2'-MOE) of SPINRAZA
United States	7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2027	Oligonucleotides having sequence of SPINRAZA (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 SPINRAZA 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 SPINRAZA

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, if volanesorsen is approved by the FDA, we plan to 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 have allowed claims to the volanesorsen composition in Canada and are pursuing additional patent applications designed to protect volanesorsen worldwide. The table below lists the issued patents in key jurisdictions:

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
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

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 foreign jurisdictions. The table below lists the current issued patents protecting IONIS-TTR$_{Rx}$ in key jurisdictions:

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$_{Rx}$
United States	9,399,774	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Methods of treating transthyretin amyloidosis by administering IONIS-TTR$_{Rx}$
Japan	JP5896175	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Composition of IONIS-TTR$_{Rx}$

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. Additional claims have granted in Europe covering the use of 5-10-5 MOE gapmers targeting ApoB. We obtained issued claims to the specific antisense sequence and chemical composition of Kynamro in key jurisdictions. The issued U.S. claims covering the composition 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 worldwide. With Kastle's acquisition of the global rights to develop and commercialize of Kynamro, we assigned our interest in these patents to Kastle. The table below lists the issued patent claims designed to protect Kynamro in key jurisdictions:

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.
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
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

We seek patent protection in significant markets and/or countries for each drug in development. We also seek to maximize patent term. In some cases, the patent term can be extended to recapture a portion of the term lost during FDA regulatory review. The patent exclusivity period for a drug will prevent generic drugs from entering the market. Patent exclusivity depends on a number of factors including initial patent term and available patent term extensions based upon delays caused by the regulatory approval process.

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 the manufacture, development and 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 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 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 approved products and 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 newly marketed drug SPINRAZA, our Phase 3 drugs, volanesorsen and IONIS-TTR$_{Rx}$, and our additional approved drug Kynamro is set forth below.

SPINRAZA

We believe that the following drugs could compete with SPINRAZA:

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	As of September 15, 2016, the 12 patients taking the proposed therapeutic dose of AVXS-101 were event free and were a median age of 17.3 months at their last follow up appointment. Additionally, two-thirds of these patients had achieved the ability to sit unassisted, including one patient whose achievement of this milestone was confirmed after September 15.	Well tolerated to date
RG7916	PTC Therapeutics/ Roche/ SMA Foundation	A small molecule drug that modulates splicing of the SMN2 gene	2	Oral	None reported	None reported
LMI070	Novartis	A small molecule drug that modulates splicing of the SMN2 gene	1/2	Oral	None reported	Study was placed on clinical hold in May 2016 due to safety findings reported in animal studies. The clinical hold was subsequently removed.

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

We believe that SPINRAZA's closest competitor is AVXS-101. AVXS-101 is currently in a Phase 1 study for infants with Type 1 SMA. AveXis announced that it will have a single-arm design for its pivotal study in SMA Type 1 patients and plans to use natural history as a comparator. The study is expected to initiate in the first half of 2017 and enroll 20 patients. AveXis has also announced that following a meeting with the CHMP it will have a single-arm design for its European pivotal study with natural history as a comparator. This study is expected to initiate in the second half of 2017 and enroll 30 patients. 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 and that they will switch to commercial GMP drug for their study in Type 2 patients. Further, no company has yet to successfully commercialize a gene therapy, which may create significant barriers for AVXS-101.

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, not pursing in the U.S.	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	Novelion Therapeutics	A synthetic form of the hormone leptin	3	Reconstituted subcutaneous injection	44.4% mean reduction in triglycerides at four months in patients with abnormal triglyceride levels	Anti-metreleptin antibodies, hypoglycemia, hypersensitivity, risk of T-cell lymphoma
Gemcabene	Gemphire Therapeutics	Monocalcium salt of a dialkyl ether dicarboxylic acid	2	Oral, once-daily	In a post hoc analysis (n=9) of patients with triglycerides >500 mg/dl, reductions of 59% and 60% from 150mg and 300mg doses, respectively, were observed	In a recent study, in the gemcabene-treatment group, the most frequently occurring adverse events were headache and infection

(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 U.S. Metreleptin is being tested in FPL patients who also have NASH. In December 2016, Novelion submitted a marketing authorization application to the EMA seeking approval for Metreleptin as replacement therapy to treat complications of leptin deficiency in a small subset of FPL patients and in patients with generalized lipodystrophy, or GL. An investigator-sponsored study is currently ongoing with the support of Novelion to evaluate Metreleptin in FPL patients who also have NASH. Metreleptin does not affect ApoC-III levels. ApoC-III levels have been shown to be elevated in FPL patients, and directly correlate to triglyceride levels. Gemcabene is being studied in patients with severe hypertriglyceridemia, defined as triglycerides above 500 mg/dL and Gemphire expects to report top-line results from its Phase 2 study in the fourth quarter of 2017. 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. If regulatory authorities require us to implement platelet monitoring procedures in the commercial setting, which have yet to be determined, it could impact the future competitive profile of volanesorsen.

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
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 GalNAC to inhibit TTR mRNA in liver cells	1	Monthly or quarterly	In healthy volunteers, a single dose showed mean max TTR knockdown of 97%, up to 98%	Injection site reactions were reported

(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 competitor is patisiran. 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. In October 2016, Alnylam discontinued development of revusiran, its drug for the cardiomyopathy form of TTR amyloidosis, due to a safety finding in its Phase 3 study. Revusiran was a subcutaneously administered RNAi molecule that was Alnylam's first generation GalNAc drug and was dosed at 500 mg per week as two subcutaneous injections. Alnylam completed Phase 1 studies of its second generation GalNAC, ALN-TTRsc02. 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$_{Rx}$ could be the first RNA-targeted drug on the market. We also believe that the overall product profile of IONIS-TTR$_{Rx.}$ as a once weekly, subcutaneous injection with no pretreatment is superior to the drugs detailed above, however potential platelet monitoring requirements in the commercial setting, which have yet to be determined, could impact the future competitive profile of IONIS-TTR$_{Rx}$.

Kynamro

Kynamro is currently approved in the U.S. 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	Novelion Therapeutics	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 21, 2017, we employed 435 people, including 28 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 21, 2017:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	71	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D.	62	Director, Chief Operating Officer
C. Frank Bennett, Ph.D.	60	Senior Vice President, Antisense Research
Sarah Boyce	45	Chief Business Officer
Richard S. Geary, Ph.D.	59	Senior Vice President, Development
Elizabeth L. Hougen	55	Senior Vice President, Finance and Chief Financial Officer
Brett P. Monia, Ph.D.	55	Senior Vice President, Drug Discovery and Corporate Development
Patrick R. O'Neil, Esq.	43	Senior Vice President, Legal, General Counsel, Chief Compliance Officer 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, Chief Compliance Officer and Corporate Secretary

Mr. O’Neil was promoted to Senior Vice President, Legal and General Counsel in January 2013. Mr. O'Neil also serves as our Chief Compliance Officer and 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, we are not likely to generate revenues or become consistently profitable.

Even if our drugs are authorized for marketing, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$, 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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. For example, we expect the product label for volanesorsen and IONIS-TTR$_{Rx}$ will require periodic platelet monitoring, which could negatively affect our ability to attract and retain patients for these drugs. 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, unaffordable.

If we or our partners fail to compete effectively, our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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;
- reimbursed more favorably by government and other third-party payors 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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, AVXS-101, RG7800, RG7916, and LMI070 could compete with SPINRAZA, Glybera and metreleptin could compete with volanesorsen, patisiran, tafamadis, diflunisal, tolcapone and ALN-TTRsc02 could compete with IONIS-TTR$_{Rx}$ and Glybera, lomitapide and evolocumab could compete with Kynamro.

Following approval, our drugs, including SPINRAZA, volanesorsen and IONIS-TTR$_{Rx}$ 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$, and Kynamro.

We depend on our collaboration with Biogen for the development and commercialization of SPINRAZA.

We have entered into a collaborative arrangement with Biogen to develop and commercialize SPINRAZA. We entered into this collaboration primarily to:

- fund our development activities for SPINRAZA;
- seek and obtain regulatory approvals for SPINRAZA; and
- successfully commercialize SPINRAZA.

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA, and successfully commercialize SPINRAZA. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaboration. If Biogen fails to further develop SPINRAZA, obtain additional regulatory approvals for SPINRAZA, or commercialize SPINRAZA, or if Biogen’s efforts are not effective, our business may be negatively affected.

Our collaboration with Biogen may not continue for various reasons. Biogen can terminate our collaboration at any time. If Biogen stops developing or commercializing SPINRAZA, we would have to seek additional funding and SPINRAZA's development and commercialization may be harmed or delayed.

Our collaboration with Biogen may not result in the successful commercialization of SPINRAZA. If Biogen does not successfully commercialize SPINRAZA, we will receive limited revenues for SPINRAZA.

If government or other third-party payors fail to provide adequate coverage and payment rates for our drugs, including SPINRAZA, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, our revenue will be limited.

In both domestic and foreign markets, sales of our current and future products will depend in part upon the availability of coverage and reimbursement from third-party payors. The majority of patients in the United States who would fit within our target patient populations for our drugs have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our drugs affordable.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. For example, in the United States, recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries and proposed federal legislation designed to, among other things, reform government program reimbursement methodologies for drug products and bring more transparency to drug pricing. Third-party coverage and reimbursement for our products or drugs may not be available or adequate in either the United States or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If Biogen cannot manufacture finished drug product for SPINRAZA or the post-launch supply of the active drug substance for SPINRAZA, SPINRAZA may not achieve or maintain commercial success.

Biogen is responsible for the long term supply of both SPINRAZA drug substance and finished drug product. Biogen may not be able to reliably manufacture SPINRAZA drug substance and drug product to support the long term commercialization of SPINRAZA. If Biogen cannot reliably manufacture SPINRAZA drug substance and drug product, SPINRAZA may not achieve or maintain commercial success, which will harm our ability to generate revenue.

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

We cannot guarantee that any of our drugs, including volanesorsen and IONIS-TTR$_{Rx}$, will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA or 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 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 our drugs. It is possible that regulatory agencies will not approve our drugs including, volanesorsen and IONIS-TTR$_{Rx}$ for marketing or additional marketing authorizations for SPINRAZA or 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 SPINRAZA, volanesorsen and IONIS-TTR$_{Rx}$, 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. For example, the FDA or foreign regulatory authorities could claim that we have not tested volanesorsen in a sufficient number of patients to demonstrate volanesorsen is safe and effective in patients with FCS or FPL to support an application for marketing authorization, especially since a small number of patients in the APPROACH FCS study experienced severe thrombocytopenia, a condition where the patient has severely low platelet levels. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays.

Failure to receive marketing authorization for our drugs, volanesorsen and IONIS-TTR$_{Rx}$, or additional authorizations for SPINRAZA or 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 volanesorsen and IONIS-TTR$_{Rx}$. If any of our drugs in clinical studies, including volanesorsen and IONIS-TTR$_{Rx}$, 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 volanesorsen and IONIS-TTR$_{Rx}$. 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;
- patients who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;
- 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.

In addition, our current drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$, and Kynamro, are chemically similar to each other. As a result, a safety observation we encounter with one of our drugs could have, or be perceived by a regulatory authority to have, an impact on a different drug we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our drugs or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our drugs: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments.

Any failure or delay in the clinical studies, including the Phase 3 studies for volanesorsen and IONIS-TTR$_{Rx}$, 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 SPINRAZA, volanesorsen and IONIS-TTR$_{Rx}$, or result in enforcement action after authorization that could limit the commercial success of our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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 volanesorsen and IONIS-TTR$_{Rx}$. 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 volanesorsen and IONIS-TTR$_{Rx}$ or additional authorizations for SPINRAZA and 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, 2016, we had an accumulated deficit of approximately $1.2 billion and stockholders' equity of approximately $99.6 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.

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, Novartis 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, Novartis 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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 SPINRAZA, volanesorsen and IONIS-TTR$_{Rx}$ 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, 2016, we had cash, cash equivalents and short-term investments equal to $665.2 million. If we do not meet our goals to successfully commercialize our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ 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:

- marketing approvals and successful commercial launch for SPINRAZA;
- 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 volanesorsen and IONIS-TTR$_{Rx}$.

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. 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, 2016, the market price of our common stock ranged from $19.59 to $62.68 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 SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro. 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.

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

Despite the implementation of security measures, our internal computer systems, and those of our clinical research organizations, manufacturers, commercial partners and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If issues were to arise and cause interruptions in our operations, it could result in a material disruption of our drug programs. For example, the loss of clinical study data from completed or ongoing clinical studies could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development or commercialization of our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro could be harmed or delayed.

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 10.3 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 Select 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 21, 2017, 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 each year from 2017 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 volanesorsen and IONIS-TTR$_{Rx}$. We produced the launch quantities for SPINRAZA and now Biogen is responsible for further manufacturing.

Item 3. Legal Proceedings

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, which are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead asked 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. In the trial for this case held in March 2016, the jury upheld all ten of the asserted claims of the patents-in-suit. The jury then decided that we and Merck are entitled to four percent of $5 billion in past sales of sofosbuvir. Gilead has stated it would appeal the jury’s finding of validity. In the meantime, Gilead asserted two additional non-jury defenses: waiver and unclean hands. Although the judge rejected the waiver defense, she granted Gilead’s motion claiming that the patents are unenforceable against it under the doctrine of unclean hands. We believe this ruling is contrary to the relevant law and the facts of the case. Accordingly, in July 2016, together with Merck we appealed the decision. Gilead cross-appealed on the issue of validity. The appeal is pending before the Court of Appeals for the Federal Circuit. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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

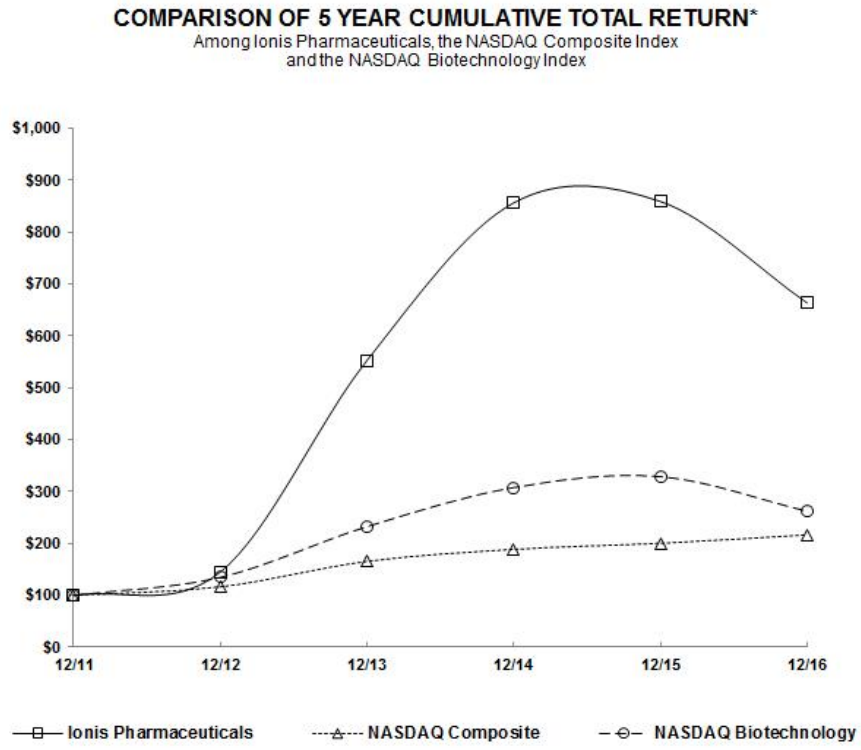
Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "IONS." Prior to our name change in December 2015, we traded under the symbol "ISIS." The following table presents quarterly information on the price range of our common stock. This information indicates the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

	HIGH	LOW
2016		
First Quarter	$ 62.68	$ 30.93
Second Quarter	$ 46.75	$ 19.59
Third Quarter	$ 40.82	$ 23.26
Fourth Quarter	$ 57.00	$ 24.58
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

As of February 21, 2017, there were approximately 587 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-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 144.80	$ 552.57	$ 856.31	$ 858.95	$ 663.38
NASDAQ Composite Index	$ 100.00	$ 116.41	$ 165.47	$ 188.69	$ 200.32	$ 216.54
NASDAQ Biotechnology Index	$ 100.00	$ 134.68	$ 232.37	$ 307.67	$ 328.76	$ 262.08

(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,				
	2016	2015	2014	2013	2012
Consolidated Statement of Operations Data:					
Revenue	$ 346,620	$ 283,703	$ 214,161	$ 147,285	$ 102,049
Research, development and patent expenses	$ 344,320	$ 322,292	$ 241,751	$ 184,033	$ 158,458
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (86,556)	$ (88,278)	$ (38,984)	$ (60,644)	$ (65,478)
Basic and diluted net loss per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (0.72)	$ (0.74)	$ (0.33)	$ (0.55)	$ (0.65)
Shares used in computing basic and diluted net loss per share	120,933	119,719	117,691	110,502	100,576

	As of December 31,				
	2016	2015	2014	2013	2012
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments	$ 665,223	$ 779,183	$ 728,832	$ 656,761	$ 374,446
Working capital	$ 664,148	$ 688,127	$ 721,265	$ 637,698	$ 349,116
Investment in Regulus Therapeutics Inc.	$ 2,414	$ 24,792	$ 81,881	$ 52,096	$ 33,622
Total assets	$ 912,467	$ 947,900	$ 946,471	$ 843,267	$ 541,382
Long-term debt and other obligations, less current portion	$ 679,118	$ 598,234	$ 588,896	$ 367,065	$ 284,294
Accumulated deficit	$ (1,181,428)	$ (1,094,872)	$ (1,006,594)	$ (967,610)	$ (906,966)
Stockholders' equity	$ 99,565	$ 200,790	$ 257,780	$ 378,390	$ 182,766

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 we are fundamentally changing medicine with the goal to transform the lives of those suffering from severe, often life-threatening, diseases. The recent U.S. approval of SPINRAZA for pediatric and adult patients with SMA highlights our progress toward this goal. Our pipeline also contains two near-term potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential. We plan to report data from our Phase 3 study of volanesorsen in patients with familial chylomicronemia, or FCS in the first quarter of 2017. We also plan to report data from our Phase 3 study of IONIS-TTR_{Rx} in patients with FAP in the second quarter of 2017.

With FDA approval in December 2016, SPINRAZA injection became the first and only approved drug to treat pediatric and adult patients with SMA. SMA is a leading genetic cause of death in infants and toddlers that is marked by progressive, debilitating muscle weakness. Biogen has filed for marketing authorization in the EU, Japan, Australia and Canada, and plans to file in other countries this year. The European Medicines Agency, or EMA, is reviewing the SPINRAZA marketing application under accelerated assessment. Biogen estimates that there are approximately 20,000 patients with SMA in the U.S., EU and Japan, with a large percentage in the United States.

Akcea Therapeutics, Inc. is our wholly owned subsidiary focused on developing and commercializing volanesorsen and three other clinical-stage drugs for serious cardiometabolic diseases caused by lipid disorders, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Each of these four drugs could potentially treat multiple patient populations. Moving these drugs into a company that we own allows us to retain substantial value from them and ensures our core focus remains on innovation. Akcea is assembling the global infrastructure to continue developing the drugs in its pipeline, to commercialize them with a focus on lipid specialists as the primary call point and to provide the specialized patient and physician support required to address rare disease patient populations.

We and Akcea are developing volanesorsen to treat two severe and rare, genetically defined diseases, FCS and familial partial lipodystrophy, or FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. The clinical development program for volanesorsen consists of three Phase 3 studies called APPROACH, BROADEN and COMPASS. The APPROACH study, in patients with FCS, is fully enrolled and we plan to report data from it in the first quarter of 2017. We plan to file for marketing authorization in the U.S., Europe and Canada in 2017 if the data are positive. We also recently completed the COMPASS study in patients with triglycerides above 500 mg/dL to expand the exposure database for volanesorsen to support global regulatory filings. In December 2016, we reported that the COMPASS study met its primary endpoint of a statistically significant 71% mean reduction in triglycerides in volanesorsen-treated patients. Safety in this study was supportive of continuing development. We estimate that FCS and FPL each affect 3,000 to 5,000 patients globally. If approved, we plan to commercialize volanesorsen for both FCS and FPL through Akcea.

IONIS-TTR$_{Rx}$ is potentially a first-in-class and best-in-class drug for the treatment of all forms of transthyretin, or TTR, amyloidosis, a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body. We are evaluating IONIS-TTR$_{Rx}$ in an ongoing Phase 3 study, NEURO-TTR, in patients with FAP. More than half of these patients also have TTR amyloid cardiomyopathy. As part of our Phase 3 study, we are evaluating cardiomyopathy in this subset of patients by cardiac imaging and biomarkers which will provide data on cardiovascular endpoints. Together the polyneuropathy and cardiomyopathy forms of TTR amyloidosis represent a large commercial opportunity for IONIS-TTR$_{Rx}$. We plan to have data from the NEURO-TTR study in the second quarter of 2017. We and GSK, our partner for IONIS-TTR$_{Rx}$, are preparing to file for marketing authorization if these data are positive. GSK is preparing to commercialize IONIS-TTR$_{Rx}$.

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 diseases that have inadequate treatment options. We are addressing a broad spectrum of diseases from common diseases affecting millions, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease, to rare diseases, such as amyotrophic lateral sclerosis and Huntington's disease. 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 AKCEA-APO(a)-L$_{Rx}$ represent 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. AKCEA-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.

The depth of our knowledge and expertise with antisense technology, together with our strong financial position, provides us the flexibility to determine the optimal development and commercialization strategy to maximize the near- and longer-term value of our drugs. We have distinct partnering strategies that we employ based on the specific drug, therapeutic area and expertise and resources our potential partners may bring to the collaboration. 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 substantial resources and expertise that augment and build upon our internal capabilities. 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 for which our partners can provide expertise, tools and resources to complement our drug discovery efforts. We also have partnerships with Bayer, GSK, Janssen, Novartis and Roche. Each of these companies brings significant expertise and global resources to develop and potentially commercialize the drugs under each partnership. We also form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas. 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 R&D revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Our R&D revenue has consistently grown year over year since 2011. We have the potential to earn nearly $13 billion in future milestone payments and licensing fees from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out or royalty arrangements. With the approval of SPINRAZA in the U.S., we are adding commercial revenue from SPINRAZA royalties to our existing R&D revenue base. Looking forward, we have the potential to increase our commercial revenue from SPINRAZA royalties if Biogen achieves marking authorization in additional countries. We also have the potential to further increase our commercial revenue with volanesorsen product sales and IONIS-TTR$_{Rx}$ royalties. We believe we have the key elements in place to achieve sustained long-term financial growth, including multiple drivers of revenue; a mature, broad and rapidly-advancing clinical pipeline; a partnership strategy that leverages partner resources; and an innovative drug technology that we continue to deploy across a range of therapeutic areas to address both rare and large patient populations.

Financial Highlights

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

	2016	2015	2014
Total revenue	$346,620	$283,703	$214,161
Total operating expenses	$392,936	$359,465	$261,891
Loss from operations	$ (46,316)	$ (75,762)	$ (47,730)
Net loss	$ (86,556)	$ (88,278)	$ (38,984)
Cash, cash equivalents and short-term investments	$665,223	$779,183	$728,832

During 2016 we increased our revenue by 22 percent over 2015. Further, our R&D revenue has consistently grown year over year since 2011. The substantial increase in 2016 revenue was primarily due to the license of SPINRAZA by Biogen and its subsequent approval by the FDA. With the approval of SPINRAZA in the U.S., we are adding commercial revenue from SPINRAZA royalties to our broad base of R&D revenue. In addition, in 2016 we continued to advance our pipeline of drugs to treat both rare and more prevalent diseases across multiple therapeutic areas. During each of the years above, we were conducting several Phase 3 studies for SPINRAZA, volanesorsen and IONIS-TTR$_{Rx}$ along with advancing numerous earlier-stage drugs. During 2016, we received more than $190 million from our partners, reflecting the successes of our partnered programs and drugs. 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. We believe our strong financial position will enable us to continue to execute on our corporate goals throughout 2017.

Business Segments

In 2015, we began reporting our financial results in two reportable segments, Ionis Core, 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 novel drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. Akcea's goal is to become the premier company offering treatments for inadequately treated lipid disorders. Moving our lipid drugs into a company that we own 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;
- Estimating our net deferred income tax asset valuation allowance; and
- Determining the fair value of convertible debt without the conversion feature.

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}$. At the onset of the agreement, we were responsible for completing the development services for IONIS-FXI$_{Rx}$, and for providing an initial supply of active pharmaceutical ingredient, or API. Since the agreement had multiple elements, we evaluated the deliverables in this arrangement when we entered into the agreement and determined that certain deliverables have stand-alone value. In February 2017, we expanded our collaboration with Bayer, refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements for further information.

Below is a list of the three units of accounting under our original 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 license we granted to Bayer has stand-alone value because it gives Bayer the exclusive 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 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 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 performed and the API we delivered 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 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 10 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 in the second quarter of 2015 because we delivered the license and earned the revenue;
- We recognized the amount attributed to the development services for IONIS-FXI$_{Rx}$ over the period of time we performed the services; and
- We are recognizing the amount attributed to the API supply as 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 partner. 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, in 2012 and 2013, we entered into several collaboration agreements with Biogen:

- In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA (nusinersen) for SMA. As part of the collaboration, we received a $29 million upfront payment and were responsible for global development of SPINRAZA 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 neurodegenerative 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.

Under our collaboration agreement, in July 2016, Biogen exercised its option to license SPINRAZA. Our other collaboration agreements with Biogen give Biogen the option to license one or more drugs resulting from the specific collaboration. Similar to our collaboration agreement for SPINRAZA, if Biogen exercises an option, it will pay us a license fee and will assume future global 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 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.

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 paragraphs.

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. 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.

Option to license

In several of our collaboration agreements, we provide our partner with an option to obtain a license to one or more of our drugs. When we have a multiple element arrangement that includes an option to obtain a license, we evaluate if the option is a deliverable at the inception of the arrangement. We do not consider the option to be a deliverable if we conclude that it is substantive and not priced at a significant and incremental discount. We consider an option substantive if, at the inception of the arrangement, we are at risk as to whether our collaborative partner will choose to exercise its option to obtain the license. In those circumstances, we do not include the associated license fee in the allocable consideration at the inception of the agreement. Rather, we account for the license fee when our partner exercises its option. For example, during 2016, we earned license fee revenue when three of our partners, AstraZeneca, Biogen and Janssen, exercised their option to license three of our drugs, which under the respective agreements we concluded to be substantive options at inception. As a result, in 2016 we recognized $98 million in research and development revenue under collaborative agreements on our statement of operations as these amounts relate to drugs in development under research and development collaboration arrangements.

Licensing and royalty revenue

We often enter into agreements to license or sell our proprietary patent rights on an exclusive or non-exclusive basis in exchange for upfront fees, milestone payments and/or royalties. We generally recognize as revenue immediately those payments for which we have no significant future performance obligations and for which we are reasonably assured of collecting the resulting receivable.

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.

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). At December 31, 2016, we held investments in two publicly traded companies, Antisense Therapeutics Limited and Regulus. 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 cost method investments in three companies, Kastle Therapeutics, Atlantic Pharmaceuticals Limited and Dynacure, SAS. Realization of our equity position in these companies 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 and 2014, we realized a net gain on investments of $20.3 million, and $21.2 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.

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.

Convertible Debt

We account for our convertible debt instruments 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 a similar debt instrument does not exist, we estimate the 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 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, which resulted in us recording the debt at a discount. At January 1, 2016, we adopted the amended accounting guidance to simplify the presentation of debt issuance costs. As a result of this amended guidance, we reclassed our debt issuance costs in all periods presented from other assets to the net carrying amount of the related debt liability on our consolidated balance sheet. We are amortizing our debt issuance costs and our 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*, in the Notes to the Consolidated Financial Statements.

Results of Operations

Years Ended December 31, 2016 and December 31, 2015

Revenue

Total revenue for 2016 was $346.6 million, compared to $283.7 million for 2015. See below for our discussion of the changes in our revenue.

Our revenue for 2016 consisted of the following:

- $170 million from Biogen for FDA approval, licensing and advancing the Phase 3 program for SPINRAZA;
- $53 million from AstraZeneca for advancing and licensing IONIS-KRAS-2.5$_{Rx}$ and selecting IONIS-AZ4-2.5-L$_{Rx}$ to move into development;
- $15 million from Janssen for licensing IONIS-JBI1-2.5$_{Rx}$ and selecting an additional development candidate;
- $15 million from Kastle Therapeutics for acquiring Kynamro;
- $7.5 million from Biogen for advancing IONIS-SOD1$_{Rx}$. IONIS-BIIB4$_{Rx}$ and IONIS-BIIB6$_{Rx;}$
- $61 million from the amortization of upfront fees; and
- $25.1 million primarily from the manufacturing services Ionis performed for its partners.

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 2016 was $325.9 million, compared to $281.4 million for 2015.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for 2016 was $20.7 million, compared to $2.3 million for 2015. Our revenue from licensing and royalties for 2016 primarily consisted of the $15 million we earned from Kastle when it acquired the global rights to develop and commercialize Kynamro.

Operating Expenses

Operating expenses for 2016 were $392.9 million, and increased compared to $359.5 million for 2015 as a result of the following:

- During 2016, we were conducting five Phase 3 studies and three open-label extension studies for SPINRAZA, IONIS-TTR$_{Rx}$ and volanesorsen. We completed target enrollment in four of these Phase 3 studies at the end of 2015, and as a result, these studies were in their most expensive stage during 2016.
- Akcea's operating expenses increased as it continued to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen, if approved for marketing.
- Our non-cash compensation expense related to equity awards increased due to an increase in the exercise price of the stock options we have granted over the past several years.

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

	Year Ended December 31,	
	2016	**2015**
Ionis Core	$ 260,233	$ 256,674
Akcea Therapeutics	73,363	46,252
Elimination of intercompany activity	(12,768)	(2,775)
Subtotal	320,828	300,151
Non-cash compensation expense related to equity awards	72,108	59,314
Total operating expenses	$ 392,936	$ 359,465

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,	
	2016	2015
Research, development and patent expenses	$ 289,221	$ 278,654
Non-cash compensation expense related to equity awards	55,099	43,638
Total research, development and patent expenses	$ 344,320	$ 322,292

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

	Year Ended December 31,	
	2016	2015
Ionis Core	$ 238,106	$ 240,061
Akcea Therapeutics	63,883	41,368
Elimination of intercompany activity	(12,768)	(2,775)
Subtotal	289,221	278,654
Non-cash compensation expense related to equity awards	55,099	43,638
Total research, development and patent expenses	$ 344,320	$ 322,292

For 2016, our total research, development and patent expenses were $289.2 million, compared to $278.7 million for 2015, and were slightly higher primarily due to the progression of our drugs in Phase 3 development. 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,	
	2016	2015
Antisense drug discovery expenses	$ 51,028	$ 49,331
Non-cash compensation expense related to equity awards	13,589	11,914
Total antisense drug discovery expenses	$ 64,617	$ 61,245

Antisense drug discovery expenses for 2016 were $51.0 million and were slightly higher compared to $49.3 million for 2015. 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,	
	2016	2015
SPINRAZA	$ 43,868	$ 35,164
Volanesorsen	26,285	21,348
IONIS-TTR$_{Rx}$	22,939	19,560
Other antisense development projects	42,999	60,028
Development overhead expenses	42,966	36,117
Total antisense drug development, excluding non-cash compensation expense related to equity awards	179,057	172,217
Non-cash compensation expense related to equity awards	21,380	16,208
Total antisense drug development expenses	$ 200,437	$ 188,425

Antisense drug development expenses were $179.1 million for 2016 compared to $172.2 million for 2015. Expenses for 2016 were slightly higher compared to 2015 primarily due to the progression of our drugs in Phase 3 development. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. Our other antisense development project expenses declined in 2016, compared to 2015, primarily due to completing the FOCUS FH Phase 3 study of Kynamro in 2015 and our shift to LICA drugs, which are in less expensive stages of development. 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,	
	2016	2015
Ionis Core	$ 132,418	$ 137,092
Akcea Therapeutics	46,639	35,125
Non-cash compensation expense related to equity awards	21,380	16,208
Total antisense drug development expenses	$ 200,437	$ 188,425

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,	
	2016	2015
Manufacturing and operations expenses	$ 30,148	$ 28,588
Non-cash compensation expense related to equity awards	6,113	4,563
Total manufacturing and operations expenses	$ 36,261	$ 33,151

Manufacturing and operations expenses were $30.1 million for 2016 and were slightly higher compared to $28.6 million for 2015. 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,	
	2016	2015
Ionis Core	$ 27,341	$ 25,632
Akcea Therapeutics	15,455	5,611
Elimination of intercompany activity	(12,648)	(2,655)
Subtotal	30,148	28,588
Non-cash compensation expense related to equity awards	6,113	4,563
Total manufacturing and operations expenses	$ 36,261	$ 33,151

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, informatics 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,	
	2016	2015
Personnel costs	$ 11,560	$ 10,210
Occupancy	7,891	7,854
Patent expenses	3,945	2,785
Depreciation and amortization	245	2,911
Insurance	1,344	1,320
Other	4,003	3,438
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	28,988	28,518
Non-cash compensation expense related to equity awards	14,017	10,953
Total R&D support expenses	$ 43,005	$ 39,471

R&D support expenses for 2016 were $29.0 million and were essentially flat compared to $28.5 million for 2015. 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,	
	2016	2015
Ionis Core	$ 27,319	$ 28,005
Akcea Therapeutics	1,789	633
Elimination of intercompany activity	(120)	(120)
Subtotal	28,988	28,518
Non-cash compensation expense related to equity awards	14,017	10,953
Total R&D support expenses	$ 43,005	$ 39,471

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,	
	2016	2015
General and administrative expenses	$ 31,607	$ 21,497
Non-cash compensation expense related to equity awards	17,009	15,676
Total general and administrative expenses	$ 48,616	$ 37,173

General and administrative expenses were $31.6 million for 2016 and increased compared to $21.5 million for 2015 primarily due to Akcea continuing to build its organization. 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,	
	2016	2015
Ionis Core	$ 22,127	$ 16,613
Akcea Therapeutics	9,480	4,884
Non-cash compensation expense related to equity awards	17,009	15,676
Total general and administrative expenses	$ 48,616	$ 37,173

Akcea Therapeutics, Inc.

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

	Year Ended December 31,	
	2016	**2015**
Development and patent expenses	$ 63,883	$ 41,368
General and administrative expenses	9,480	4,884
Total operating expenses, excluding non-cash compensation expense related to equity awards	73,363	46,252
Non-cash compensation expense related to equity awards	10,149	6,496
Total Akcea Therapeutics operating expenses	$ 83,512	$ 52,748

Operating expenses for Akcea were $73.4 million for 2016 and increased compared to $46.3 million for 2015. The increase in expenses was primarily because Akcea was conducting more and later-stage clinical studies in 2016 than it conducted in 2015, including the continuation of the Phase 3 studies for volanesorsen in patients with FCS and FPL. In 2016, we began charging Akcea for Ionis' internal development costs associated with the ongoing work we are performing for Akcea's drugs. For each period presented, we allocated a portion of Ionis' R&D support expenses, which are included in research and development expenses in the table above, to Akcea for work we performed on behalf of Akcea.

Akcea also incurred additional general and administrative costs as it continued to build its organization and advance the pre-commercialization activities necessary to launch volanesorsen, if approved for marketing. We expect that these costs will continue to increase in 2017. For each year presented, we 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 Akcea's behalf.

All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for 2016 was $5.4 million compared to $4.3 million for 2015. Investment income increased primarily due to an improvement in the market conditions during 2016 compared to 2015.

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,	
	2016	**2015**
2¾ percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 2,761	$ 2,530
Interest expense payable in cash	1,684	1,684
1 percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	22,354	20,678
Interest expense payable in cash	5,000	4,999
Non-cash interest expense for long-term financing liability	6,693	6,665
Other	303	176
Total interest expense	$ 38,795	$ 36,732

Interest expense for 2016 was $38.8 million, and was relatively flat compared to $36.7 million for 2015. In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. As a result of this exchange, we expect cash interest expense in 2017 to be essentially flat compared to 2016 because we increased the principal outstanding on our debt but significantly lowered our interest rate.

Gain on Investment in Regulus Therapeutics Inc.

In 2015, we recorded a gain on our investment in Regulus of $20.2 million related to our sale of a portion of our Regulus common stock.

Early Retirement of Debt

As a result of the debt exchange we completed in December 2016, we recorded a $4.0 million non-cash loss on early retirement of debt, reflecting the early retirement of the majority of our remaining 2¾ percent convertible notes in December 2016. We did not recognize any loss on early retirement of debt in 2015.

Income Tax Expense (Benefit)

In 2016, we recorded a net tax expense of $2.9 million, compared to $0.4 million in 2015. Our tax expense increased in 2016 compared to 2015 primarily due to the taxable income resulting from our strong financial performance in 2016 and excess tax benefits related to share-based compensation. Included in our tax expense for 2015, is $4.3 million of tax benefit we recorded in 2015 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. 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.

Net Loss and Net Loss per Share

Net loss for 2016 was $86.6 million, compared to $88.3 million for 2015. Basic and diluted net loss per share for 2016 was $0.72 compared to $0.74 for 2015. We had a lower net loss in 2016 primarily due to the increase in revenue earned in 2016 compared to 2015.

Net Operating Loss Carryforward

At December 31, 2016, we had federal and California tax net operating loss carryforwards of approximately $679.8 million and $973.1 million, respectively. Our federal tax loss carryforwards begin to expire in 2024. A portion of our California tax loss carryforwards continued to expire in 2016. At December 31, 2016, we also had federal and California research and development tax credit carryforwards of approximately $189.6 million and $48.0 million, respectively. Our Federal research and development tax credit carryforwards will begin to expire in 2018. Our California research and development tax credit carryforwards are available indefinitely.

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.

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. We earned $115.7 million in milestone payments and $91.2 million when Bayer licensed IONIS-FXI$_{Rx}$ during 2015 compared to milestone payments of $135.0 million in 2014. Our revenue in 2015 was primarily comprised of:

- $91.2 million from Bayer in connection with our exclusive license agreement for IONIS-FXI$_{Rx}$;
- $72.6 million from Biogen for advancing the Phase 3 program for SPINRAZA, advancing IONIS-DMPK-2.5$_{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.

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 was primarily a result of the $9.5 million in 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. The expected increase in operating expenses was primarily due:

- We incurred higher costs associated with our Phase 3 programs for SPINRAZA, volanesorsen and IONIS-TTR$_{Rx}$,
- Akcea's operating expenses increased as it began building its commercial infrastructure and advanced the pre-commercialization activities necessary to successfully launch volanesorsen, if approved for marketing; and
- Our stock compensation expense increased due to the increase in our stock price in January 2015 compared to January 2014 since we grant the majority of our stock options in January.

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

	Year Ended December 31,	
	2015	2014
Ionis Core	$ 256,674	$ 208,811
Akcea Therapeutics	46,252	21,697
Elimination of intercompany activity	(2,775)	—
Subtotal	300,151	230,508
Non-cash compensation expense related to equity awards	59,314	31,383
Total operating expenses	$ 359,465	$ 261,891

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	$ 240,061	$ 195,007
Akcea Therapeutics	41,368	20,901
Elimination of intercompany activity	(2,775)	—
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, total research, development and patent expenses were $278.7 million compared to $215.9 million for 2014, and were higher primarily due to the progression of our drugs we had in Phase 3 trials. 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,	
	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 were $49.3 million for 2015 and were slightly higher compared to $43.6 million for 2014, 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 expenses for our major antisense drug development projects (in thousands):

	Year Ended December 31,	
	2015	2014
SPINRAZA	$ 35,164	$ 19,064
Volanesorsen	21,348	9,337
IONIS-TTR$_{Rx}$	19,560	10,927
Other antisense development products	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 expenditures were $172.2 million for 2015 compared to $120.9 million for 2014. Expenses in 2015 were higher compared to 2014 primarily due to the progression of our three drugs we had in Phase 3 trials.

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

Manufacturing and Operations

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

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

	Year Ended December 31,	
	2015	2014
Ionis Core	$ 25,632	$ 22,425
Akcea Therapeutics	5,611	2,338
Elimination of intercompany activity	(2,655)	—
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

Manufacturing and operations expenses for 2015 were $28.6 million 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.

R&D Support

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	$ 28,005	$ 26,100
Akcea Therapeutics	633	507
Elimination of intercompany activity	(120)	—
Subtotal	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

General and Administrative Expenses

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 for 2015 were $21.5 million and increased compared to $14.6 million for 2014 primarily due to the addition of Akcea and an increase in personnel costs. 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	$ 16,613	$ 13,804
Akcea Therapeutics	4,884	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	$ 41,368	$ 20,901
General and administrative expenses	4,884	796
Total operating expenses, excluding non-cash compensation expense related to equity awards	46,252	21,697
Non-cash compensation expense related to equity awards	6,496	—
Total Akcea Therapeutics operating expenses	$ 52,748	$ 21,697

Akcea's operating expenses were $46.3 million for 2015 and increased compared to $21.7 million for 2014. The increase in expenses was primarily due to Akcea's Phase 3 program for volanesorsen, which continued to advance, and the progression of its other drugs, including AKCEA-APO(a)-L_{Rx} and AKCEA-ANGPTL3$_{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, if approved for marketing. 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 totaled $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 included 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	
	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 in 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.

Gain on Investment in Regulus Therapeutics Inc.

In 2015, we realized 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 $39.0 million for 2014. Basic and diluted net loss per share for the year ended December 31, 2015 was $0.74 compared to $0.33 for 2014. We had a higher net loss in 2015 compared to 2014 primarily due to the increase in expenses related to our drugs we had in Phase 3 studies.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we 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, 2016, we have earned approximately $2.1 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, 2016, 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, 2016, we had cash, cash equivalents and short-term investments of $665.2 million and stockholders' equity of $99.6 million. In comparison, we had cash, cash equivalents and short-term investments of $779.2 million and stockholders' equity of $200.8 million at December 31, 2015. During 2016, we received $192 million in cash from our partners in 2016.

Already in 2017, we have generated more than $250 million, including $175 million from Novartis and $75 million from Bayer.

At December 31, 2016, we had consolidated working capital of $664.1 million compared to $688.1 million at December 31, 2015. During the fourth quarter of 2016, we sold 1.8 million shares of Regulus' stock for total proceeds of $4.5 million.

As of December 31, 2016, our debt and other obligations totaled $774.1 million compared to $644.8 million at December 31, 2015. The increase was primarily due to the additional 1 percent senior convertible notes we issued in December 2016 in exchange for $61.1 million principal amount of our 2¾ percent notes. As a result of the exchange, we kept our cash interest expense essentially flat, reduced the potential dilution from our convertible notes and extended the maturity to November 2021. See Note 3, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for additional information on this transaction.

The following table summarizes our contractual obligations as of December 31, 2016. 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)	$ 719.8	$ 6.9	$ 13.7	$ 699.2	$ —
Financing arrangements (principal and interest payable)	$ 13.4	$ 0.3	$ 13.1	$ —	$ —
Facility rent payments	$ 119.0	$ 6.5	$ 13.9	$ 14.7	$ 83.9
Other obligations (principal and interest payable)	$ 1.2	$ 0.1	$ 0.1	$ 0.1	$ 0.9
Operating leases	$ 22.9	$ 2.1	$ 3.2	$ 2.9	$ 14.7
Total	$ 876.3	$ 15.9	$ 44.0	$ 716.9	$ 99.5

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

1 Percent Convertible Senior 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 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. As a result, the principal balance of the 2¾ percent notes following the repurchase in November 2014 was $61.2 million.

In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. At December 31, 2016, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At December 31, 2016 we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes
Outstanding principal balance	$ 685.5
Original issue date ($500 million of principal)	November 2014
Additional issue date ($185.5 million of principal)	December 2016
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	10.3

Interest is payable semi-annually for the 1 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. 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.

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, after June 1, 2016, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of December 31, 2016 we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which were used to fund our capital equipment needs and is consistent with our historical practice to finance these costs.

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

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.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2016 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 of $100 million in the company to fund Akcea's operations and in January 2017, we provided Akcea with a convertible line of credit for up to $150 million. 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. For example in January 2017, we and Akcea initiated a collaboration with Novartis and we will receive a $75 million upfront payment.

Off-Balance Sheet Arrangements

We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

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, 2016.

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, 2016, 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, 2016.

Attestation Report of the Registered Public Accounting Firm

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2016, 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.

We have audited Ionis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2016, 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, 2016, 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, 2016 and 2015, 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, 2016 of Ionis Pharmaceuticals, Inc. and our report dated March 1, 2017 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 1, 2017

Item 9B. Other Information

Not applicable.

PART III

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 2017 Annual Meeting of Stockholders to be held on May 27, 2017.

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, 2016.

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)	9,177,979	$ 40.48	4,434,959	(b)
Total	9,177,979	$ 40.48	4,434,959	

(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) Of these shares, 585,713 remained available for purchase under the ESPP as of December 31, 2016. 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.

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 72.

(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 1st day of March, 2017.

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)	March 1, 2017
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Chief Operating Officer and Secretary	March 1, 2017
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	March 1, 2017
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 1, 2017
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	March 1, 2017
/s/ JOSEPH KLEIN Joseph Klein, III	Director	March 1, 2017
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	March 1, 2017
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	March 1, 2017
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 1, 2017

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991. - 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.
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed June 17, 2014. - 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.
3.3	Certificate of Amendment to Restated Certificate of Incorporation filed December 18, 2015. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
3.4	Amended and Restated Bylaws. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock. - Filed as an exhibit to Registrant's Report on Form 8-K dated filed December 13, 2000 and incorporated herein by reference.
4.2	Specimen Common Stock Certificate. - 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.
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. - Filed as an exhibit to the Registrant's Report on Form 8-K filed August 13, 2012 and incorporated herein by reference.
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. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 21, 2014 and incorporated herein by reference.
10.1	Form of Indemnity Agreement entered into between the Registrant and its Directors and Officers with related schedule. - 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.
10.2*	Registrant's 1989 Stock Option Plan, as amended. - 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.
10.3*	Registrant's Amended and Restated 2000 Employee Stock Purchase Plan. - 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.
10.4	Form of Employee Assignment of Patent Rights. - 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.
10.5	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. - 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.
10.6	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. - 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.
10.7	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. - 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.
10.8	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. - 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.

10.9 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. - 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.

10.10 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. - 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.

10.11 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. - 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.

10.12 Second Amendment to Lease Agreement dated May 15, 2011 between the Registrant and BMR-Gazelle Court LLC, with First Amendment to Lease Agreement included. - 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.

10.13 Registrant's Amended and Restated 10b5-1 Trading Plan dated September 12, 2013. - 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.

10.14* Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended. - 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.

10.15* Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement. - 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.

10.16* 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. - 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.

10.17* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and Stanley T. Crooke. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 5, 2008 and incorporated herein by reference.

10.18* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and B. Lynne Parshall. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 5, 2008 and incorporated herein by reference.

10.19* Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan - 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.

10.20* Form of Option Agreement under the 2011 Equity Incentive Plan. - 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.

10.21* Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan. - 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.

10.22 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. - 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.

10.23* Form of Option Agreement under the 1989 Stock Option Plan. - 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.

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

10.25 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. - 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.

10.26 Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC. - 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.

10.27 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. - 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.

10.28 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. - 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.

10.29 Amendment No. 1 to Amended and Restated License Agreement between the Registrant and OncoGenex Technologies Inc. dated December 18, 2009. - 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.

10.30 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. - 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.

10.31 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. - 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.

10.32 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. - 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.

10.33 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. - 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.

10.34 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. - 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.

10.35 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. - 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.

10.36 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. - 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.

10.37 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. - 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.

10.38 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. - 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.

10.39 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. - 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.

10.40 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. - 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.

10.41 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. - 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.

10.42 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. - 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.

10.43 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. - 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.

10.44 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. - 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.

10.45 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. - 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.

10.46 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. - 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.

10.47 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. - 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.

10.48 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. - 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.

10.49 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. - 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.

10.50 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. - 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.

10.51 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. - 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.

10.52	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. - 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.
10.53	Line of Credit Agreement between the Registrant and Morgan Stanley Private Bank, National Association dated June 16, 2015. - 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.
10.54	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. - 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.
10.55	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. - 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.
10.56	Amendment No.1 to Loan Documents between the Registrant and Morgan Stanley Private Bank, National Association dated December 30, 2015. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed January 5, 2016 and incorporated herein by reference.
10.57	Amendment No.2 to Line of Credit Agreement between the Registrant and Morgan Stanley Private Bank, National Association dated February 24, 2016. Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2015 and incorporated herein by reference.
10.58	Amendment No.3 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated January 18, 2016. Portions of this exhibit have been omitted and separately filed with the SEC. - Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference.
10.59	Amendment #7 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated March 4, 2016. Portions of this exhibit have been omitted and separately filed with the SEC. - Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference.
10.60	First Amendment to Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 21, 2016. Portions of this exhibit have been omitted and separately filed with the SEC.
10.61	Letter Agreement between the Registrant and Biogen MA Inc. dated October 28, 2016. Portions of this exhibit have been omitted and separately filed with the SEC. Portions of this exhibit have been omitted and separately filed with the SEC.
14.1	Registrant's Code of Ethics and Business Conduct.
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney - Filed as part of the Annual Report on Form 10-K for the year ended December 31, 2013, and incorporated herein by reference.
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, 2016, 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).

* 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.

We have audited the accompanying consolidated balance sheets of Ionis Pharmaceuticals, Inc. as of December 31, 2016 and 2015, 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, 2016. 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, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, 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, 2016, 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 March 1, 2017 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 1, 2017

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

	December 31,	
	2016	**2015**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 84,685	$ 128,797
Short-term investments	580,538	650,386
Contracts receivable	108,043	11,356
Inventories	7,489	6,899
Investment in Regulus Therapeutics Inc.	2,414	24,792
Other current assets	14,763	14,773
Total current assets	797,932	837,003
Property, plant and equipment, net	92,845	90,233
Patents, net	20,365	19,316
Deposits and other assets	1,325	1,348
Total assets	$ 912,467	$ 947,900
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 21,120	$ 28,355
Accrued compensation	24,186	16,065
Accrued liabilities	36,013	28,105
Current portion of long-term obligations	1,185	9,029
Current portion of deferred contract revenue	51,280	67,322
Total current liabilities	133,784	148,876
Long-term deferred contract revenue	91,198	134,306
1 percent convertible senior notes	500,511	339,847
2¾ percent convertible senior notes	124	49,523
Long-term obligations, less current portion	14,926	2,341
Long-term financing liability for leased facility	72,359	72,217
Total liabilities	812,902	747,110
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 121,636,273 and 120,351,480 shares issued and outstanding at December 31, 2016 and December 31, 2015, respectively	122	120
Additional paid-in capital	1,311,229	1,309,107
Accumulated other comprehensive income (loss)	(30,358)	(13,565)
Accumulated deficit	(1,181,428)	(1,094,872)
Total stockholders' equity	99,565	200,790
Total liabilities and stockholders' equity	$ 912,467	$ 947,900

See accompanying notes.

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

	Years Ended December 31,		
	2016	**2015**	**2014**
Revenue:			
Research and development revenue under collaborative agreements	$ 325,898	$ 281,360	$ 202,514
Licensing and royalty revenue	20,722	2,343	11,647
Total revenue	346,620	283,703	214,161
Expenses:			
Research, development and patent expenses	344,320	322,292	241,751
General and administrative	48,616	37,173	20,140
Total operating expenses	392,936	359,465	261,891
Loss from operations	(46,316)	(75,762)	(47,730)
Other income (expense):			
Investment income	5,416	4,302	2,682
Interest expense	(38,795)	(36,732)	(22,209)
Gain on investments, net	56	75	1,256
Gain on investment in Regulus Therapeutics Inc.	—	20,211	19,902
Loss on early retirement of debt	(3,983)	—	(8,292)
Loss before income tax (expense) benefit	(83,622)	(87,906)	(54,391)
Income tax (expense) benefit	(2,934)	(372)	15,407
Net loss	$ (86,556)	$ (88,278)	$ (38,984)
Basic and diluted net loss per share	$ (0.72)	$ (0.74)	$ (0.33)
Shares used in computing basic and diluted net loss per share	120,933	119,719	117,691

See accompanying notes.

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

	Years Ended December 31,		
	2016	**2015**	**2014**
Net loss	$ (86,556)	$ (88,278)	$ (38,984)
Unrealized (losses) gains on investments, net of tax	(17,219)	(33,101)	40,079
Reclassification adjustment for realized gains (losses) included in net loss	447	(20,211)	(21,412)
Currency translation adjustment	(21)	—	—
Comprehensive loss	$ (103,349)	$ (141,590)	$ (20,317)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2016, 2015 and 2014
(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, 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
Net loss	—	—	—	—	(86,556)	(86,556)
Change in unrealized gains (losses), net of tax	—	—	—	(16,772)	—	(16,772)
Foreign currency translation	—	—	—	(21)	—	(21)
Issuance of common stock in connection with employee stock plans	1,285	2	13,706	—	—	13,708
2¾ percent convertible senior notes redemption, equity portion	—	—	(128,888)	—	—	(128,888)
1 percent convertible senior notes, equity portion, net of issuance costs	—	—	43,335	—	—	43,335
Share-based compensation expense	—	—	72,108	—	—	72,108
Excess tax benefits from share-based compensation awards	—	—	1,861	—	—	1,861
Balance at December 31, 2016	121,636	122	1,311,229	(30,358)	(1,181,428)	99,565

See accompanying notes.

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

	Years Ended December 31,		
	2016	**2015**	**2014**
Operating activities:			
Net loss	$ (86,556)	$ (88,278)	$ (38,984)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	7,481	6,984	6,380
Amortization of patents	1,552	1,381	1,142
Amortization of licenses	—	1,873	1,882
Amortization of premium on investments, net	6,813	7,812	7,470
Amortization of debt issuance costs	1,225	1,133	595
Amortization of 2¾ convertible senior notes discount	2,564	2,347	6,723
Amortization of 1 percent convertible senior notes discount	21,326	19,728	2,256
Amortization of long-term financing liability for leased facility	6,693	6,665	6,622
Share-based compensation expense	72,108	59,314	31,383
Gain on investment in Regulus Therapeutics Inc.	—	(20,211)	(19,902)
Loss on early retirement of debt	3,983	—	8,292
Gain on investments, net	(56)	(75)	(1,256)
Non-cash losses related to patents, licensing and property, plant and equipment	2,297	1,881	1,305
Tax benefit from other unrealized gains on securities	—	—	(12,835)
Changes in operating assets and liabilities:			
Contracts receivable	(96,687)	(7,453)	7,199
Inventories	(590)	(609)	1,743
Other current and long-term assets	1,659	(4,319)	(1,750)
Accounts payable	(10,677)	9,211	4,824
Income taxes	1,069	—	(4,034)
Accrued compensation	8,121	3,763	134
Deferred rent	125	205	153
Accrued liabilities	4,595	(2,345)	8,358
Deferred contract revenue	(59,150)	22,118	(11,415)
Net cash provided by (used in) operating activities	(112,105)	21,125	6,285
Investing activities:			
Purchases of short-term investments	(300,912)	(493,467)	(391,883)
Proceeds from the sale of short-term investments	364,572	419,584	294,727
Purchases of property, plant and equipment	(7,107)	(7,692)	(7,518)
Acquisition of licenses and other assets, net	(4,421)	(4,056)	(3,586)
Proceeds from the sale of Regulus Therapeutics, Inc.	4,467	25,527	22,949
Proceeds from the sale of strategic investments	—	52	2,463
Net cash provided by (used in) investing activities	56,599	(60,052)	(82,848)
Financing activities:			
Proceeds from equity, net	12,599	24,888	23,071
Proceeds from issuance of 1 percent convertible senior notes, net of issuance costs	—	—	487,035
Repurchase of $140 million of the principal amount of the 2¾ percent convertible senior notes	—	—	(441,394)
Proceeds from borrowing on line of credit facility	4,000	8,500	—
Excess tax benefits from share-based compensation awards	1,861	396	1,463
Principal payments on debt and capital lease obligations	(7,066)	(9,058)	(10,587)
Net cash provided by financing activities	11,394	24,726	59,588
Net decrease in cash and cash equivalents	(44,112)	(14,201)	(16,975)
Cash and cash equivalents at beginning of year	128,797	142,998	159,973
Cash and cash equivalents at end of year	$ 84,685	$ 128,797	$ 142,998

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

Supplemental disclosures of cash flow information:			
Interest paid	$ 7,313	$ 6,800	$ 6,353
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 3,439	$ 1,162	$ 2,151
1 percent convertible senior notes principal issued related to our December 2016 debt exchange	$ 185,450	$ —	$ —
2¾ percent convertible senior notes principal extinguished related to our December 2016 debt exchange	$ 61,099	$ —	$ —

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 and its wholly owned subsidiaries, Akcea Therapeutics UK Ltd, which Akcea formed in August 2016 and Akcea Intl Ltd., which Akcea formed in February 2017. 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 2016, 2015 and 2014, 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:

- □□percent convertible senior notes;
- 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}$. At the onset of the agreement, we were responsible for completing the development services for IONIS-FXI$_{Rx}$, and for providing an initial supply of active pharmaceutical ingredient, or API. Since the agreement had multiple elements, we evaluated the deliverables in this arrangement when we entered into the agreement and determined that certain deliverables have stand-alone value. In February 2017, we expanded our collaboration with Bayer, refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements for further information. Below is a list of the three units of accounting under our original 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 license we granted to Bayer has stand-alone value because it gives Bayer the exclusive 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 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 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 performed and the API we delivered 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 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 10 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 in the second quarter of 2015 because we delivered the license and earned the revenue;
- We recognized the amount attributed to the development services for IONIS-FXI$_{Rx}$ over the period of time we performed the services; and
- We are recognizing the amount attributed to the API supply as 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 partner. 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, in 2012 and 2013, we entered into several collaboration agreements with Biogen:

- In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA (nusinersen) for spinal muscular atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we were responsible for global development of SPINRAZA 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 neurodegenerative 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.

Under our collaboration agreement, in July 2016, Biogen exercised its option to license SPINRAZA. Our other collaboration agreements with Biogen give Biogen the option to license one or more drugs resulting from the specific collaboration. Similar to our collaboration agreement for SPINRAZA, if Biogen exercises an option, it will pay us a license fee and will assume future global 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 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.

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 paragraphs.

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 Food and Drug Administration, or 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. 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*.

Option to license

In several of our collaboration agreements, we provide our partner with an option to obtain a license to one or more of our drugs. When we have a multiple element arrangement that includes an option to obtain a license, we evaluate if the option is a deliverable at the inception of the arrangement. We do not consider the option to be a deliverable if we conclude that it is substantive and not priced at a significant and incremental discount. We consider an option substantive if, at the inception of the arrangement, we are at risk as to whether our collaborative partner will choose to exercise its option to obtain the license. In those circumstances, we do not include the associated license fee in the allocable consideration at the inception of the agreement. Rather, we account for the license fee when our partner exercises its option. For example, during 2016, we earned license fee revenue when three of our partners, AstraZeneca, Biogen and Janssen, exercised their option to license three of our drugs, which under the respective agreements we concluded to be substantive options at inception. As a result, in 2016 we recognized $98 million in research and development revenue under collaborative agreements on our statement of operations as these amounts relate to drugs in development under research and development collaboration arrangements.

Licensing and royalty revenue

We often enter into agreements to license and sell our proprietary patent rights on an exclusive or non-exclusive basis in exchange for upfront fees, milestone payments and/or royalties. We generally recognize as revenue immediately those payments for which we have no significant future performance obligations and for which we are reasonably assured of collecting the resulting receivable.

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, 2016, 2015 and 2014, research and development expenses were $340.4 million, $319.5 million and $238.9 million, respectively. A portion of the costs included in research and development expenses are costs associated with our partner agreements. For the years ended December 31, 2016, 2015 and 2014, research and development costs of approximately $187.1 million, $161.7 million and $85.6 million, respectively, were related to our partner 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 10.1 years at December 31, 2016.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2016 and 2015 was $28.8 million and $27.5 million, respectively. Accumulated amortization related to patents was $8.4 million and $8.2 million at December 31, 2016 and 2015, 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)
2017	$ 1.4
2018	$ 1.3
2019	$ 1.2
2020	$ 1.1
2021	$ 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 2016, 2015 and 2014, patent expenses were $3.9 million, $2.8 million and $2.9 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $2.3 million, $1.1 million and $1.3 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 partner agreement. At December 31, 2016, 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). At December 31, 2016, we held equity investments in two publicly held companies, Antisense Therapeutics Limited and Regulus Therapeutics. 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. At December 31, 2016,we held cost method investments in three companies, Atlantic Pharmaceuticals Limited, Kastle Therapeutics and Dynacure, SAS. Realization of our equity position in these private companies 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, 2016, 2015 or 2014. Total inventory was $7.5 million and $6.9 million as of December 31, 2016 and 2015, 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, 2016	December 31, 2015
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 63,287	$ 56,822
Building and building systems	25 to 40	48,909	48,163
Land improvements	20	2,853	2,853
Leasehold improvements	5 to 20	41,736	39,061
Furniture and fixtures	5 to 10	5,937	5,842
		162,722	152,741
Less accumulated depreciation		(80,075)	(72,706)
		82,647	80,035
Land		10,198	10,198
Total		$ 92,845	$ 90,233

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 $2.3 million, $1.9 million and $1.3 million for the years ended December 31, 2016, 2015 and 2014, 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 primarily 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, 2016, 2015 and 2014 (in thousands):

	Year Ended December 31,		
	2016	2015	2014
Beginning balance accumulated other comprehensive (loss) income	$ (13,565)	$ 39,747	$ 21,080
Unrealized (losses) gains on securities, net of tax (1)	(17,219)	(33,101)	40,079
Amounts reclassified from accumulated other comprehensive (loss) income (2)	447	(20,211)	(21,412)
Currency translation adjustment	(21)	—	—
Net other comprehensive (loss) income for the period	(16,793)	(53,312)	18,667
Ending balance accumulated other comprehensive (loss) income	$ (30,358)	$ (13,565)	$ 39,747

(1) Other comprehensive income includes income tax expense of $12.8 million for the year ended December 31, 2014. There was no tax expense for other comprehensive income for the years ended December 31, 2016 or 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.

Convertible debt

We account for convertible debt instruments 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 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, which resulted in us recording our debt at a discount. At January 1, 2016, we adopted the amended accounting guidance to simplify the presentation of debt issuance costs. As a result of this amended guidance, we reclassed our debt issuance costs in all periods presented from other assets to the net carrying amount of the related debt liability on our consolidated balance sheet. We are amortizing our debt issuance costs and 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, and Akcea Therapeutics, which includes the consolidated operations of our wholly owned subsidiary, Akcea Therapeutics, Inc. We formed Akcea to develop and commercialize drugs to treat patients with serious cardiometabolic diseases caused by lipid 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. 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 2016 and 2015, there were no transfers between our Level 1 and Level 2 investments. When we recognize transfers between levels of the fair value hierarchy, we recognize the transfer on the date the event or change in circumstances that caused the transfer occurs. During 2016 and 2015, we did not have any investments that were classified as Level 3 investments.

The following tables present the major security types we held at December 31, 2016 and 2015 that are regularly measured and carried at fair value. The tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2016	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 54,137	$ 54,137	$ —
Corporate debt securities (2)	396,221	—	396,221
Debt securities issued by U.S. government agencies (2)	55,179	—	55,179
Debt securities issued by the U.S. Treasury (2)	29,286	29,286	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	109,111	—	109,111
Investment in Regulus Therapeutics Inc.	2,414	2,414	—
Total	$ 646,348	$ 85,837	$ 560,511

	At December 31, 2015	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
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 U.S. and political subdivisions of the states (4)	127,656	—	127,656
Investment in Regulus Therapeutics Inc.	24,792	24,792	—
Total	$ 771,630	$ 116,295	$ 655,335

(1) Included in cash and cash equivalents on our consolidated balance sheet.

(2) Included in short-term investments on our consolidated balance sheet.

(3) $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.

(4) $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.

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, our investment in Regulus included a lack of marketability discount, and as a result, we classified it as a Level 3 investment at the beginning of 2015. We 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. We transferred these securities to Level 1 in the first quarter of 2015, when the trading restrictions 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 year ended December 31, 2015 (in thousands):

	Year Ended December 31, 2015
Beginning balance of Level 3 investments	$ 81,881
Transfers into Level 3 investments	—
Total gains (losses) included in accumulated other comprehensive income (loss)	22,377
Transfers out of Level 3 investments	(104,258)
Ending balance of Level 3 investments	$ —

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 to receive in exchange for the goods or services. Under the current accounting guidance, we recognize revenue from milestone payments we earn under the milestone method. Under the new guidance, the milestone method of revenue recognition is eliminated. This new 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 approach, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to our opening accumulated deficit balance. As we have a significant number of collaborations that span several years with associated revenue, we are currently evaluating which adoption method we will use and assessing the impact 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 requires 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 annual periods ending after December 15, 2016, and interim and annual periods thereafter. We adopted this guidance in these financial statements for our year ended December 31, 2016. This guidance did not have any effect on our consolidated financial statements and disclosures.

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 unrealized gains and losses 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.

In February 2016, the FASB issued amended accounting guidance related to leasing, which requires us to record all leases longer than one year on our balance sheet. When we record leases on our balance sheet under the new guidance, we will record a liability with a value equal to the present value of payments we will make over the life of the lease and an asset representing the underlying leased asset. The new accounting guidance requires us to determine if our leases are operating or financing leases, similar to current accounting guidance. We will record expense for operating type leases on a straight-line basis as an operating expense and we will record expense for finance type leases as interest expense. The new lease standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted. We must adopt the new standard on a modified retrospective basis, which requires us to reflect our leases on our consolidated balance sheet for the earliest comparative period presented. We are currently assessing the timing of adoption as well as the effects it will have on our consolidated financial statements and disclosures.

In March 2016, the FASB issued amended guidance to simplify certain aspects of share-based payment accounting. Under the amended guidance, we will recognize excess tax benefits and tax deficiencies as income tax expense or benefit in our statement of operations on a prospective basis. As we have a valuation allowance, this change will impact our net operating loss carryforward and our valuation allowance disclosures. Additionally, we will classify excess tax benefits as an operating activity and classify amounts we withhold in shares for the payment of employee taxes as a financing activity on our statement of cash flows for each period we present. Lastly, the amended guidance allows us to account for forfeitures when they occur or continue to estimate them. We will continue to estimate our forfeitures. The amended share-based payment standard is effective for annual and interim periods beginning after December 15, 2016, with early adoption permitted in any interim or annual period. We adopted this guidance on January 1, 2017. The amended guidance will not impact our financial results.

In June 2016, the FASB issued guidance that changes the measurement of credit losses for most financial assets and certain other instruments. If we have credit losses, this updated guidance requires us to record allowances for these instruments under a new expected credit loss model. This model requires us to estimate the lifetime expected credit loss, which represents the portion of the amortized cost basis we do not expect to collect. This change will result in us remeasuring our allowance in each reporting period we have credit losses. The new standard is effective for annual and interim periods beginning after December 15, 2019. Early adoption is permitted for periods beginning after December 15, 2018. When we adopt the new standard, we will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. We are currently assessing the timing of adoption as well as the effects it will have on our consolidated financial statements and disclosures.

2. Investments

As of December 31, 2016, we had 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, 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.

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2016:

One year or less	55 %
After one year but within two years	32 %
After two years but within three and a half years	13 %
Total	100 %

As illustrated above, at December 31, 2016, 87 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, 2016, we had an ownership interest of less than 20 percentin three private companies and two public companies with which we conduct business. The privately held companies are Atlantic Pharmaceuticals Limited, Kastle Therapeutics and Dynacure, SAS and the publicly traded companies are Antisense Therapeutics Limited and Regulus. We account for equity investments in the privately held companies 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 and 2014, we realized a net gain on investments of $20.3 million, and $21.2 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. During 2016, we recognized nominal gains from sales of our investments. As of December 31, 2016, our carrying balance of our investment in Regulus was $2.4 million on our consolidated balance sheet.

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

		Gross Unrealized		
December 31, 2016	**Cost** (1)	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities:				
Corporate debt securities	$ 195,087	$ 25	$ (161)	$ 194,951
Debt securities issued by U.S. government agencies	26,548	—	(10)	26,538
Debt securities issued by the U.S. Treasury	29,298	2	(14)	29,286
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	72,775	2	(134)	72,643
Total securities with a maturity of one year or less	323,708	29	(319)	323,418
Corporate debt securities	202,408	36	(1,174)	201,270
Debt securities issued by U.S. government agencies	28,807	1	(167)	28,641
Debt securities issued by states of the U.S. and political subdivisions of the states	36,816	1	(349)	36,468
Total securities with a maturity of more than one year	268,031	38	(1,690)	266,379
Total available-for-sale securities	$ 591,739	$ 67	$ (2,009)	$ 589,797
Equity securities:				
Regulus Therapeutics Inc.	$ 2,133	$ 281	$ —	$ 2,414
Total equity securities	$ 2,133	$ 281	$ —	$ 2,414
Total available-for-sale and equity securities	$ 593,872	$ 348	$ (2,009)	$ 592,211

December 31, 2015	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
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 U.S. 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 U.S. 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

(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, 2016 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	255	$ 280,393	$ (1,197)	$ 32,753	$ (138)	$ 313,146	$ (1,335)
Debt securities issued by U.S. government agencies	29	43,851	(177)	—	—	43,851	(177)
Debt securities issued by the U.S. Treasury	2	18,782	(14)	—	—	18,782	(14)
Debt securities issued by states of the U.S. and political subdivisions of the states	135	80,896	(398)	6,934	(85)	87,830	(483)
Total temporarily impaired securities	421	$ 423,922	$ (1,786)	$ 39,687	$ (223)	$ 463,609	$ (2,009)

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, 2016	December 31, 2015
1 percent convertible senior notes	$ 500,511	$ 339,847
2¾ percent convertible senior notes	124	49,523
Long-term financing liability for leased facility	72,359	72,217
Fixed rate note with Morgan Stanley	12,500	—
Leases and other obligations	3,611	2,856
Total	$ 589,105	$ 464,443
Less: current portion	(1,185)	(515)
Total Long-Term Obligations	$ 587,920	$ 463,928

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 was $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.

In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. As a result of the debt exchange we completed in December 2016, we recorded a $4.0 million non-cash loss on early retirement of debt, reflecting the early retirement of the majority of our remaining 2¾ percent convertible notes in December 2016.

At December 31, 2016, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At December 31, 2016 we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes
Outstanding balance	$ 685.5
Original issue date ($500 million of principal)	November 2014
Additional issue date ($185.5 million of principal)	December 2016
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	10.3

Interest is payable semi-annually in arrears on May 15 and November 15 of each year for the 1 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 10.3 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.

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 Issued in November 2014	1 Percent Convertible Senior Notes Issued in December 2016
Nonconvertible debt borrowing rate	7.4 percent	6.8 percent
Effective interest rate	7.8 percent	7.2 percent
Amortization period of debt discount	7 years	5 years

Interest expense for the year ended December 31, 2016, 2015 and 2014 included $25.1 million, $23.2 million and $9.6 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 1 percent 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,	
	2016	2015
Fair value of outstanding notes	$ 700,969	$ 555,000
Principal amount of convertible notes outstanding	$ 685,450	$ 500,000
Unamortized portion of debt discount	$ 175,699	$ 152,786
Long-term debt	$ 500,511	$ 339,847
Carrying value of equity component	$ 219,011	$ 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, after June 1, 2016, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of December 31, 2016 we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which were used to fund our capital equipment needs and is consistent with our historical practice to finance these costs.

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

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2016 are as follows (in thousands):

2017	$ 7,271
2018	7,211
2019	19,801
2020	6,915
2021	692,365
Thereafter	840
Subtotal	$ 734,403
Less: current portion	(52)
Less: fixed and determinable interest	(35,959)
Less: unamortized portion of debt discount	(175,721)
Plus: Deferred rent	2,130
Total	$ 524,801

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 January 2019.

Annual future minimum payments under operating leases as of December 31, 2016 are as follows (in thousands):

	Operating Leases
2017	$ 1,954
2018	1,690
2019	1,474
2020	1,527
2021	1,411
Thereafter	14,714
Total minimum payments	$ 22,770

Rent expense was $2.0 million each of the years ended December 31, 2016 and 2015. Rent expense for 2014 was $1.8 million. 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 $2.1 million and $2.0 million at December 31, 2016 and 2015, 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, 2016 and 2015, the facility and associated parcel of land had a net book value of $60.0 million and $62.2 million, respectively, which included $12.1 million and $9.9 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, 2016 and 2015 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, 2016 for our primary research and development facility are as follows (in thousands):

	Future Rent Payments
2017	$ 6,550
2018	6,943
2019	6,943
2020	7,359
2021	7,359
Thereafter	83,846
Total minimum payments	$ 119,000

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, 2016, 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, 2016.

Common Stock

At December 31, 2016 and 2015, we had 300,000,000 shares of common stock authorized, of which 121,636,273 and 120,351,480 were issued and outstanding, respectively. As of December 31, 2016, total common shares reserved for future issuance were 14,703,837.

During the years ended December 31, 2016, 2015 and 2014, we issued 1,285,000, 1,908,000 and 1,972,000 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 $13.7 million, $24.9 million and $23.1 million in 2016, 2015 and 2014, 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, 2016, a total of 2,732,089 options were outstanding, of which options to purchase 2,542,372 shares were exercisable, and 25,552 shares were available for future grant under the 1989 Plan.

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, 2016, a total of 5,830,078 options were outstanding, of which 1,827,264 were exercisable, 737,113 restricted stock unit awards were outstanding, and 3,661,538 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, 2016, a total of 615,812 options were outstanding, of which 368,877 were exercisable, 41,151 restricted stock unit awards were outstanding, and 747,869 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 3,374,596 million shares authorized under the plan as of December 31, 2016. 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 2016, employees purchased and we issued to employees 46,051 shares under the ESPP at a weighted average price of $30.47 per share. At December 31, 2016, there were 585,713 shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity for the year ended December 31, 2016 (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, 2015	8,041	$ 33.21		
Granted	2,428	$ 54.79		
Exercised	(994)	$ 12.63		
Cancelled/forfeited/expired	(297)	$ 53.65		
Outstanding at December 31, 2016	9,178	$ 40.48	4.46	$ 122,738
Exercisable at December 31, 2016	4,898	$ 28.73	3.40	$ 107,969

The weighted-average estimated fair values of options granted were $26.72, $27.44 and $17.54 for the years ended December 31, 2016, 2015 and 2014, respectively. The total intrinsic value of options exercised during the years ended December 31, 2016, 2015 and 2014 were $28.0 million, $84.7 million and $62.8 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $12.6 million, $23.6 million and $22.4 million for the years ended December 31, 2016, 2015 and 2014, respectively. For the year ended December 31, 2016, the weighted-average fair value of options exercised was $40.83. As of December 31, 2016, total unrecognized compensation cost related to non-vested stock-based compensation plans was $48.1 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 1.1 years.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2016 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2015	751	$ 47.47
Granted	346	$ 41.79
Vested	(270)	$ 39.22
Cancelled/forfeited	(49)	$ 49.38
Non-vested at December 31, 2016	778	$ 47.68

For the years ended December 31, 2016, 2015 and 2014, the weighted-average grant date fair value of RSUs granted was $41.79, $65.69 and $44.94 per RSU, respectively. As of December 31, 2016, total unrecognized compensation cost related to RSUs was $13.3 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, 2016, 2015 and 2014 (in thousands), which was allocated as follows and includes $10.1 million and $6.5 million of stock-based compensation expense for Akcea employees in 2016 and 2015, respectively:

	Year Ended December 31,		
	2016	2015	2014
Research, development and patents	$ 55,099	$ 43,638	$ 25,843
General and administrative	17,009	15,676	5,540
Total	$ 72,108	$ 59,314	$ 31,383

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, 2016, 2015 and 2014, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	December 31,		
	2016	**2015**	**2014**
Risk-free interest rate	1.5 %	1.5 %	1.7 %
Dividend yield	0.0 %	0.0 %	0.0 %
Volatility	58.7 %	53.8 %	50.1 %
Expected life	4.5 years	4.5 years	4.7 years

Board of Director Stock Options:

	December 31,		
	2016	**2015**	**2014**
Risk-free interest rate	1.3 %	2.1 %	2.2 %
Dividend yield	0.0 %	0.0 %	0.0 %
Volatility	53.1 %	52.2 %	54.2 %
Expected life	6.5 years	6.9 years	6.9 years

ESPP:

	December 31,		
	2016	**2015**	**2014**
Risk-free interest rate	0.4 %	0.1 %	0.1 %
Dividend yield	0.0 %	0.0 %	0.0 %
Volatility	86.4 %	51.7 %	60.1 %
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,		
	2016	**2015**	**2014**
Current:			
Federal	$ 1,067	$ 379	$ 263
State	1,867	(7)	(4,295)
Total current	2,934	372	(4,032)
Deferred:			
Federal	—	—	(8,948)
State	—	—	(2,427)
Total deferred	—	—	(11,375)
Income tax expense (benefit)	$ 2,934	$ 372	$ (15,407)

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 2016 and 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, 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 year ended December 31, 2014, we recorded a $12.8 million tax benefit, in continuing operations and a $12.8 million tax expense, in other comprehensive income.

The reconciliation between our effective tax rate on loss from continuing operations and the statutory U.S. tax rate is as follows (in thousands):

	Year Ended December 31,					
	2016		2015		2014	
Pre-tax loss	$ (83,622)		$ (87,906)		$ (54,391)	
Statutory rate	(29,268)	35.0%	(30,767)	35.0%	(19,035)	35.0%
State income tax net of federal benefit	(276)	0.3%	1	0.0%	(3,125)	5.7%
Net change in valuation allowance	55,927	(66.9)%	69,499	(79.1)%	29,547	(54.3)%
Loss on debt extinguishment	—	0.0%	—	0.0%	2,406	(4.4)%
Tax credits	(26,954)	32.2%	(41,284)	47.0%	(23,628)	43.4%
California franchise tax refund	—	0.0%	—	0.0%	(2,795)	5.1%
Deferred tax true-up	2,591	(3.1)%	1,496	(1.7)%	977	(1.8)%
Other	914	(1.1)%	1,427	(1.6)%	246	(0.5)%
Effective rate	$ 2,934	(3.5)%	$ 372	(0.4)%	$ (15,407)	28.2%

Significant components of our deferred tax assets and liabilities as of December 31, 2016 and 2015 are as follows (in thousands):

	Year Ended December 31,	
	2016	2015
Deferred Tax Assets:		
Net operating loss carryovers	$ 194,372	$ 218,493
R&D credits	193,845	153,601
Deferred revenue	54,203	45,110
Stock-based compensation	48,209	31,093
Other	26,228	19,655
Total deferred tax assets	$ 516,857	$ 467,952
Deferred Tax Liabilities:		
Convertible debt	$ (62,669)	$ (55,928)
Unrealized gain in other comprehensive income	-	(5,288)
Intangible and capital assets	(2,030)	(2,643)
Net deferred tax asset	$ 452,158	$ 404,093
Valuation allowance	(452,158)	(404,093)
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 as it pertains to the income tax accounting rules, we have provided a full valuation allowance for the deferred tax assets in our balance sheet as of December 31, 2016. 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.

Historically, we recognized excess tax benefits associated with share-based compensation to stockholders' equity only when realized. We followed 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 did not realize our excess tax benefits related to share-based compensation until after we utilize all our other tax benefits available to us. During the year ended December 31, 2016, we realized $1.9 million of such excess tax benefits, and accordingly, we recorded a corresponding credit to additional paid-in capital.

In March 2016, the FASB issued amended guidance to simplify certain aspects of share-based payment accounting which affects how we account for unrecognized tax benefits. As of December 31, 2016, we had $82.5 million of unrealized excess tax benefits associated with share-based compensation. We adopted this amended guidance on January 1, 2017. Upon adoption we will recognize the balance of these unrecognized tax benefits as a deferred tax asset which will be offset by our full valuation allowance. The adoption of this guidance did not affect our accumulated loss.

At December 31, 2016, we had federal and California tax net operating loss carryforwards of approximately $679.8 million and $973.1 million, respectively. Our federal tax loss carryforwards will begin to expire in 2024, unless we use them before then. Our California loss carryforwards continue to expire in 2016. At December 31, 2016 we also had federal and California research and development tax credit carryforwards of approximately $189.6 million and $48.0 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.

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,		
	2016	2015	2014
Beginning balance of unrecognized tax benefits	$ 51,257	$ 27,365	$ 23,964
Settlement of prior period tax positions	(4,033)	—	—
Decrease for prior period tax positions	—	—	(1,653)
Increase for prior period tax positions	7,928	215	—
Increase for current period tax positions	11,847	23,677	5,054
Ending balance of unrecognized tax benefits	$ 66,999	$ 51,257	$ 27,365

Included in the balance of unrecognized tax benefits at December 31, 2016, is $46.4 million that, if recognized, would not impact our income tax benefit or effective tax rate as long as our deferred tax asset remains subject to a full 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, 2016.

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 2003 and forward are subject to examination by the California tax authorities.

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnerships

AstraZeneca

Cardiometabolic and Renal Diseases Partnership

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 as drugs under this collaboration advance, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for regulatory milestones. In December 2016, we earned a $25 million milestone payment when we moved the first development candidate into preclinical development, IONIS-AZ4-2.5-L_{Rx}, our first generation 2.5 plus LIgand-Conjugated Antisense, or LICA, drug. We will earn the next milestone payment of $10 million under this collaboration if we advance a drug under our cardiometabolic research program with AstraZeneca. 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 Partnership

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 and in patients with diffuse large B cell lymphoma. 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. The first development candidate identified under the anti-cancer research program was IONIS-KRAS-2.5$_{Rx}$, which AstraZeneca licensed from us in December 2016. IONIS-KRAS-2.5$_{Rx}$ is a Generation 2.5 antisense drug we designed to directly target KRAS, one of the most frequently mutated genes in cancer.

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 February 2018. 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$_{Rx}$, IONIS-KRAS-2.5$_{Rx}$ and two other drugs under the research program, we could receive license fees and substantive milestone payments of up to more than $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 2016, we have received $76 million in milestone payments and upfront fees under this oncology collaboration, not including the $15 million milestone payment and $13 million license fee we earned for IONIS-KRAS-2.5$_{Rx}$ in December 2016. We will earn the next milestone payment of $17.5 million if we advance a drug under our cancer 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 2016, 2015 and 2014 we earned revenue of $64.9 million, $6.4 million and $27.7 million, respectively, from our relationship with AstraZeneca, which represented 19 percent, 2 percent and 13 percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2016 and 2015 included deferred revenue of $51.5 million and $63.3 million, respectively, related to our relationship with AstraZeneca.

Biogen

We have four strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our recently approved drug to treat pediatric and adult patients with SMA. Additionally, we and Biogen are currently developing four other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$, and three drugs to treat undisclosed neurodegenerative diseases, IONIS-BIIB4$_{Rx}$, IONIS-BIIB5$_{Rx}$ and IONIS-BIIB6$_{Rx}$. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. From inception through December 2016, we have received nearly $500 million from our Biogen collaborations, not including the $60 million milestone payment we earned for the FDA’s approval of SPINRAZA that we received in February 2017.

SPINRAZA (nusinersen)

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. In December 2016, the FDA approved SPINRAZA for the treatment of SMA in pediatric and adult patients. SPINRAZA is currently under Accelerated Assessment with the EMA for marketing authorization. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

Under the terms of our collaboration agreement, we received an upfront payment of $29 million in January 2012, which we amortized through December 2016. 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 SPINRAZA prior to licensing and up to $150 million in substantive milestone payments if Biogen achieves pre-specified regulatory milestones. We are also eligible to receive tiered royalties up to the mid-teens on any sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We are obligated to pay Cold Spring Harbor Laboratory and the University of Massachusetts nominal amounts for license fees and milestone payments we receive and a low single digit royalty on sales of SPINRAZA. From inception through December 2016, we have received $259 million in payments for advancing SPINRAZA, including the $75 million license fee we received from Biogen when Biogen licensed SPINRAZA, which we recognized as revenue in the third quarter of 2016. Additionally in February 2017, we received a $60 million substantive milestone payment that we earned in December 2016. We will earn the next milestone payment of up to $50 millionif Biogen receives regulatory approval in Europe or Japan for SPINRAZA.

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 completed a Phase 1/2 clinical study in patients with DM1. Based on the data reported in December 2016, we plan to pursue a more potent drug using our LICA technology. From inception through December 2016, we have received nearly $39 million in payments for advancing IONIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen entered into a separate collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurodegenerative 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. From inception through December 2016, we have received $43 million in milestone payments and upfront fees under this collaboration. 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 long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative 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 Biogen is pursuing 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. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. We are currently advancing three drugs, IONIS-SOD1$_{Rx}$, IONIS-BIIB5$_{Rx}$, and IONIS-BIIB6$_{Rx}$ under this collaboration. 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 2016, we have received $142 million in milestone payments and upfront fees 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 2016, 2015 and 2014, we earned revenue of $207.9 million, $106.2 million and $123.2 million, respectively, from our relationship with Biogen, which represented 60 percent, 37 percent and 58 percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2016 and 2015 included deferred revenue of $67.5 million and $91.6 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 were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis.

Under the terms of the agreement, we received a $100 million upfront payment in the second quarter of 2015. We recorded revenue of $91.2 million related to the license for IONIS-FXI$_{Rx}$ in June 2015 and we recognized the majority of the remaining amount related to development activities for IONIS-FXI$_{Rx}$ through November 2016.

In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. In conjunction with the decision to advance these programs, we will receive a $75 million payment from Bayer. We plan to conduct a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to rapidly develop IONIS-FXI-L$_{Rx}$ through Phase 1. Following these studies and Bayer's decision to further advance these programs, Bayer will be responsible for all global development, regulatory and commercialization activities for both drugs. We are eligible to receive additional milestone payments as each drug advances toward the market. In total over the term of our collaboration, we are eligible to receive up to $385 million in license fees, milestone payments and other payments, including up to $125 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 both drugs combined. We will earn the next milestone payment of $10 million if we advance a program under this collaboration.

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 2016 and 2015 we earned revenue of $5.4 million and $93.4 million, respectively, from our relationship with Bayer, which represented two percent and 33 percent, respectively, of our total revenue for those periods. Our consolidated balance sheet at December 31, 2016 and 2015 included deferred revenue of $1.4 million and $6.7 million, respectively, related to our relationship with Bayer.

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 four drugs in development, including our Phase 3 drug IONIS-TTR$_{Rx}$. We are currently conducting a Phase 3 study for IONIS-TTR$_{Rx}$ and we plan to report data from this study in the second quarter of 2017. GSK has the exclusive option to license drugs resulting from this alliance after Phase 2 proof-of-concept for a license fee, including IONIS-TTR$_{Rx}$. 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.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for IONIS-TTR_{Rx}. We have completed enrollment in the Phase 3 study we are conducting in patients with TTR familial amyloid polyneuropathy, or FAP. From inception through December 2016, we have earned $70 million from GSK related to the development of IONIS-TTR_{Rx}, primarily in milestone payments. 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 addition to IONIS-TTR_{Rx}, we have three drugs in development with GSK, including 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. GSK is currently developing IONIS-HBV_{Rx} and IONIS-HBV-L_{Rx}, and if GSK exercises its exclusive option for either of these drugs, it will be responsible for all further global development, regulatory and commercialization activities. We are also developing IONIS-GSK4-L_{Rx} which is an antisense drug we designed to treat an ocular disease.

Under the terms of the agreement, we received $38 million in upfront and expansion payments, which we are amortizing through September 2017. Under our agreement, if GSK successfully develops all four drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of up to nearly $900 million, including up to $157.5 million for the achievement of development milestones, up to $338.5 million for the achievement of regulatory milestones and up to $255 million for the achievement of commercialization milestones. Through December 2016, we have received $155 million in milestone payments and upfront fees under this alliance with GSK. We will earn the next milestone payment of up to $1.5 million if we further advance a program under this collaboration and we will earn a payment of $45 million if GSK licenses IONIS-TTR_{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.

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 2016, 2015 and 2014, we earned revenue of $12.3 million, $33.3 million and $37.3 million respectively, from our relationship with GSK, which represented four percent, 12 percent and 17 percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2016 and 2015 included deferred revenue of $2.1 million and $4.9 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 up to 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. Through December 2016, we have received $47 million, including the $10 million license fee we earned in July 2016 when Janssen licensed IONIS-JBI1-2.5_{Rx} from us, which we recognized as revenue in the third quarter of 2016. We also earned a $5 million milestone payment in December 2016 when Janssen selected a development candidate for a second program. 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 2016 and 2015 we earned revenue of $27.3 million and $8.9 million, respectively, from our relationship with Janssen. During 2014 we did not earn any revenue from our relationship with Janssen. Our balance sheet at December 31, 2016 and 2015 included deferred revenue of $17.5 million and $26.3 million, respectively, related to our relationship with Janssen.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration, option and license agreement, Novartis has an exclusive option to develop and commercialize these drugs. Akcea is responsible for completing a Phase 2 dose ranging study and conducting an end-of-Phase 2 meeting with the FDA for each drug. If Novartis exercises an option for one of these drugs, Novartis will be responsible for all further global development, regulatory and commercialization activities for each drug.

Akcea will receive a $75 million upfront payment, of which Akcea will retain $60 million and will pay us $15 million as a sublicense fee under our license agreement with Akcea. Beginning in 2017, we and Akcea will recognize revenue from this collaboration with Novartis. If Novartis exercises its option for a drug, Novartis will pay Akcea a license fee equal to $150 million for each drug it licenses. In addition, Akcea is eligible to receive up to $600 million and $530 million in milestone payments related to AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, respectively. Akcea retains the right to co-commercialize any such drug through its specialized sales force focused on lipid specialists in selected markets. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee.

The agreement with Novartis will continue until the earlier of the date that all of Novartis' options to obtain the exclusive licenses under the agreement expire unexercised or, if Novartis exercises its options, until the expiration of all payment obligations under the agreement. In addition, the agreement as a whole or with respect to any drug under the agreement, may terminate early under the following situations:

- Novartis may terminate the agreement as a whole or with respect to any drug at any time by providing written notice to us;
- Either we or Novartis may terminate the agreement with respect to any drug by providing written notice to the other party in good faith that we or Novartis has determined that the continued development or commercialization of the drug presents safety concerns that pose an unacceptable risk or threat of harm in humans or would violate any applicable law, ethical principles, or principles of scientific integrity;
- Either we or Novartis may terminate the agreement for a drug by providing written notice to the other party upon the other party's uncured failure to perform a material obligation related to the drug under the agreement, or the entire agreement if the other party becomes insolvent; and
- We may terminate the agreement if Novartis disputes or assists a third party to dispute the validity of any or our patents.

Additionally, in January 2017, we and Akcea entered into a stock purchase agreement, or SPA, with Novartis. Under the SPA, Novartis purchased 1,631,435 shares of our common stock for $100 million. Additionally, the SPA requires Novartis to purchase an additional $50 million of common stock in the future. The additional purchase will be for either our stock or Akcea's stock.

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. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through April 2017. In December 2016, we updated development activities for IONIS-HTT_{Rx} and as a result we are eligible for an additional $3 million payment. We are eligible to receive up to $365 million in a license fee and substantive milestone payments including up to $70 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. We are also eligible to receive tiered royalties up to the mid-teens on any sales of any product resulting from this alliance. Through December 2016, we have received $53.6 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; and
- 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.

During 2016, 2015 and 2014, we earned revenue of $7.1 million, $31.2 million and $8.7 million, respectively from our relationship with Roche, which represented two percent, 11 percent and four percent, respectively, of our total revenue for those years. Our balance sheet at December 31, 2016 and 2015 included deferred revenue of $1.7 million and $8.8 million, respectively related to our relationship with Roche.

Satellite Company Partnerships

Achaogen, Inc.

In 2006, we exclusively licensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In connection with the license, Achaogen issued to us $1.5 million of Achaogen stock. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. 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. In December 2016, Achaogen announced positive data for its CARE Phase 3 study for plazomicin and that its EPIC Phase 3 study met its primary endpoints. Achaogen plans to submit an NDA, which will include EPIC and CARE data, to the FDA in the second half of 2017 and also plans to submit an MAA to the EMA in 2018. Through December 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. 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 low single digit royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development and commercialization of plazomicin.

During 2016 and 2015, 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, including FXI and Apo(a) and two other 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 other 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 2016, we have received over $70 million from Alnylam.

During 2016, 2015 and 2014, we earned revenue from our relationship with Alnylam totaling $1.1 million, $1.3 million and $9.9 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 completed a Phase 2a efficacy and safety trial and has also completed 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, 2016 and 2015, we owned less than 10 percent of ATL's equity. During 2016, 2015 and 2014, 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 January 2017, Atlantic announced that it received agreement from the FDA to initiate a rolling submission of its NDA for alicaforsen. 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, 2013 and 2016, 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, 2016 and 2015, we owned approximately 9 percent and 11 percent, respectively, of Atlantic Pharmaceuticals' equity. Because the payments were made in equity, we did not record any revenue. During 2016 we did not earn any revenue and during 2015 and 2014, our revenue was negligible from our relationship with Atlantic Pharmaceuticals.

Dynacure, SAS

In October 2016, we entered into a collaboration with Dynacure to discover, develop and commercialize an antisense drug for the treatment of neuromuscular diseases. We and Dynacure will share research responsibilities and to identify a drug candidate. Upon exercising its option to license the drug, Dynacure will assume all responsibility for development and commercialization. Under the terms of the agreement, we obtained a 15 percent equity ownership in Dynacure. If Dynacure advances a target under this collaboration, we could receive cash or equity up to more than $210 million in a license fee and milestone payments including up to $34.5 million for the achievement of development milestones, up to $111 million for the achievement of regulatory milestones and up to $60 million for the achievement of commercialization milestones. In addition, we are eligible to receive royalties on future product sales of the drug under this collaboration. We will receive an additional equity position in Dynacure if Dynacure initiates a Phase 1 study for a target under this collaboration. During 2016, we did not earn any revenue from our relationship with Dynacure.

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

In January 2005, we entered into an agreement with OncoGenex to allow for the development of an 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 apatorsen. We will earn the next milestone payment of $1.3 million if OncoGenex initiates a Phase 3 study for apatorsen.

In early 2017, OncoGenex Pharmaceuticals, Inc. entered into a definitive merger agreement under which OncoGenex will acquire Achieve Life Sciences in an all-stock transaction. The merger is expected to close mid-2017. Upon closing OncoGenex Pharmaceuticals, Inc. will be renamed Achieve Life Sciences, Inc.

During 2016 we earned $1.4 million in revenue from our relationship with OncoGenex. During 2015 and 2014, 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 2016, 2015 and 2014, we did not earn any revenue from our relationship with Regulus. During 2016, we sold a portion of our Regulus stock for proceeds of $4.5 million. 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, 2016, we owned approximately 1.1 million shares, with a net carrying value of $2.4 million. In January 2017, we sold our remaining investment in Regulus.

The University of Texas MD Anderson Cancer Center

In May 2016, we entered into a collaboration agreement with the University of Texas MD Anderson Cancer Center to identify cancer targets and create novel antisense drugs to treat cancer together. In the collaboration, we and MD Anderson will work together to validate novel "undruggable" cancer targets selected based on human genomic data. We will lead the drug discovery efforts against mutually agreed upon novel targets and MD Anderson will lead development activities through clinical proof of concept. Following clinical proof of concept, we and MD Anderson plan to identify a partner to complete development and to commercialize each drug with us leading business development efforts. Under the five-year collaboration, we and MD Anderson will evenly share costs specific to our collaboration.

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 research related payments to CHDI up to $4 million, upon completion of our Phase 1/2 study of IONIS-HTT$_{Rx}$. If Roche licenses IONIS-HTT$_{Rx}$, we will make an additional payment to CHDI.

During 2016 and 2014, we did not earn any revenue from our relationship with CHDI. During 2015, our revenue earned from our relationship with CHDI was negligible.

Cystic Fibrosis Foundation

In August 2016, we entered into a collaboration agreement with the Cystic Fibrosis Foundation to discover and advance a drug for the treatment of Cystic Fibrosis. Under this agreement, we received upfront payments of $1 million and we are eligible to receive additional milestone payments up to $2 million. Under the agreement, we and the Cystic Fibrosis Foundation will evenly share the first $3 million of costs specific to our collaboration. We will pay the Cystic Fibrosis Foundation up to $18 million in payments upon achieving specific regulatory and sales events if we advance a drug under our collaboration. We will earn the next milestone payment of $0.5 million if we further advance IONIS-ENAC-2.5$_{Rx}$.

During 2016 we earned $0.6 million from our relationship with the Cystic Fibrosis Foundation.

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 neurological 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 2016, 2015 and 2014, we did not earn any revenue from our relationship with AMI.

Kastle Therapeutics

In May 2016, we entered into an agreement with Kastle under which Kastle acquired the global rights to develop and commercialize Kynamro. Kynamro is approved in the United States for use in patients with homozygous familial hypercholesterolemia to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol and non-high density lipoprotein-cholesterol as an adjunct to lipid lowering medications and diet. We previously licensed Kynamro to Sanofi Genzyme. As a result, Sanofi Genzyme earns a three percent royalty on sales of Kynamro and three percent of non-royalty cash payments we receive from Kastle. Under the terms of our agreement with Kastle, we are eligible to receive up to $95 million, which includes a $15 million upfront payment we received in May 2016, a $10 million payment we are entitled to receive in May 2019 and up to $70 million in sales milestones. In December 2016, we amended our agreement with Kastle. As a result of the amendment, through 2017, Kastle will only pay us the three percent royalty we owe Sanofi Genzyme on sales of Kynamro. Beginning in 2018, we will be eligible to earn tiered royalties on global sales of Kynamro that average in the mid to low teens, increasing slightly in years 2020 and 2021. In addition in May 2016, we received a 10 percent common equity position in Kastle. Because realization of our equity position is uncertain, we recorded a full valuation allowance.

During 2016, we earned revenue of $15.1 million from our relationship with Kastle.

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 SPINRAZA. We are obligated to pay the University of Massachusetts nominal amounts for license fees and milestone payments we receive and a low single digit royalty on sales of SPINRAZA.

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 SPINRAZA. 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 low single digit royalty on sales of SPINRAZA. During 2016, we paid Cold Spring Harbor Laboratory $3.4 million.

7. Segment Information and Concentration of Business Risk

In 2015, we began reporting our financial results in two reportable segments, Ionis Core, 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 to treat patients with serious cardiometabolic diseases caused by lipid disorders. Moving our lipid drugs into a company that we own 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. Through 2016, Akcea had not earned any revenue, however in 2017, Akcea will begin recognizing revenue related to its collaboration with Novartis.

The following is our segment information for 2016, 2015 and 2014 (in thousands).

2016	**Ionis Core**	**Akcea Therapeutics**	**Elimination of Intercompany Activity**	**Total**
Revenue:				
Research and development	$ 338,546	$ —	$ (12,648)	$ 325,898
Licensing and royalty	20,722	—	—	20,722
Total segment revenue	$ 359,268	$ —	$ (12,648)	$ 346,620
Income (loss) from operations	$ 37,196	$ (83,512)	$ —	$ (46,316)

2015	**Ionis Core**	**Akcea Therapeutics**	**Elimination of Intercompany Activity**	**Total**
Revenue:				
Research and development	$ 284,135	$ —	$ (2,775)	$ 281,360
Licensing and royalty	2,343	—	—	2,343
Total segment revenue	$ 286,478	$ —	$ (2,775)	$ 283,703
Loss from operations	$ (23,014)	$ (52,748)	$ —	$ (75,762)

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)

The following table shows our total assets by segment at December 31, 2016 and 2015 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
December 31, 2016	$ 1,067,770	$ 10,684	$ (165,987)	$ 912,467
December 31, 2015	$ 994,191	$ 66,068	$ (112,359)	$ 947,900

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:

	2016	2015	2014
Partner A	60 %	37 %	58 %
Partner B	19 %	2 %	13 %
Partner C	4 %	12 %	17 %
Partner D	2 %	33 %	0 %
Partner E	2 %	11 %	4 %

Contracts receivables at December 31, 2016 and December 31, 2015 were comprised of approximately 92 percent and 99 percent for each year from two 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 2016 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $1.7 million, $1.5 million and $1.0 million in matching contributions for the years ended December 31, 2016, 2015 and 2014, 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.

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, which are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit, Gilead asked 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. In the trial for this case held in March 2016, the jury upheld all ten of the asserted claims of the patents-in-suit. The jury then decided that we and Merck are entitled to four percent of $5 billion in past sales of sofosbuvir. Gilead has stated it would appeal the jury's finding of validity. In the meantime, Gilead asserted two additional non-jury defenses: waiver and unclean hands. Although the judge rejected the waiver defense, she granted Gilead's motion claiming that the patents are unenforceable against it under the doctrine of unclean hands. We believe this ruling is contrary to the relevant law and the facts of the case. Accordingly, in July 2016, together with Merck we appealed the decision. Gilead cross-appealed on the issue of validity. The appeal is pending before the Court of Appeals for the Federal Circuit. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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, 2016 and 2015 are as follows (in thousands, except per share data).

2016 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 36,874	$ 38,470	$ 110,927	$ 160,349
Operating expenses	$ 91,526	$ 87,397	$ 94,819	$ 119,194
Income (loss) from operations	$ (54,652)	$ (48,927)	$ 16,108	$ 41,155
Net income (loss)	$ (62,917)	$ (56,855)	$ 7,351	$ 25,865
Basic net income (loss) per share (1)	$ (0.52)	$ (0.47)	$ 0.06	$ 0.21
Diluted net income (loss) per share (1) (2) (3)	$ (0.52)	$ (0.47)	$ 0.06	$ 0.21

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) (4)	$ (0.14)	$ 0.29	$ (0.30)	$ (0.59)

(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 December 31, 2016, 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, 2016 consisted of the following (in thousands):

Three Months Ended December 31, 2016	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 25,865	121,340	$ 0.21
Effect of diluted securities:			
Shares issuable upon exercise of stock options	—	2,189	
Shares issuable upon restricted stock award issuance	—	403	
Shares issuable related to our ESPP	—	21	
Income available to common shareholders, plus assumed conversions	$ 25,865	123,953	$ 0.21

For the three months ended December 31, 2016, the calculation excludes the 1 percent and 2¾ percent notes because the effect on diluted earnings per share would be anti-dilutive.

(3) For the three months ended September 30, 2016, 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 September 30, 2016 consisted of the following (in thousands):

Three Months Ended September 30, 2016	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 7,351	120,989	$ 0.06
Effect of diluted securities:			
Shares issuable upon exercise of stock options	—	2,129	
Shares issuable upon restricted stock award issuance	—	202	
Shares issuable related to our ESPP	—	58	
Income available to common shareholders, plus assumed conversions	$ 7,351	123,378	$ 0.06

For the three months ended September 30, 2016, the calculation excludes the 1 percent and 2¾ percent notes because the effect on diluted earnings per share would be anti-dilutive.

(4) 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.

CONFIDENTIAL TREATMENT REQUESTED

UNDER 17 C.F.R §§ 200.80(B)4, AND 240.24B-2

Exhibit 10.60

December 21, 2016

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel

Re: *First Amendment To Research Collaboration, Option and License Agreement of December 22, 2014*

Dear Madame or Sir:

Reference is made to the Research Collaboration, Option and License Agreement of December 22, 2014 (the "***Agreement***"), by and between Janssen Biotech Inc. ("***JBI***"), and Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.; hereinafter "***Ionis***"), or individually as "***Party***" or collectively as "***Parties***." This document is a "***First Amendment***" to the Agreement and the "***First Amendment Effective Date***" shall be the date of the last signature below.

In general, the Parties agreed to modify the Agreement to reflect alignment on the terms and conditions which will enable JBI to propose, and for Ionis to accept, a third target ([***]), and for JBI to Develop and Commercialize an [***] Compound that JBI selects as the JBI [***] Development Candidate. This First Amendment includes changes to the companion financials and describes the consideration associated with entering into this First Amendment.

To effectuate the agreed upon changes, the Parties agree to the provisions described herein.

Definitions. The Parties agree to introduce new definitions to the Agreement as follows:

"***GLP Toxicology Study***" means a GLP toxicology study necessary to meet the requirements for filing an IND.

"***Ionis [***] Field***" means any prophylactic, therapeutic or other use or form of administration of any ASO that is designed to bind to the RNA that encodes [***] for any indication other than treatment of a disease of the gastrointestinal tract.

"***[***]***" means the gene, [***].

"***[***] Compound***" means any ASO that is designed to bind to the RNA that encodes [***], where such ASO is discovered by Ionis prior to [***], including [***].

"***IONIS-[***]$_{Rx}$***" means the compound known as [***].

"***JBI [***] Development Candidate***" means the [***] Compound selected by JBI. Such JBI [***] Development Candidate will be a "*Product*" under the Agreement.

"***JBI [***] Field***" means [***] delivery of the JBI [***] Development Candidate for treatment of diseases of the gastrointestinal tract, ***unless*** expanded to include the Expanded GI Field.

Defined terms used but not defined herein have the meaning ascribed to such terms in the Agreement.

Agreement Provisions

Confirmation - Section 1.2.3 – JBI proposed a third gene target designated [***] and Ionis accepts this designation.

Confirmation - Section 1.2.4 – [***] is now a Collaboration Target.

Amendment of Section 2.1.3 – Section 2.1.3 of the Agreement is amended to include a new item (e) as follows:

"(e) The research, development, manufacture, commercialization or other exploitation of IONIS-[***]$_{Rx}$ or any other ASO that is designed to bind to the RNA that encodes [***], in each case by Ionis independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party), in each case in the Ionis [***] Field."

Amendment of Section 4.1.1 Solely with respect to the JBI [***] Development Candidate – The Parties agree that, solely with respect to the JBI [***] Development Candidate, Section 4.1.1 of the Agreement is deleted in its entirety and replaced with the following language:

"**4.1.1 Development and Commercialization License**. Subject to the terms and conditions of this Agreement, effective upon JBI's exercise of the Option for the JBI [***] Development Candidate in accordance with this Agreement, Ionis grants to JBI (i) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize the JBI [***] Development Candidate in the JBI [***] Field, and (ii) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology other than the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize the JBI [***] Development Candidate in the JBI [***] Field. The grants described under subsection (i) and subsection (ii) in no way limit Ionis' ability to grant additional licenses to Third Parties under the Licensed Technology in the Ionis [***] Field."

Addition of New Section 4.1.6 – [***] Administration of JBI [***] Development Candidate. The Parties acknowledge that the JBI [***] Field is initially limited to [***] delivery of the JBI [***] Development Candidate for treatment of diseases of the gastrointestinal tract. Following JBI's exercise of its Option for the JBI [***] Development Candidate but prior to [***] with the JBI [***] Development Candidate, JBI may elect to expand the JBI [***] Field to include the [***] delivery of the JBI [***] Development Candidate for the treatment of diseases of the gastrointestinal tract ("***Expanded GI Field***") by providing the JRC written notice of such [***] election. Within [***] days after timely providing such election notice to the JRC:

a) In the case where JBI selected IONIS-[***]$_{Rx}$ as the JBI [***] Development Candidate and, as of the date the JRC receives such election notice, Ionis has [***], then JBI's rights under this Section 4.1.6 shall be limited to a right to negotiate with Ionis in good faith regarding both (i) [***] and (ii) [***]; or

b) In the case where (x) JBI selected IONIS-[***]$_{Rx}$ as the JBI [***] Development Candidate but, as of the date the JRC receives such election notice, Ionis *has not* [***], or (y) JBI did not select IONIS-[***]$_{Rx}$ as the JBI [***] Development Candidate, the Parties shall negotiate in good faith both (i) [***] and (ii) [***].

The JBI [***] Field will only be expanded to include the Expanded GI Field if the Parties mutually agree on the [***] described in subsection (a) or (b) in this Section 4.1.6 (as applicable). If JBI progresses a JBI [***] Development Candidate in the Expanded GI Field all other provisions of the Agreement shall apply to the Expanded GI Field and Net Sales from [***] delivered and a [***] delivered JBI [***] Development Candidate will be aggregated when calculating payments due under the Agreement royalty tiers.

Addition of New Section 5.7 - Development and Commercialization Cooperation. If JBI selects IONIS-[***]$_{Rx}$ as the JBI [***] Development Candidate, then within [***] ([***]) months after JBI exercises its Option, the Parties will convene to negotiate commercially reasonable terms for managing the continued Development and Commercialization of IONIS-[***]$_{Rx}$ by both Parties, including procedures for the mutual exchange of [***] and [***] information associated with IONIS-[***]$_{Rx}$.

Addition of New Section 5.8 – Back-Up JBI [***] Development Candidate. If JBI has exercised its Option for the JBI [***] Development Candidate and subsequently delivers written notice to Ionis that JBI will discontinue Development of such JBI [***] Development Candidate for reasons of [***] (e.g., [***] or [***] issues), then, upon JBI's written request to Ionis, JBI may select as a replacement of such JBI [***] Development Candidate any other [***] Compound ("***Back-Up [***] Development Candidate***") that is not being developed or commercialized (i.e., such [***] Compound has at least started a [***]) by Ionis, its Affiliates or its sublicensee as of the date Ionis receives such request from JBI. JBI will select any such Back-Up [***] Development Candidate within [***] days following the date Ionis receives the discontinuation notice and, unless mutually agreed by Ionis, JBI will be [***]. Upon any such selection of a Back-Up [***] Development Candidate, such Back-Up [***] Development Candidate will become the "*JBI [***] Development Candidate*" and a "*Product*" under and subject to the terms of the Agreement.

Financial Provisions

Pre-Licensing Milestone Event Payment. To compensate Ionis for the Pre-Licensing Milestone Event described in Section 6.3, JBI shall pay $5,000,000 to Ionis within forty-five (45) days following the First Amendment Effective Date.

License Fee. Following receipt by JBI of a Development Candidate Data Package detailing that the Development Candidate criteria have been met for [***] delivery of a JBI [***] Development Candidate, JBI will select a JBI [***] Development Candidate which will trigger the Option provisions of Article 3 and License Fee under Section 6.4. Notwithstanding, the terms of Sections 3.1 and 3.2, the Option Deadline for JBI to provide Ionis with written notice of its intent to exercise its Option for the JBI [***] Development Candidate shall be on or before [***], and JBI shall pay the Option Fee described in Section 6.4 no later than the 45th day following JBI's notice of its intent to exercise such Option.

Post-Licensing Milestone Event Payments. The following Post-Licensing Milestone Event payments described in Table 2 of Section 6.5 are amended as follows solely with respect to the JBI [***] Development Candidate:

	Post-Licensing Milestone Event	**Milestone Event Payment**
i)	[***]	$[***]; and
ii)	[***]	$[***]

*_*_*_*_*_*

Except as otherwise expressly provided herein, the Agreement shall remain in full force and effect without any amendments or modifications. This First Amendment may be executed in separate counterparts, each of which, whether delivered by electronic mail, or otherwise is deemed to be an original, and all of which taken together shall constitute one and the same instrument. This First Amendment shall be effective as of the First Amendment Effective Date. If the above reflects your understanding of the rights and obligations of the Parties under the Agreement, please acknowledge your agreement of the foregoing by executing the countersignature below.

Very truly yours,

/s/ Austin Clayton

Austin Clayton
Corporate Secretary
Janssen Biotech, Inc.

AGREED & ACCEPTED:

/s/ B. Lynne Parshall

Name:	B. Lynne Parshall
Title:	Chief Operating Officer
Date:	December 21, 2016

Ionis Pharmaceuticals, Inc.

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(B)4, AND 240.24B-2

October 28, 2016

Exhibit 10.61

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: (760) 918-3592

Re: ALS Target Identification Strategy

Dear Lynne:

Reference is hereby made to that certain Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis Pharmaceuticals, Inc. (formerly known as Isis Pharmaceuticals, Inc.) ("***Ionis***") and Biogen MA Inc. (as successor in interest to Biogen Idec MA Inc.) ("***Biogen***") dated September 5, 2013, as supplemented and/or amended to date (the "***Neurology II Agreement***"). Any capitalized terms not defined herein will have the meaning set forth in the Neurology II Agreement.

1. Purpose. The Parties desire to conduct certain additional research activities under the Neurology II Agreement with the goal of using ASOs to target ALS. The Parties acknowledge and agree that the provisions of the Neurology II Agreement applicable to ALS Targets do not address the additional activities contemplated by the Parties. Therefore, the Parties agree that the Neurology II Agreement is hereby amended as, and to the extent necessary to give effect to the provisions, set forth in this letter agreement.

2. Designation of ALS Targets. Notwithstanding anything to the contrary in Section 1.2.3(a) of the Neurology II Agreement, Biogen may designate up to [***] ([***]) ALS Targets as High Interest Targets in each consecutive [***] period, or portion thereof, starting on the date of this letter agreement and ending on [***]; *provided*, Biogen will only designate the number of such High Interest Targets as Biogen reasonably anticipates to have the resources to conduct the work for such targets as contemplated by this letter agreement over the applicable [***] period, or portion thereof. The Parties agree that, notwithstanding the provisions of clause (a)(i)(B) of Section 1.2.1 of the Neurology II Agreement, the Research Term with respect to ALS Targets shall be extended until [***], but no later than [***] unless otherwise agreed by the Parties.

3. Target Validation for ALS Targets. Notwithstanding anything to the contrary in Section 1.2.3(c) of the Neurology II Agreement and in addition to the activities contemplated by Section 1.2.3(c) of the Neurology II Agreement, Ionis shall provide [***] to Biogen in amounts sufficient for Biogen to conduct [***] as set forth in the Neurological Disease Research Plan with respect to each ALS Target designated as a High Interest Target pursuant to paragraph 2 of this letter agreement, and Biogen shall [***], to conduct the research using such [***] as set forth in the Neurological Disease Research Plan for each such ALS Target. If, with respect to any ALS Target, Biogen notifies Ionis that it has elected to convert such ALS Target to a Neurology Target that is not an ALS Target under paragraph 5 of this letter agreement, then Biogen shall promptly following such notification return all [***] with respect to such ALS Target to Ionis. If Biogen has not commenced [***] in at least [***] of the [***] as set forth in the Neurological Disease Research Plan for a particular ALS Target by the [***] year anniversary of the date Ionis provided Biogen the [***] for such ALS Target under this Section 3, then such ALS Target will no longer be a High Interest Target and Biogen will return to Ionis all [***] for such ALS Target.

4. License Grant to Biogen. In accordance with Section 4.4.1 of the Neurology II Agreement, subject to the terms and conditions of the Neurology II Agreement (including Biogen's exclusivity covenants under Section 2.1.1 thereof), Ionis hereby grants to Biogen a non-exclusive, royalty-free license under any Licensed Technology solely to the extent necessary to conduct the activities as set forth in the Neurological Disease Research Plan with respect to each ALS Target. Biogen will pay to Ionis any and all costs arising under any Third Party agreement directly resulting from the license under this paragraph 4.

5. Designation of Collaboration Targets. With respect to each ALS Target designated as a High Interest Target under paragraph 2 of this letter agreement, Biogen may at any time during the Research Term, by written notice to Ionis, either (i) designate such ALS Target as a Collaboration Target pursuant to Section 1.5 of the Neurology II Agreement or (ii) elect to convert such ALS Target to a Neurology Target that is not an ALS Target under the Neurology II Agreement, as further set forth in paragraph 6 below. Notwithstanding the final sentence of Section 1.5 of the Neurology II Agreement, there shall be no limit on the number of ALS Targets that Biogen may designate as Collaboration Targets pursuant to Section 1.5 of the Neurology II Agreement, *provided that*, if Biogen has designated more than [***] ALS Targets as Collaboration Targets pursuant to Section 1.5 of the Neurology II Agreement in any rolling [***] period, such excess targets will be treated the same as "*Deferred Targets*" under the Neurology II Agreement until the earlier of (a) [***] or (b) [***] and, notwithstanding the provisions of [***] of the Neurology II Agreement, Biogen will [***] of the Neurology II Agreement with respect to such target until such time. [***] will be [***] under [***] of the Neurology II Agreement with respect to any Collaboration Target that is treated the same as a Deferred Target pursuant to this paragraph 5. Ionis shall conduct discovery, research and optimization activities for each Collaboration Target designated under this paragraph 5 in accordance with the Neurology II Agreement.

6. Effect of Decision not to Designate ALS Target as Collaboration Target. If Biogen elects to convert an ALS Target to a Neurology Target that is not an ALS Target pursuant to clause (ii) of the first sentence of paragraph 5 above, then (a) such Neurology Target shall be deemed removed from the High Interest Target List and (b) the provisions of the Neurology II Agreement applicable to Neurology Targets shall apply. Accordingly, Biogen may thereafter add such Neurology Target to the High Interest Target List in accordance with Section 1.2.3(a) of the Neurology II Agreement and, in such event, the provisions of the Neurology II Agreement applicable to High Interest Targets that are not ALS Targets shall apply. If Biogen does not add such Neurology Target to the High Interest Target List, Ionis may, with prior written notice to Biogen, advance such Neurology Target for ALS or for another indication in accordance with the Neurology II Agreement, *provided that* the provisions of the Neurology II Agreement applicable to Isis Neurology Targets, including without limitation Section 1.4 and Section 2.1.1(b), shall apply to such Neurology Target. Notwithstanding the foregoing, if Ionis presents to Biogen Target Sanction Data Packages with respect to more than [***] Isis Neurology Targets that were formerly ALS Targets under this letter agreement within any rolling [***] period, and Biogen wishes to designate more than [***] of such Isis Neurology Targets as Collaboration Targets pursuant to Section 1.4 of the Neurology II Agreement, then such excess targets will be treated the same as "*Deferred Targets*" under the Neurology II Agreement until the earlier of (a) [***] or (b) [***] and, notwithstanding the provisions of [***] of the Neurology II Agreement, Biogen will [***] of the Neurology II Agreement with respect to such target until such time. [***] will be [***] under [***] of the Neurology II Agreement with respect to any Collaboration Target that is treated the same as a Deferred Target pursuant to this paragraph 6.

7. Ionis FTEs. In addition to the [***] ([***]) Ionis FTEs dedicated to the activities under the Core Research Plan, the Neurological Disease Research Plan and the target validation activities under Section 1.11 of the Neurology II Agreement, Ionis shall dedicate an additional [***] ([***]) FTEs to conduct the activities contemplated by this letter agreement, the funding for which FTEs shall be in accordance with paragraph 8 below.

8. Funding of Ionis Activities for ALS Targets. During the period starting on the date of this letter agreement and ending on the termination of the Research Term, for each consecutive [***] ([***])-[***] period (or portion thereof) in which Biogen designates ALS Targets as High Interest Targets pursuant to paragraph 2 of this letter agreement, Biogen will pay Ionis [***] amount of [***] U.S. Dollars ($[***]) in consideration of the activities to be conducted by Ionis for such ALS Targets as set forth in this letter agreement. Ionis will invoice Biogen directly for such amount promptly after Biogen designates the first (1st) such ALS Target as a High Interest Target pursuant to paragraph 2 of this letter agreement for each such consecutive [***] ([***])-[***] period (or portion thereof), and Biogen shall pay each such invoice within forty-five (45) days of receipt thereof.

9. Adjustments to ALS Pre-Licensing Milestone Event Payments for ALS Collaboration Programs under this Letter Agreement. Solely with respect to ALS Collaboration Programs arising from High Interest Targets designated pursuant to this letter agreement, the ALS Pre-Licensing Milestone Event payments as set forth in Table 2 of Section 6.5 of the Neurology II Agreement shall be amended and replaced with the following in Table X:

TABLE X			
ALS Pre-Licensing Milestone Event	Column1 Milestone Event Payment for each of the [***] ALS Collaboration Program and the [***] ALS Collaboration Programs arising under this letter agreement	Column 2 Milestone Event Payment for each of the [***] ALS Collaboration Program and the [***] ALS Collaboration Program arising under this letter agreement	Column 3 Milestone Event Payment for each of the [***] ALS Collaboration Program and [***] ALS Collaboration Program thereafter arising under this letter agreement
[***]	$[***]	$[***]	$[***]
[***]	$[***]	$[***]	$[***]

Except as contemplated herein, all other provisions of the Neurology II Agreement will remain in full force and effect.

If you accept the terms and conditions set forth in this letter agreement, please so indicate by executing a copy of this letter agreement and returning it to Biogen. This letter agreement may be executed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from electronic transmission, store and printing of copies of this letter agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[*The remainder of this page is intentionally left blank.*]

Sincerely,

Biogen MA Inc.

By: */s/ Chris Henderson*
Name: Chris Henderson
Title: VP, Neurodegeneration & Repair

AGREED AND CONFIRMED ON BEHALF OF IONIS PHARMACEUTICALS, INC.:

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: Chief Operating Officer

Date:

Cc: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: (760) 268-4922

Exhibit 14.1

PHILOSOPHY OF IONIS CODE OF ETHICS AND BUSINESS CONDUCT

Reviewed & Approved – 12/2016
Next Review – 12/2017
Document Owner – Legal

Ionis Pharmaceuticals, Inc. (hereinafter referred to as "Ionis" or the "Company") will adhere to high legal and ethical standards. As such, this Code of Ethics and Business Conduct (hereinafter referred to as the "Code of Ethics") applies to each of Ionis' employees (including its executive officers) and each member of the Ionis Board of Directors. This Code of Ethics also applies to all employees and members of the Board of Directors of Ionis' majority-owned subsidiaries. References to Ionis and the Company are references to Ionis and its majority-owned subsidiaries.

COMPLIANCE WITH LAWS AND REGULATIONS

As a U.S. company, Ionis is governed by and required to comply with U.S. federal law. In addition to complying with federal law, Ionis will conduct all its activities in compliance with all applicable national, state and local laws, regulations and judicial decrees wherever it conducts business.

At no time will you take any action on behalf of the Company that you know, or reasonably should know, violates any law or regulation. Whenever possible, you will strive to comply with the spirit of the law as well as its letter.

No code of conduct can cover all circumstances or anticipate every situation. When you encounter situations not addressed specifically by this Code of Ethics, you should apply its overall philosophy and concepts to the situation. You should also refer to specific Company policies on the subject in question or similar subjects. If you still have a question about the appropriateness of an action, you should review the particular circumstances with Ionis' COO, CEO or the Audit Committee of the Board of Directors.

ETHICAL CONDUCT

You should strive to act in a manner using good judgment, high ethical standards and honesty in your business dealings on behalf of the Company. Unethical practices and activities do not serve the interests of the Company or the community, even if they do not technically violate the law.

Your Responsibilities

- Know and comply with the Ionis Code of Ethics and Company policies that apply to business activities.
- Be honest, fair and trustworthy in all business activities and relationships.
- Provide and support a culture that values integrity and ethical conduct.
- Avoid all conflicts of interest between work and personal affairs.
- Report suspected violations of law, the Ionis Code of Ethics or Company Policies.
- Cooperate in any investigation into possible violations of law, the Ionis Code of Ethics or Company Policies.

Business Practices

It is Ionis' policy to deal with its business associates, partners, suppliers, competitors and any governments or governmental agencies with which it interacts in an ethical manner. As such, you will comply with the principles outlined below and will take steps to ensure similar compliance by the persons you directly manage.

Interaction with Competitors

As a vigorous competitor in the marketplace, Ionis will seek economic knowledge about our competitors. However, you will not engage in illegal or improper acts to acquire any competitor information. In addition, you will not hire competitors' employees for the purpose of obtaining confidential information, urge competitors' personnel, customers or suppliers to disclose confidential information, or seek such information from competitors' employees subsequently hired by the Company.

Bribes, Kickbacks and Similar Payments

You are prohibited from paying or receiving any bribe, kickback or other similar payment to or from any public official, or government, or other individual, to secure any concession, contract or other favorable treatment for Ionis or you. This prohibition extends to the payment or receipt of money or anything else of substantial value when you have reason to believe that some part of the payment or "fee" will be used for a bribe, kickback or other similar activity.

Because Ionis is a global company and does business worldwide, you must comply with the United States Foreign Corrupt Practices Act of 1977. For more detail, please read the "Foreign Corrupt Practices Act," attached as Appendix A.

Books, Records and Information Management

Ionis' books of account and records must be accurately maintained and fully disclose the nature of transactions reflected in them. Penalties for violating the laws and regulations in this area could be severe for the Company and the employees involved. Ionis will maintain these books according to the following record-keeping requirements and in compliance with the spirit and letter of applicable laws and regulations:

- All books, records and accounts must be kept in reasonable detail and must accurately and fairly reflect all transactions and dispositions of the Company's assets.
- All disbursements of funds and all receipts must be properly and promptly recorded.
- No undisclosed or unrecorded fund or account may be established for any purposes.
- False or artificial entries must never be made in any of the books or records of the Company, or in any public record for any reason, nor should the Company's records be falsely altered in any way.

Retention of Records

Legal practice requires the retention of certain records for various periods of time, particularly those relating to taxes, personnel, contracts and corporate structure. When litigation or a government investigation or audit is pending or imminent, you must not destroy any relevant records until the matter is closed. Destruction of records to avoid disclosure in a legal proceeding or investigation may constitute a criminal offense.

Audit Integrity

No officer or director of Ionis, or any other person acting under their direction, will take any action to fraudulently influence, coerce, manipulate, or mislead any independent accountant engaged in the performance of an audit of the Company's financial statements for the purpose of rendering the Company's financial statements materially misleading.

Conflicts of Interest

As an employee you cannot without the Company's express written consent, engage in any employment or business activity other than for the Company. Unless expressly consented to in writing by the Company, your personal activities should not involve the use of Company property, facilities, influence or other resources, and should not reflect discredit upon the Company.

You will not engage in any activity through which you stand to benefit personally from any sale or purchase of goods and services by the Company. This provision does not apply to benefits arising out of your employment with the Company, or to ownership of equity in a publicly traded company which was purchased on the open market and represents (i) less than 1% of such company's outstanding equity and (ii) less than 5% of your equity portfolio.
You must promptly disclose in writing any actual or potential conflicts of interest to Ionis' COO, CEO or General Counsel. Ionis will review the matter, as set forth above, and communicate its position in writing.

Pre-Clearance Procedure

All employees must pre-clear any employment or business activity other than for the Company. To do so, you should contact either (i) the CEO, (ii) COO or (iii) General Counsel and explain to them the proposed business activity you wish to engage in. If you are an executive officer, the Nominating, Governance and Review Committee will evaluate the proposed business activity and will notify you whether such activity has been approved. For all other employees, the CEO or COO will evaluate the proposed business activity and will notify you whether such activity has been approved. In some cases, the individual(s) reviewing your request may discuss your request with other members of the Ionis management team. Remember, just because you have to pre-clear a certain activity, does not mean that Ionis will prevent you doing it.

Members of the Board of Directors must request and receive a determination of no conflict from the Nominating, Governance and Review Committee before engaging in any activity, including acting as an employee or director for any entity that directly or indirectly competes with Ionis.

Certain Pre-Cleared Business Activities

Ionis' management has already pre-cleared certain business activities that should not cause a conflict of interest. For these activities, employees generally do not need to obtain written permission from the Company. However, please use your common sense because even with pre-cleared activities, conflicts of interest can arise. If you are ever in doubt, you should follow the pre-clearance procedures outlined above. The pre- cleared business activities include:

- Working in the food service or hospitality industry after normal business hours;
- Owning rental property (unless Ionis rents the property);
- Philanthropic or pro bono activities;
- Farming;
- Home-based retail (e.g. Amway, Tupperware, cosmetics), provided you do not solicit sales during Ionis business hours or at the Ionis workplace; and
- Fitness instructor.

Dishonesty and Theft

You will not knowingly:

- Engage in fraud or embezzlement affecting Company property, funds, securities or other assets; or
- Willfully damage or destroy property or materials belonging to the Company, its employees or customers.

In addition, without proper supervisory authorization, you will not knowingly:

- Remove property, material or money from the Company, its employees, or its customers for personal gain, personal use, resale or to give to another party;
- Receive property, materials or money belonging to the Company, its employees or its customers for personal gain, personal use, resale or to give to another party;
- Access, remove, publish, destroy or alter private or confidential information existing in physical Company records or electronically stored information;
- Remove, publish, destroy or alter other physical Company records or electronically stored information affecting the Company, its employees or corporate partners; or
- Copy, reprint, duplicate, or recreate in whole or in part, computer programs or related systems developed or modified by Ionis personnel, or acquired from outside vendors.

Insider Trading

The Company opposes the misuse of material nonpublic information in the trading of securities. You agree that you will at all times adhere to the Company's insider trading policy.

WAIVERS FOR EXECUTIVE OFFICERS AND DIRECTORS

Any waiver of this Code of Ethics for executive officers or members of the Board of Directors must be approved by the Nominating, Governance and Review Committee and must be promptly disclosed to the Company's stockholders, including the reasons for the waiver.

REPORTING SUSPECTED VIOLATIONS

Ionis is committed to complying with all applicable securities laws and to filing fair and accurate disclosures with the SEC. Each Employee who reports suspected accounting improprieties or violations of this Code of Ethics or of any laws specifically including federal mail fraud, wire fraud, or securities fraud statutes will be taken seriously and the allegations will be thoroughly investigated.

An employee who suspects accounting improprieties or violations of this Code of Ethics or of any laws specifically including federal mail fraud, wire fraud, or securities fraud statutes should take the following steps:

1. The employee should immediately communicate his/her concern to the General Counsel, the COO or the CEO. To ensure the highest quality response, employees should communicate directly with one of these designated Ionis officials. However, any concern may be made anonymously and will be taken seriously.
2. Any officer receiving such a complaint will immediately communicate the complaint to the Audit Committee or you may directly report a suspected violation to the Chairman of the Audit Committee.
3. The Audit Committee together with management will conduct, if appropriate, a confidential, but not anonymous investigation which will involve talking to the complainant (if known), the accused, and as circumstances warrant, any witnesses, and anyone who may have similar complaints.
4. All parties involved in the investigation will be required to cooperate fully, maintain complete confidentiality and take no action which might be considered retaliatory.
5. Once the investigation is complete, the Audit Committee will make a determination as to what happened, the level of severity and the appropriate remedial action, and will take such action.

Ionis will not discharge, demote, suspend, threaten, harass, or in any other manner discriminate against an employee because you (1) have provided information, caused information to be provided, or otherwise assisted in an investigation regarding any conduct which you reasonably believe constitutes a violation of this Code of Ethics or of the federal mail fraud, wire fraud, or securities fraud statutes, any SEC rule or any provision of federal law relating to fraud against stockholders, when the information or assistance is provided to or the investigation is conducted by a federal regulatory or law enforcement agency, any Member of Congress or Congressional committee, or a person with supervisory authority over the employee or (2) have filed, caused to be filed, testified, participated in or otherwise assisted in a proceeding filed or about to be filed (with any knowledge of Ionis) relating to an alleged violation of the federal mail fraud, wire fraud, or securities fraud statutes, any SEC rule or any provision of federal law relating to fraud against stockholders. An employee who alleges such discharge or discrimination may file a civil complaint with the Secretary of Labor.

CONSEQUENCES OF VIOLATING IONIS' CODE OF ETHICS

If you violate the law, the Ionis Code of Ethics or Ionis' policies, you may be subject to disciplinary action, up to and including termination. If necessary, Ionis may suspend your employment during an investigation into an alleged breach. Additional actions may include reassignment of work duties and limitation in future job opportunities. Ionis may

refer violations of law to local or federal law enforcement authorities for possible prosecution.

APPENDIX A – The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act (FCPA) prohibits U.S. companies from making improper payments or gifts to foreign officials. Company policy requires that all directors, officers, employees, agents and consultants of Ionis comply with the FCPA.

Definition of Foreign Official

Under the FCPA, the term "foreign official" includes elected and appointed governmental officials, candidates for public office, foreign political parties, officers and employees of government owned or controlled enterprises, and public international organizations. When in doubt, Ionis employees should consult the Company's Legal Counsel for advice on whether a potential recipient of a payment is a "foreign official."

Prohibited Acts

The following acts are prohibited by the FCPA:

1. Authorizing, paying, promising or delivering any payment, gift or favor intended to influence any foreign official on a matter within that person's responsibilities. For example, any payment to any foreign official for the purposes of obtaining or retaining sales of products or services to Ionis, sales by Ionis of Ionis products or services, to win a bid or contract, or to obtain more favorable tax treatment is prohibited.
2. Any indirect payment to a third party if the payor knows that the third party may make a prohibited payment. For example, any payment to an Ionis agent or consultant where the payor is aware or has a firm belief that such agent or consultant may make an improper payment to a foreign official is prohibited. The Ionis payor may not avoid this prohibition by deliberately ignoring or purposefully avoiding knowledge that a bribe may be paid.
3. Establishing any undisclosed or unrecorded "slush" funds or assets; making any false or artificial entries in company books or records; failing to keep books, records and accounts in reasonable detail to reflect accurately the handling of money and other assets; and failing to maintain internal accounting controls sufficient to verify that no improper payments have been made.

Permissible Payments

The following payments may be made:

1. Payments to a foreign official for the purpose of expediting or securing the performance of a routine governmental action. Payments for the following routine governmental actions are permissible: obtaining permits, licenses or other official documents to qualify to do business in a foreign country; processing governmental papers, such as visas and work orders; assuring police protection, mail pickup and delivery, or scheduling inspections associated with contract performance or inspections related to the transit of goods across country; and providing phone service, power and water supply, loading and unloading cargo or protecting perishable products or commodities from deterioration. Routine governmental action does not include any decision by a foreign official to encourage, to award, to continue or to modify the terms relating to any business with any Ionis entity.
2. Any payment that is lawful under the written laws and regulations of the foreign country.
3. Any reasonable expenditure directly related to the promotion, demonstration or explanation of Ionis products or services or the execution or performance of a contract with a foreign government or agency, such as the travel and lodging expenses of a foreign official on a trip for such purposes.

Penalties

Violations of the anti-bribery provisions of the FCPA may result in criminal fines of up to $2,000,000 for corporations and $100,000 and five years imprisonment for individuals. Violations of the accounting provisions may result in fines of up to $2,500,000 for corporations and $1,000,000 and ten years imprisonment for individuals. Under alternative fine provisions, a violator may be fined up to twice the amount of the gain or loss resulting from a violation.

Payments and the FCPA

Neither Ionis nor any director, officer, employee, agent or consultant of the Company will directly or indirectly make or promise illegal payments or contributions, or engage in any other illegal conduct in order to influence customers, suppliers or governmental entities, including their officials or employees, to secure or retain business, to encourage any such employees or officials to fail to perform or to perform improperly their official functions or to influence legislation, nor undertake any of the acts prohibited by the FCPA, as summarized above. Neither Ionis nor any director, officer, employee, agent or consultant of the Company will submit to extortion as a condition of doing business.

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Akcea Therapeutics, Inc., a Delaware Corporation

Akcea Therapeutics UK Limited, a United Kingdom Limited Private Company

Akcea Intl Ltd., a Cayman Islands Limited Liability Company

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. 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.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 March 1, 2017, 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, 2016.

/s/ ERNST & YOUNG LLP

San Diego, California
March 1, 2017

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: March 1, 2017

/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: March 1, 2017

/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, 2016, 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: March 1, 2017

/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.