UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

☐ QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Quarterly Period Ended March 31, 2016

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

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 (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 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 12(b)-2 of the Securities Exchange Act of 1934). Yes ☐ No ☐

The number of shares of voting common stock outstanding as of April 29, 2016 was 120,782,993.

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TRADEMARKS

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

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

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

KYNAMRO® is a registered trademark of Kastle Therapeutics LLC

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

	March 31, 2016 (Unaudited)	December 31, 2015
ASSETS		
Current assets:		
Cash and cash equivalents	$ 93,337	$ 128,797
Short-term investments	610,467	650,386
Contracts receivable	16,480	11,356
Inventories	6,520	6,899
Investment in Regulus Therapeutics Inc.	19,703	24,792
Other current assets	17,403	14,773
Total current assets	763,910	837,003
Property, plant and equipment, net	90,365	90,233
Patents, net	20,144	19,316
Deposits and other assets	1,400	1,348
Total assets	$ 875,819	$ 947,900
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 19,464	$ 28,355
Accrued compensation	6,338	16,065
Accrued liabilities	26,172	28,105
Current portion of long-term obligations	8,826	9,029
Current portion of deferred contract revenue	63,695	67,322
Total current liabilities	124,495	148,876
Long-term deferred contract revenue	123,084	134,306
1 percent convertible senior notes	345,265	339,847
2¾ percent convertible senior notes	50,190	49,523
Long-term obligations, less current portion	2,372	2,341
Long-term financing liability for leased facility	72,251	72,217
Total liabilities	717,657	747,110
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 120,717,810 and 120,351,480 shares issued and outstanding at March 31, 2016 and December 31, 2015, respectively	121	120
Additional paid-in capital	1,331,945	1,309,107
Accumulated other comprehensive loss	(16,115)	(13,565)
Accumulated deficit	(1,157,789)	(1,094,872)
Total stockholders' equity	158,162	200,790
Total liabilities and stockholders' equity	$ 875,819	$ 947,900

See accompanying notes.

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

	Three Months Ended March 31,	
	2016	**2015**
Revenue:		
Research and development revenue under collaborative agreements	$ 35,214	$ 61,892
Licensing and royalty revenue	1,660	691
Total revenue	36,874	62,583
Expenses:		
Research, development and patent expenses	80,964	64,447
General and administrative	10,562	7,466
Total operating expenses	91,526	71,913
Loss from operations	(54,652)	(9,330)
Other income (expense):		
Investment income	1,457	845
Interest expense	(9,490)	(9,021)
Loss before income tax benefit	(62,685)	(17,506)
Income tax (expense) benefit	(232)	789
Net loss	$ (62,917)	$ (16,717)
Basic and diluted net loss per share	$ (0.52)	$ (0.14)
Shares used in computing basic and diluted net loss per share	120,598	118,948

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2016	**2015**
Net loss	$ (62,917)	$ (16,717)
Unrealized (losses) gains on securities, net of tax	(2,550)	7,367
Comprehensive loss	$ (65,467)	$ (9,350)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2016	**2015**
Operating activities:		
Net loss	$ (62,917)	$ (16,717)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:		
Depreciation	1,841	1,571
Amortization of patents	376	312
Amortization of licenses	1	469
Amortization of premium on investments, net	2,039	1,749
Amortization of debt issuance costs	298	275
Amortization of 2¾ percent convertible senior notes discount	620	565
Amortization of 1 percent convertible senior notes discount	5,175	4,788
Amortization of long-term financing liability for leased facility	1,672	1,662
Stock-based compensation expense	20,103	13,305
Non-cash losses related to patents, licensing and property, plant and equipment	396	93
Tax benefit from other unrealized gains on securities	—	(798)
Changes in operating assets and liabilities:		
Contracts receivable	(5,124)	(23,031)
Inventories	379	(549)
Other current and long-term assets	(2,747)	(2,451)
Accounts payable	(11,417)	(2,695)
Accrued compensation	(9,728)	(6,891)
Deferred rent	48	62
Accrued liabilities	(1,934)	(6,704)
Deferred contract revenue	(14,849)	(7,841)
Net cash used in operating activities	(75,768)	(42,826)
Investing activities:		
Purchases of short-term investments	(41,366)	(40,213)
Proceeds from the sale of short-term investments	81,805	78,460
Purchases of property, plant and equipment	(628)	(878)
Acquisition of licenses and other assets, net	(382)	(719)
Net cash provided by investing activities	39,429	36,650
Financing activities:		
Proceeds from equity awards	2,736	14,116
Principal payments on debt and capital lease obligations	(1,857)	(2,590)
Net cash provided by financing activities	879	11,526
Net decrease in cash and cash equivalents	(35,460)	5,350
Cash and cash equivalents at beginning of period	128,797	142,998
Cash and cash equivalents at end of period	$ 93,337	$ 148,348
Supplemental disclosures of cash flow information:		
Interest paid	$ 31	$ 37
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 2,524	$ 1,198

See accompanying notes.

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three months ended March 31, 2016 and 2015 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2015. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of our financial position at such dates and our operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2015 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

The condensed consolidated financial statements include the accounts of Ionis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiary, Akcea Therapeutics, Inc., which we incorporated in December 2014.

2. Significant Accounting Policies

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 condensed balance sheet.

Arrangements with multiple deliverables

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

Identifying deliverables and units of accounting

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

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

We determined that each of these three units of accounting have stand-alone value. The 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 ongoing development services by using our internal estimates of the cost to perform the specific services and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the development services. The significant inputs we used to determine the selling price of the ongoing development services included:

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

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

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

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

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

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

Timing of revenue recognition

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

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

- We recognized the portion of the consideration attributed to the IONIS-FXI$_{Rx}$ license immediately because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the ongoing development services for IONIS-FXI$_{Rx}$ over the period of time we are performing the services; and
- We will recognize the amount attributed to the API supply when we deliver it to Bayer. During the three months ended March 31, 2016, we recognized $0.4 million related to a portion of the API we delivered to Bayer during the quarter.

Multiple agreements

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

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

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

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

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

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

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

Milestone payments

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

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

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

The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing authorization from the 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. We also consider milestones associated with our alliance with Alnylam Pharmaceuticals, Inc. substantive because we provide Alnylam ongoing access to our technology to develop and commercialize RNA interference, or RNAi, therapeutics. In evaluating if a milestone is substantive we consider whether:

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

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

Licensing and royalty revenue

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

Cash, cash equivalents and short-term investments

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

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

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs. We did not record any inventory write-offs for the three months ended March 31, 2016 and 2015. Total inventory was $6.5 million and $6.9 million as of March 31, 2016 and December 31, 2015, respectively.

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 condensed consolidated balance sheet and we expense them as the services are provided.

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. We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs. We recorded charges primarily related to the write-down of intangible assets of $0.4 million and $0.1 million for the three months ended March 31, 2016 and 2015, respectively.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs 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.

Use of estimates

The preparation of condensed 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 condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

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 the three months ended March 31, 2016 and 2015, 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:

- 1 percent convertible senior notes;
- 2¾ percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

Accumulated other comprehensive income (loss)

Accumulated other comprehensive income (loss) is comprised of unrealized gains and losses on investments, net of taxes, and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive income to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income (loss) for the three months ended March 31, 2016 and 2015 (in thousands):

	Three Months Ended March 31,	
	2016	2015
Beginning balance accumulated other comprehensive income (loss)	$ (13,565)	$ 39,747
Other comprehensive income (loss) before reclassifications, net of tax (1)	(2,550)	7,367
Net current period other comprehensive income (loss)	(2,550)	7,367
Ending balance accumulated other comprehensive income (loss)	$ (16,115)	$ 47,114

(1) Other comprehensive income from the three months ended March 31, 2015 includes income tax expense of $5.1 million. There was no tax benefit for other comprehensive loss for the three months ended March 31, 2016.

Convertible debt

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

We assign a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing the debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method.

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 carrying amount of the related debt liability on our consolidated balance sheet. We are amortizing these costs over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method.

Segment information

We have two operating segments, our Ionis Core segment and Akcea Therapeutics, which includes the operations of our wholly-owned subsidiary, Akcea Therapeutics, Inc. We formed Akcea to develop and commercialize drugs for 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.

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 condensed 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 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 historical exercise patterns. For the three months ended March 31, 2016 and 2015, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2016	2015
Risk-free interest rate	1.5%	1.5%
Dividend yield	0.0%	0.0%
Volatility	57.9%	53.5%
Expected life	4.5 years	4.5 years

ESPP:

	Three Months Ended March 31,	
	2016	2015
Risk-free interest rate	0.5%	0.1%
Dividend yield	0.0%	0.0%
Volatility	69.4%	56.2%
Expected life	6 months	6 months

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four-year period. The weighted-average grant date fair value of RSUs granted to employees for the three months ended March 31, 2016 was $43.88 per share.

We did not grant stock options or RSUs to our Board of Directors during the three months ended March 31, 2016 and 2015.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2016 and 2015 (in thousands). Our consolidated non-cash stock-based compensation expense includes $3.2 million and $0.6 million of stock-based compensation expense for Akcea employees for the three months ended March 31, 2016 and 2015.

	Three Months Ended March 31,	
	2016	2015
Research, development and patent expenses	$ 14,770	$ 10,486
General and administrative	5,333	2,819
Total	$ 20,103	$ 13,305

Non-cash stock-based compensation expense was $20.1 million for the three months ended March 31, 2016, and increased compared to $13.3 million for the same period in 2015 The amount of stock compensation expense we recognized in the first quarter of 2016 has increased compared to the same period in 2015 because the average fair value of unvested stock options has risen due to the increase in the exercise price of the stock options we have granted over the past several years. As of March 31, 2016, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $88.9 million and $23.8 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.5 years and 1.7 years, respectively.

Impact of recently issued accounting standards

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects in exchange for the goods or services. This guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance as originally issued is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. In July 2015, the FASB issued updated accounting guidance to allow for an optional one year deferral from the original effective date. As a result, we will adopt this guidance beginning on January 1, 2018. The guidance allows us to select one of two methods of adoption, either the full retrospective approach, meaning the guidance would be applied to all periods presented, or modified retrospective, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to our opening retained earnings balance. We are currently determining the adoption method and the effects the adoption will have on our consolidated financial statements and disclosures.

In August 2014, the FASB issued accounting guidance on how and when to disclose going-concern uncertainties in the financial statements. This guidance will require us to perform interim and annual assessments to determine our ability to continue as a going concern within one year from the date that we issue our financial statements. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. We will adopt this guidance in our fiscal year beginning January 1, 2017. We do not expect this guidance to have any effect on our consolidated financial statements.

In January 2016, the FASB issued amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires us to measure and record equity investments, except those accounted for under the equity method of accounting that have a readily determinable fair value, at fair value and for us to recognize the changes in fair value in our net income (loss), instead of recognizing changes in value through accumulated other comprehensive income, as we currently do under the existing guidance. The amended guidance also changes several disclosure requirements for financial instruments, including the methods and significant assumptions we use to estimate fair value. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2017. We will adopt this guidance on January 1, 2018 and we will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. We are currently determining the effects the adoption will have on our consolidated financial statements and disclosures.

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. 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 will adopt this guidance on January 1, 2017. We are currently assessing the timing of adoption, adoption methods as well as the effects this amended guidance will have on our consolidated financial statements and disclosures. The following are the main aspects of the updated guidance that will impact us:

- *Recognition of excess tax benefits and tax deficiencies:* The updated guidance requires us to recognize excess tax benefits and tax deficiencies as income tax expense or benefit in our statement of operations on a prospective basis.

- *Classification of certain share-based payment activities on our statement of cash flows:* The updated guidance requires us to classify the following items on our statement of cash flows as follows:
  - We will classify excess tax benefits as an operating activity. We may adopt this update either prospectively in the period of adoption or adjust our cash flow statement for each period we present.
  - We will classify amounts we withhold in shares for the payment of employee taxes as a financing activity. For this update, we must adjust our cash flow statement for each period we present.

- *Accounting for forfeitures:* The updated guidance allows us to choose to account for forfeitures when they occur or continue to estimate them. If we adopt this change and begin accounting for forfeitures when they occur, we must adopt it using a modified retrospective approach, which requires us to reflect an adjustment on our consolidated balance sheet through a cumulative-effect adjustment to our stockholders' equity at the beginning of the period of adoption.

3. Investments

As of March 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 March 31, 2016:

One year or less	51%
After one year but within two years	32%
After two years but within three and a half years	17%
Total	100%

As illustrated above, at March 31, 2016, 83 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 March 31, 2016, we had an ownership interest of less than 20 percent in one private company and two public companies with which we conduct business. The privately-held company is Atlantic Pharmaceuticals Limited and the publicly-traded companies are Antisense Therapeutics Limited and Regulus. We account for equity investments in the privately-held company under the cost method of accounting and we account for equity investments in the publicly-traded companies at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments.

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

March 31, 2016	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities (1):				
Corporate debt securities	$ 161,995	$ 29	$ (59)	$ 161,965
Debt securities issued by U.S. government agencies	42,545	3	(1)	42,547
Debt securities issued by the U.S. Treasury	13,101	3	(3)	13,101
Debt securities issued by states of the United States and political subdivisions of the states (2)	78,231	14	(97)	78,148
Total securities with a maturity of one year or less	295,872	49	(160)	295,761
Corporate debt securities	242,995	608	(416)	243,187
Debt securities issued by U.S. government agencies	36,951	2	(12)	36,941
Debt securities issued by states of the United States and political subdivisions of the states	40,201	26	(82)	40,145
Total securities with a maturity of more than one year	320,147	636	(510)	320,273
Total available-for-sale securities	$ 616,019	$ 685	$ (670)	$ 616,034
Equity securities:				
Regulus Therapeutics Inc.	$ 7,162	$ 12,541	$ —	$ 19,703
Total equity securities	$ 7,162	$ 12,541	$ —	$ 19,703
Total available-for-sale and equity securities	$ 623,181	$ 13,226	$ (670)	$ 635,737

December 31, 2015	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities (1):				
Corporate debt securities	$ 181,670	$ 5	$ (250)	$ 181,425
Debt securities issued by U.S. government agencies	50,559	1	(19)	50,541
Debt securities issued by the U.S. Treasury	2,604	—	(3)	2,601
Debt securities issued by states of the United States and political subdivisions of the states (2)	79,414	18	(88)	79,344
Total securities with a maturity of one year or less	314,247	24	(360)	313,911
Corporate debt securities	258,703	3	(1,705)	257,001
Debt securities issued by U.S. government agencies	38,956	—	(244)	38,712
Debt securities issued by states of the United States and political subdivisions of the states	48,552	3	(243)	48,312
Total securities with a maturity of more than one year	346,211	6	(2,192)	344,025
Total available-for-sale securities	$ 660,458	$ 30	$ (2,552)	$ 657,936
Equity securities:				
Regulus Therapeutics Inc.	$ 7,162	$ 17,630	$ —	$ 24,792
Total equity securities	$ 7,162	$ 17,630	$ —	$ 24,792
Total available-for-sale and equity securities	$ 667,620	$ 17,660	$ (2,552)	$ 682,728

(1) Our available-for-sale securities are held at amortized cost.

(2) Includes investments classified as cash equivalents on our condensed consolidated balance sheet.

Investments we consider to be temporarily impaired at March 31, 2016 were as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment		More than 12 months of temporary impairment		Total temporary impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	168	$ 203,743	$ (442)	$ 16,040	$ (33)	$ 219,783	$ (475)
Debt securities issued by U.S. government agencies	8	28,890	(13)	1,000	—	29,890	(13)
Debt securities issued by the U.S. Treasury	1	10,523	(3)	—	—	10,523	(3)
Debt securities issued by states of the United States and political subdivisions of the states	204	65,721	(92)	18,936	(87)	84,657	(179)
Total temporarily impaired securities	381	$ 308,877	$ (550)	$ 35,976	$ (120)	$ 344,853	$ (670)

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.

4. 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 the three months ended March 31, 2016, there were no transfers between our Level 1 and Level 2 investments. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

We measure the following major security types at fair value on a recurring basis. The following summary breaks down the fair-value hierarchy that we valued each security with at March 31, 2016 and December 31, 2015 (in thousands):

	At March 31, 2016	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 74,091	$ 74,091	$ —
Corporate debt securities (2)	405,152	—	405,152
Debt securities issued by U.S. government agencies (2)	79,488	—	79,488
Debt securities issued by the U.S. Treasury (2)	13,101	13,101	—
Debt securities issued by states of the United States and political subdivisions of the states (3)	118,293	—	118,293
Investment in Regulus Therapeutics Inc.	19,703	19,703	—
Total	$ 709,828	$ 106,895	$ 602,933

	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 United States and political subdivisions of the states (3)	127,656	—	127,656
Investment in Regulus Therapeutics Inc.	24,792	24,792	—
Total	$ 771,630	$ 116,295	$ 655,335

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

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

(3) At March 31, 2016 and December 31, 2015, $5.6 million and $7.5 million, respectively, were included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

We did not have investments that were valued with significant unobservable inputs, or Level 3 investments, at March 31, 2016 and December 31, 2015.

Other Fair Value Disclosures

Our 1 percent and 2¾ percent notes had a fair value of $455.1 million and $124.7 million, respectively, at March 31, 2016. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

5. Line of Credit Arrangement

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. Under the credit agreement, we can borrow up to a maximum of $30 million of revolving credit for general working capital purposes. Under the credit agreement interest is payable monthly in arrears on the outstanding principal at a rate based on our option of:

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

Additionally, we will pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility beginning after June 2016. As of March 31, 2016 we had $8.5 million in outstanding borrowings under the credit facility, which we used to fund our capital equipment needs in 2015 and is consistent with our historical practice to finance these costs. As of March 31, 2016, our outstanding borrowings under this credit facility were at a weighted average interest rate of 1.69 percent.

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

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnership

Biogen

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

Nusinersen

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize nusinersen for the treatment of SMA. We are currently conducting a Phase 3 study evaluating nusinersen in infants with SMA, for which we completed enrollment in May 2016. We are also conducting a Phase 3 study evaluating nusinersen in children with SMA, for which we completed target enrollment in 2015. We plan to have data from both of these Phase 3 studies in the first half of 2017. In addition, we are evaluating nusinersen in two Phase 2 open-label studies, one in children with SMA and one in infants with SMA. Patients from all of these studies continue to have access to nusinersen through open-label extension dosing. We are responsible for completing the studies we are currently conducting. Biogen has the option to license nusinersen. If Biogen exercises its option, it will pay us a license fee and will assume all other global development, regulatory and commercialization responsibilities. Biogen may exercise this option upon completion of and data review of the first successful Phase 2/3 trial or completion of both Phase 2/3 trials. An amendment in December 2014 provided for additional opt-in scenarios, based on the filing or the acceptance of a new drug application or marketing authorization application with the FDA or EMA. In June 2015, we and Biogen amended the development plan for nusinersen to include conducting the open-label extension study for the Phase 3 studies in infants and children.

Under the terms of the agreement, we received an upfront payment of $29 million, which we are amortizing through February 2017. We are also eligible to receive a license fee, milestone payments and tiered royalties up to the mid-teens on any sales of nusinersen. Over the term of the collaboration, we are eligible to receive up to $346 million in a license fee and payments, including up to $121 million in substantive milestone and other payments associated with the clinical development of nusinersen prior to licensing and up to $150 million in substantive milestone payments if Biogen achieves pre-specified regulatory milestones. From inception through March 2016, we have received nearly $150 million in payments for advancing nusinersen. In the first quarter of 2016, we earned $9.5 million in milestone payments for advancing nusinersen. In May 2016, we earned a $2 million milestone payment when we completed enrollment in the Phase 3 study in infants. We will earn the next payment of $75 million if Biogen licenses nusinersen and we will earn the next milestone payment of up to $60 million if Biogen receives regulatory approval for nusinersen.

IONIS-DMPK-2.5$_{Rx}$

In June 2012, we and Biogen entered into a second and separate collaboration agreement to develop and commercialize a novel antisense drug, IONIS-DMPK-2.5$_{Rx}$, targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. We are currently evaluating IONIS-DMPK-2.5$_{Rx}$ in a Phase 1/2 clinical study in patients with DM1. Biogen has the option to license the drug through the completion of the first Phase 2 trial. If Biogen exercises its option, it will assume all other global development, regulatory and commercialization responsibilities. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through October 2018. In June 2015, we and Biogen amended the development plan for IONIS-DMPK-2.5$_{Rx}$ under which we are eligible to earn additional milestone payments of up to $4.2 million for further advancing the Phase 1/2 study of IONIS-DMPK-2.5$_{Rx}$. Over the term of the collaboration, we are eligible to receive up to $263 million in a license fee and substantive milestone payments, including up to $63 million in development milestone payments and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on any sales of IONIS-DMPK-2.5$_{Rx}$. From inception through March 2016, we have received nearly $39 million in payments for advancing IONIS-DMPK-2.5$_{Rx}$. We will earn the next milestone payment of $1.4 million if we further advance IONIS-DMPK-2.5$_{Rx}$ and we will earn a $35 million milestone payment if we initiate a Phase 2 study for IONIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen entered into a third and separate collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-BIIB4$_{Rx}$ under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We are eligible to receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials. We are also eligible to receive up to $130 million in milestone payments per program if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any drugs resulting from each of the three programs. From inception through March 2016, we have received $43 million in payments under this collaboration. In February 2016, we earned a $3 million milestone payment for further advancing IONIS-BIIB4$_{Rx}$. We will earn the next milestone payment of up to $10 million for the continued development of IONIS-BIIB4$_{Rx}$.

Strategic Neurology

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

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen could potentially require us to refund.

For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered single-digit royalties on sales from any drugs using non-antisense modalities developed under this collaboration. From inception through March 2016, we have received more than $140 million in payments under this collaboration. We will earn the next milestone payment of up to $10 million if we advance a program 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 the three months ended March 31, 2016, we earned revenue of $21.3 million from our relationship with Biogen, which represented 58 percent of our total revenue for that period. In comparison, we earned revenue of $39.2 million for the same period in 2015, which represented 63 percent. Our condensed consolidated balance sheet at March 31, 2016 included deferred revenue of $85.7 million related to our relationship with Biogen.

Research, Development and Commercialization Partners

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Our alliance currently comprises five drugs in development, including our Phase 3 drug IONIS-TTR$_{Rx}$. We are responsible for completing the Phase 3 study we are currently conducting for IONIS-TTR$_{Rx}$. GSK has the option to license IONIS-TTR$_{Rx}$. If GSK exercises its option it will pay us a license fee. GSK has the exclusive option to license the other drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee. If GSK exercises its exclusive option for any drugs resulting from this alliance, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received $38 million in upfront and expansion payments, which we are amortizing through March 2017.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for IONIS-TTR_{Rx}. We are currently evaluating IONIS-TTR_{Rx} in a broad Phase 3 development program. We have completed enrollment in the Phase 3 study in patients with FAP. From inception through March 2016, we have earned $60 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 September 2015, we and GSK amended the development plan for IONIS-TTR_{Rx} to support the Phase 3 cardiomyopathy study, which GSK plans to conduct.

In addition to IONIS-TTR_{Rx}, we have four drugs in development with GSK. We are developing two antisense drugs we designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV, infection; IONIS-HBV_{Rx} and IONIS-HBV-L_{Rx}, a follow-on drug using our LICA technology. We are also developing IONIS-GSK4-L_{Rx} and IONIS-RHO-2.5_{Rx}, which are antisense drugs we designed to treat ocular diseases. In March 2016, we and GSK amended the development plan for IONIS-HBV_{Rx} to allow GSK to conduct all further development activities for this program.

Under our agreement, if GSK successfully develops all five drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.0 billion, including up to $168.5 million for the achievement of development milestones, up to $363.5 million for the achievement of regulatory milestones and up to $338 million for the achievement of commercialization milestones. Through March 2016, we have received more than $145 million in payments under this alliance with GSK. In the first quarter of 2016, we earned a $1.5 million milestone payment when GSK initiated a Phase 1 study of IONIS-HBV-L_{Rx}. We will earn the next milestone payment of up to $1.5 million if we further advance a program under this collaboration. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

Our alliance with GSK will continue until the earlier of the date that all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- GSK may terminate any program, other than the IONIS-TTR_{Rx} program, at any time by providing written notice to us;
- GSK may terminate the IONIS-TTR_{Rx} program by providing written notice to us after reviewing specific data from the Phase 3 study for the program; and
- Either we or GSK may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During the three months ended March 31, 2016, we earned revenue of $5.0 million, from our relationship with GSK, which represented 14 percent of our total revenue for that period. In comparison, we earned revenue of $16.5 million for the same period in 2015, which represented 26 percent of our total revenue for that period. Our condensed consolidated balance sheet at March 31, 2016 included deferred revenue of $4.4 million related to our relationship with GSK.

Kastle Therapeutics

In May 2016, we entered into an agreement with Kastle Therapeutics 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. Under the terms of the agreement, we are eligible to receive up to $95 million, which includes a $15 million up-front payment we earned in May 2016, a $10 million payment we will receive in May 2019 and up to $70 million in sales milestones. Beginning in 2017, we will earn tiered royalties on global sales of Kynamro that average in the mid to low teens. In addition, we also received a 10 percent common equity position in Kastle. Sanofi Genzyme will earn a three percent royalty on sales of Kynamro and three percent of the cash payments we receive from Kastle.

7. Segment Information and Concentration of Business Risk

We have 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 for patients with serious cardiometabolic diseases caused by lipid disorders. Moving our lipid drugs into a company that we own and control ensures that our core focus at Ionis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs. To date, Akcea has not earned any revenue.

The following table shows our segment revenue and loss from operations for the three months ended March 31, 2016 and March 31, 2015 (in thousands), respectively.

March 31, 2016	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Research and development	$ 35,214	$ —	$ —	$ 35,214
Licensing and royalty	1,660	—	—	1,660
Total segment revenue	$ 36,874	$ —	$ —	$ 36,874
Loss from operations	$ (38,567)	$ (16,049)	$ (36)	$ (54,652)

March 31, 2015	Ionis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 61,892	$ —	$ 61,892
Licensing and royalty	691	—	691
Total segment revenue	$ 62,583	$ —	$ 62,583
Loss from operations	$ (2,325)	$ (7,005)	$ (9,330)

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

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
March 31, 2016	$ 936,903	$ 65,131	$ (126,215)	$ 875,819
December 31, 2015	$ 995,852	$ 66,306	$ (114,258)	$ 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 ten percent or more of our total revenue, was as follows:

	Three Months Ended March 31,	
	2016	2015
Partner A	58%	63%
Partner B	14%	26%

Contracts receivables from two significant partners comprised approximately 98 percent and 99 percent of our contracts receivables at March 31, 2016 and December 31, 2015, respectively.

ITEM 2 MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In this Report on Form 10-Q, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us," means Ionis Pharmaceuticals, Inc. and its wholly owned subsidiary, Akcea Therapeutics, Inc.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the business of Akcea Therapeutics, Inc., a wholly owned subsidiary of Ionis Pharmaceuticals, and the therapeutic and commercial potential of our technologies and products in development, including nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2015, which is on file with the U.S. Securities and Exchange Commission and are available from us, and those identified within this Item in the section entitled "Risk Factors" beginning on page 32 of this Report. 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.

Overview

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

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

Nusinersen has the potential to be a transformational drug for infants and children with SMA. We are evaluating nusinersen in a broad development program designed to support marketing authorization for infants and children with this devastating disease. In April 2016, at the American Academy of Neurology, or AAN, meeting, we reported an update on our ongoing Phase 2 open-label study, with a cut-off of January 26, 2016, in infants with SMA treated with nusinersen. At the AAN meeting, we reported that we had no deaths or events of permanent ventilation since December 2014 with continued increases in median event-free survival, muscle function scores as well as achievement of new developmental milestones. We and Biogen are committed to advancing nusinersen as rapidly as possible. We have completed enrollment in CHERISH, the Phase 3 study in children with SMA and ENDEAR, the Phase 3 study in infants with SMA.

IONIS-TTR_{Rx} is potentially a first-in-class and best-in-class drug for the treatment of all forms of TTR amyloidosis. It is one drug, given as one subcutaneous injection, once a week. We and GSK are evaluating IONIS-TTR_{Rx} in a broad development program designed to support marketing authorization of IONIS-TTR_{Rx} for all forms of TTR amyloidosis: familial amyloid polyneuropathy, or FAP, and the cardiomyopathy form of TTR amyloidosis, which includes both familial amyloid cardiomyopathy, or FAC, and wild-type TTR, or wt-TTR. Together, these forms of TTR amyloidosis represent a large potential market for IONIS-TTR_{Rx}.

Volanesorsen has the potential to significantly improve the lives of patients who, because of their severely elevated triglycerides, are at constant risk of pancreatitis, which can require hospitalization and can be life-threatening. We demonstrated in our Phase 2 studies that volanesorsen robustly reduced ApoC-III and triglycerides in patients, including in FCS patients, and also had a beneficial impact on insulin sensitivity. To maximize the value of volanesorsen and other earlier-stage drugs for serious cardiometabolic diseases caused by lipids, we formed Akcea Therapeutics to focus on developing and commercializing these drugs. Akcea's pipeline includes volanesorsen, IONIS-APO(a)-L_{Rx}, IONIS-ANGPTL3-L_{Rx} and IONIS-APOCIII-L_{Rx}. Moving these drugs into a company that we own and control allows us to retain substantial value from them and ensures Ionis' core focus remains on innovation. Akcea is building development and commercialization expertise in lipid and cardiometabolic diseases, including highly trained, specialized medical, marketing and sales teams, to successfully commercialize volanesorsen and the other lipid drugs in its pipeline.

In addition to our Phase 3 programs, we have a pipeline of drugs with the potential to be first-in-class and/or best-in-class drugs to treat patients with inadequately treated diseases. Our pipeline has over a dozen drugs in Phase 2 development, and includes drugs to treat patients with diseases spanning numerous therapeutic areas, including severe and rare diseases, viral infections, ocular diseases, metabolic disorders and cardiovascular diseases. We believe that our technology is the most versatile and most efficient drug discovery technology today and we plan to expand the therapeutic reach of our technology by adding three to five new drugs to our pipeline every year. Additionally, we actively patent the advances we have made across all areas of our technology and the drugs we are developing. In this way, we have amassed a substantial intellectual property position that provides us with extensive protection for our drugs and our technology.

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our products. Our partners bring resources and expertise that augment and build upon our internal capabilities. We have strategic partnerships with Biogen and AstraZeneca through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas that are outside of our expertise or in which our partners can provide tools and resources to complement our drug discovery efforts. We also form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas, such as we did with Janssen. Additionally, we form development and commercialization partnerships that enable us to leverage our partner's global expertise and resources needed to support large commercial opportunities, such as we did with Bayer. Lastly, we also work with a consortium of companies that can exploit our drugs and technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Through our partnerships, we have created a broad and sustaining base of potential license fees, upfront payments, milestone payments, royalties, and earn out payments while controlling our drug development expenses. We have the potential to earn significant revenue from all of our partnerships. Since 2007, we have received more than $1.7 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn more than $11.5 billion in future milestone payments and licensing fees from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out or royalty arrangements.

Financial Highlights

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

	Three Months Ended March 31,	
	2016	**2015**
Total revenue	$ 36,874	$ 62,583
Total operating expenses	$ 91,526	$ 71,913
Loss from operations	$ (54,652)	$ (9,330)
Net loss	$ (62,917)	$ (16,717)

For the first three months of 2016 we earned $36.9 million of revenue which included $15 million in milestone payments, primarily related to the progression of our Phase 3 program for nusinersen. As nusinersen and our other partnered programs advance, we have the opportunity to earn significant revenue this year. Already in the second quarter, we earned a $15 million up-front payment from Kastle. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners. Our financial projections include numerous significant milestone payments in the second half of this year, compared to 2015 when our revenue was more evenly spread throughout the year.

A substantial portion of our development expenses are from our continued Phase 3 programs for nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen. We are currently conducting five Phase 3 studies and three open-label extension studies for these drugs, of which four of the Phase 3 studies have completed target enrollment. As a result, these Phase 3 studies are now in their most expensive development stage. Our operating expenses for the first three months of 2016 were in line with our expectations. As our Phase 3 programs continue to progress in 2016, we expect the costs associated with these programs to continue to increase modestly. Akcea operating expenses also increased as it continues to build its commercial infrastructure and advanced the pre-commercialization activities necessary to successfully launch volanesorsen within the next couple years. Additionally, our non-cash compensation expense related to equity awards increased because the average fair value of unvested stock options has risen due to the increase in the exercise price of the stock options we have granted over the past several years.

Recent Events

Our Corporate and Drug Development Highlights *(Q1 2016 and subsequent activities)*

- We and our collaborators presented more than a dozen posters and presentations at the AAN meeting including an update on our ongoing Phase 2 study of nusinersen in infants with SMA as well as overviews on our programs on Huntington's disease, myotonic dystrophy type 1, Alzheimer's disease, Parkinson's disease and spinocerebellar ataxia type 2.
  - We reported positive interim data from an ongoing open-label Phase 2 clinical study with a data cut-off of January 26, 2016, on nusinersen in infants with SMA. The data reported show that there have been no new events in the study since December 2014 with continued increases in median event-free survival, muscle function scores as well as achievement of new developmental milestones. Data showing increases in neuromuscular electrophysiology measurements were also reported.
  - IONIS-HTT$_{Rx}$ was highlighted in an oral presentation as the first HTT-lowering drug to be tested in patients with Huntington's disease, or HD. IONIS-HTT$_{Rx}$ is the first drug to enter clinical development designed to directly target the cause of HD.
  - IONIS-DMPK-2.5$_{Rx}$ was highlighted in several oral presentations and posters showing preclinical data that supports the therapeutic potential for IONIS-DMPK-2.5$_{Rx}$ in patients with myotonic dystrophy type 1.
  - Additional presentations included preclinical data on new targets for neurological diseases, including TAU for Alzheimer's disease, LRRK2 for Parkinson's disease and ATXN2 for spinocerebellar ataxia type 2.
- We sold the rights to Kynamro to Kastle Therapeutics.
  - We are eligible to receive up to $95 million, which includes a $15 million up-front payment, a $10 million payment we will earn after three years and up to $70 million in sales related milestones payments.
  - Starting in 2017, we are also be eligible to earn royalties that average in the low teens on sales of Kynamro.
  - We received a 10 percent equity position in Kastle's parent company.
  - Sanofi Genzyme, the specialty care global business unit of Sanofi, will be eligible to receive a three percent royalty on sales of Kynamro and three percent of cash we receive from Kastle.

- We and our collaborators continued to advance our pipeline of first-in-class or best-in-class drugs. As a result, we earned more than $15 million in milestone payments in the first quarter of 2016.
    - We continued to advance nusinersen in the ongoing open-label study, SHINE, in infants and children with SMA, for which we earned a $7.5 million milestone payment from Biogen.
    - GSK initiated a Phase 1 study of IONIS-HBV-L_{Rx}, a LICA drug in development to treat patients with hepatitis B virus, for which we earned a $1.5 million milestone payment from GSK.
- The European Medicines Agency granted IONIS-HTT_{Rx} orphan drug designation for the treatment of patients with HD.
- A jury found in favor of Merck and us in a patent dispute related to Gilead's HCV medicines, including Sovaldi and Harvoni.
    - The jury upheld all claims from the two patents in the cases, including two methods and eight composition of matter claims. We and Merck are co-inventors on these patents. We will receive 20 percent of the damages awarded to Merck that exceed the costs Merck incurred to conduct the litigation and we will also receive 20 percent of all future payments, including 20 percent of royalties, Merck receives from Gilead.

Critical Accounting Policies

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

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

There have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations," included in our Annual Report on Form 10-K for the year ended December 31, 2015.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2016 was $36.9 million, compared to $62.6 million for same period in 2015.

Our revenue fluctuates based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees. Already in the second quarter of 2016, we generated $17 million, including a $15 million upfront payment from Kastle and $2 million in a milestone payment from Biogen for advancing nusinersen. Additionally, our financial projections include numerous significant milestone payments in the second half of this year, compared to 2015 when our revenue was more evenly spread throughout the year.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three months ended March 31, 2016 was $35.2 million, compared to $61.9 million for same period in 2015. The change in our revenue is primarily due to variations in the timing of revenue from milestone payments. Our revenue for the first three months of 2016 primarily consisted of the following:

- $12.5 million from Biogen for advancing the Phase 3 program for nusinersen and advancing IONIS-BIIB4$_{Rx}$;
- $1.5 million from GSK when GSK initiated the Phase 1 study for IONIS-HBV-L_{Rx}; and
- $22.9 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 the three months ended March 31, 2016 was $1.7 million, compared to $0.7 million for 2015.

Operating Expenses

Operating expenses for the three months ended March 31, 2016 were $91.5 million, and increased compared to $71.9 million for the same period in 2015 as a result of the following:

- We are currently conducting five Phase 3 studies and three open-label extension studies for our Phase 3 drugs: nusinersen, IONIS-TTR$_{Rx}$ and volanesorsen, of which four of the Phase 3 studies have completed target enrollment. As a result, these Phase 3 studies are now in their most expensive stage. As our Phase 3 programs continue to progress in 2016, we expect the costs associated with these programs to continue to increase modestly.
- Akcea operating expenses increased as it continues to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen within the next couple of years.

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

	Three Months Ended March 31,	
	2016	2015
Ionis Core	$ 58,600	$ 52,161
Akcea Therapeutics	12,859	6,447
Elimination of intercompany activity	(36)	—
Subtotal	71,423	58,608
Non-cash compensation expense related to equity awards	20,103	13,305
Total operating expenses	$ 91,526	$ 71,913

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):

	Three Months Ended March 31,	
	2016	2015
Research, development and patent expenses	$ 66,194	$ 53,961
Non-cash compensation expense related to equity awards	14,770	10,486
Total research, development and patent expenses	$ 80,964	$ 64,447

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

	Three Months Ended March 31,	
	2016	2015
Ionis Core	$ 55,270	$ 48,288
Akcea Therapeutics	10,960	5,673
Elimination of intercompany activity	(36)	—
Subtotal	66,194	53,961
Non-cash compensation expense related to equity awards	14,770	10,486
Total research, development and patent expenses	$ 80,964	$ 64,447

For the three months ended March 31, 2016, our total research, development and patent expenses were $66.2 million, compared to $54.0 million for the same period in 2015, and were higher primarily due to the progression of our drugs currently in Phase 3 trials. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

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

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

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

	Three Months Ended March 31,	
	2016	2015
Antisense drug discovery expenses	$ 11,597	$ 10,661
Non-cash compensation expense related to equity awards	3,496	2,918
Total antisense drug discovery expenses	$ 15,093	$ 13,579

Antisense drug discovery expenses for the three months ended March 31, 2016 were $11.6 million, and, as expected were slightly higher, compared to $10.7 million for the same period in 2015. Expenses were higher because we conducted more research activities to support our partnerships during the three months ended March 31, 2016 compared to same period in 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):

	Three Months Ended March 31,	
	2016	2015
Nusinersen	$ 9,402	$ 6,120
Volanesorsen	5,414	2,371
IONIS-TTR$_{Rx}$	4,488	3,231
Other antisense development projects	9,884	10,389
Development personnel and overhead expenses	10,383	8,673
Total antisense drug development, excluding non-cash compensation expense related to equity awards	39,571	30,784
Non-cash compensation expense related to equity awards	6,088	3,714
Total antisense drug development expenses	$ 45,659	$ 34,498

Antisense drug development expenses were $39.6 million for the three months ended March 31, 2016, compared to $30.8 million for the same period in 2015. Expenses for the three months ended March 31, 2016 were higher compared to the same period in 2015 primarily due to the progression of our drugs currently in Phase 3 trials. We have completed target enrollment in four of our Phase 3 studies. As a result, these Phase 3 studies are now in their most expensive development stage. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended March 31,	
	2016	2015
Ionis Core	$ 29,257	$ 25,613
Akcea Therapeutics	10,314	5,171
Non-cash compensation expense related to equity awards	6,088	3,714
Total antisense drug development expenses	$ 45,659	$ 34,498

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):

	Three Months Ended March 31,	
	2016	**2015**
Manufacturing and operations expenses	$ 7,996	$ 5,633
Non-cash compensation expense related to equity awards	1,602	1,171
Total manufacturing and operations expenses	$ 9,598	$ 6,804

Manufacturing and operations expenses were $8.0 million for the three months ended March 31, 2016, and increased compared to $5.6 million for the same period in 2015. The increase in manufacturing and operations expenses was primarily related to the manufacturing activities needed to support the increase in our drug development activities. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended March 31,	
	2016	**2015**
Ionis Core	$ 7,690	$ 5,260
Akcea Therapeutics	306	373
Non-cash compensation expense related to equity awards	1,602	1,171
Total manufacturing and operations expenses	$ 9,598	$ 6,804

R&D Support

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

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

	Three Months Ended March 31,	
	2016	2015
Personnel costs	$ 2,244	$ 2,676
Occupancy	1,852	1,833
Patent expenses	758	597
Depreciation and amortization	57	543
Insurance	339	312
Other	1,780	922
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	7,030	6,883
Non-cash compensation expense related to equity awards	3,584	2,683
Total R&D support expenses	$ 10,614	$ 9,566

R&D support expenses for the three months ended March 31, 2016 were $7.0 million, and were flat compared to $6.9 million for the same period in 2015. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended March 31,	
	2016	2015
Ionis Core	$ 6,726	$ 6,754
Akcea Therapeutics	340	129
Elimination of intercompany activity	(36)	2,683
Subtotal	7,030	9,566
Non-cash compensation expense related to equity awards	3,584	2,683
Total R&D support expenses	$ 10,614	$ 9,566

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):

	Three Months Ended March 31,	
	2016	2015
General and administrative expenses	$ 5,229	$ 4,647
Non-cash compensation expense related to equity awards	5,333	2,819
Total general and administrative expenses	$ 10,562	$ 7,466

General and administrative expenses were $5.2 million for the three months ended March 31, 2016, and increased compared to $4.6 million for the same period in 2015 primarily due to the continued build out of Akcea. 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):

	Three Months Ended March 31,	
	2016	2015
Ionis Core	$ 3,330	$ 3,873
Akcea Therapeutics	1,899	774
Non-cash compensation expense related to equity awards	5,333	2,819
Total general and administrative expenses	$ 10,562	$ 7,466

Akcea Therapeutics, Inc.

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

	Three Months Ended March 31,	
	2016	2014
Development and patent expenses	$ 10,960	$ 5,673
General and administrative expenses	1,899	774
Total operating expenses, excluding non-cash compensation expense related to equity awards	12,859	6,447
Non-cash compensation expense related to equity awards	3,190	558
Total Akcea Therapeutics operating expenses	$ 16,049	$ 7,005

Expenses for Akcea were $12.9 million for the three months ended March 31, 2016, and increased compared to $6.4 million for the same period in 2015. The increase in expenses was primarily due to Akcea's Phase 3 program for volanesorsen, which continued to advance, and the progression of its other drugs, including IONIS-APO(a)-L_{Rx} and IONIS-ANGPTL3$_{Rx}$. Akcea has also incurred additional general and administrative costs as it continues to build the commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen within the next couple of years. We expect that these costs will continue to increase during the remainder of 2016. For each period presented, 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 each period presented, 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. In 2016, we began charging Akcea for Ionis' internal development costs associated with the ongoing work we are performing for Akcea's drugs. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three months ended March 31, 2016 was $1.5 million, compared to $0.8 million for 2015. The increase in investment income was primarily due to a higher average cash balance and an improvement in the market conditions during the three months ended March 31, 2016 compared to same period in 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):

	Three Months Ended March 31,	
	2016	2015
2¾ percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 668	$ 612
Interest expense payable in cash	421	421
1 percent notes:		
Non-cash amortization of the debt discount and debt issuance costs	5,425	5,016
Interest expense payable in cash	1,250	1,250
Non-cash interest expense for long-term financing liability	1,672	1,662
Other	54	60
Total interest expense	$ 9,490	$ 9,021

Interest expense for the three months ended March 31, 2016 was $9.5 million, compared to $9.0 million for the same period in 2015.

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

Net Loss and Net Loss per Share

Net loss for the three months ended March 31, 2016 was $62.9 million, compared to $16.7 million for the same period in 2015. Basic and diluted net loss per share for the three months ended March 31, 2016 was $0.52, compared to $0.14 for the same period in 2015. Our net loss increased for the three months ended March 31, 2016 compared to the same period in 2015 primarily due to variations in the timing of revenue from milestone payments and to a lesser extent, an increase in operating expenses primarily associated with our four Phase 3 studies that have completed target enrollment. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners. For example, our financial projections include numerous significant milestone payments in the second half of this year, compared to 2015 when our revenue was more evenly spread throughout the year.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through March 31, 2016, we have earned approximately $1.5 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through March 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 March 31, 2016, we had cash, cash equivalents and short-term investments of $703.8 million and stockholders' equity of $158.2 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.

At March 31, 2016, we had consolidated working capital of $639.4 million compared to $688.1 million at December 31, 2015. Working capital decreased in 2016 primarily due to the decrease our cash and short-term investments which were used to fund our operations.

As of March 31, 2016, our debt and other obligations totaled $644.7 million compared to $644.8 million at December 31, 2015.

The following table summarizes our contractual obligations as of March 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)	$ 530.0	$ 5.0	$ 10.0	$ 10.0	$ 505.0
2¾ percent convertible senior notes (principal and interest payable)	$ 68.0	$ 1.7	$ 3.4	$ 62.9	$ —
Facility rent payments	$ 123.9	$ 6.5	$ 13.6	$ 14.4	$ 89.4
Financing arrangements (principal and interest payable)	$ 8.8	$ 8.8	$ —	$ —	$ —
Other obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Operating leases	$ 24.3	$ 2.1	$ 3.5	$ 3.0	$ 15.7
Total	$ 756.3	$ 24.2	$ 30.6	$ 90.4	$ 611.1

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

Convertible Debt Summary

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

At March 31, 2016 our outstanding convertible debt was as follows (amounts in millions except price per share data):

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

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

1 Percent Convertible Senior Notes

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

2¾ Percent Convertible Senior Notes

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

Financing Arrangements

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

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

Additionally, we will pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility beginning after June 2016. As of March 31, 2016 we had $8.5 million in outstanding borrowings under the credit facility, which we used to fund our capital equipment needs in 2015 and is consistent with our historical practice to finance these costs. As of March 31, 2016, our outstanding borrowings under this credit facility were at a weighted average interest rate of 1.69 percent.

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

In October 2008, we entered into an equipment financing loan agreement. As of March 31, 2016, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.39 percent. The carrying balance under this loan agreement at March 31, 2016 and December 31, 2015 was $0.3 million and $0.5 million, respectively. Our remaining outstanding balance is due in June 2016 and interest is payable monthly.

Research and Development Facility Lease Obligation

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

In addition to contractual obligations, we had outstanding purchase orders as of March 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 in the company to fund Akcea's operations. As Akcea continues to progress we may seek additional capital to fund Akcea's future operating needs. As such, we may pursue various financing alternatives, like issuing shares of Ionis' or Akcea's stock in private or public financings, issuing Ionis or Akcea debt instruments, or securing lines of credit. We may also consider entering into collaborations specific to Akcea's pipeline with partners to provide for additional operating cash.

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. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2015.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2016, we had an accumulated deficit of approximately $1.2 billion and stockholders' equity of approximately $158.2 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of March 31, 2016, we had cash, cash equivalents and short-term investments equal to $703.8 million. If we do not meet our goals to successfully commercialize our drugs, including nusinersen, IONIS-TTR$_{Rx}$, volanesorsen and Kynamro, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

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

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2016, the market price of our common stock ranged from $30.93 to $71.50 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, marketing authorization, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ITEM 3. 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 and reputable financial institutions, corporations, and U.S. government agencies 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 4. CONTROLS AND PROCEDURES

We maintain disclosure controls and procedures 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 our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision 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 March 31, 2016. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2016.

We also performed an evaluation of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. That evaluation 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.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of the Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, 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. Under our agreement with Merck, Merck is responsible for the costs of this suit. 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 4 percent of $5 billion in past sales of sofosbuvir. Gilead has stated it will appeal the jury’s finding of validity. In the meantime, several non-jury issues remain to be resolved by the judge in the case. First, Gilead has two remaining non-jury challenges to validity of the patents: unclean hands and waiver. We expect the judge to rule on those challenges by the third quarter of 2016. The other outstanding issue is the determination of damages for Gilead’s ongoing infringement, which the judge will decide. To allow the rest of the case advance to the appeal stage without delay, the judge has severed the issue of ongoing damages from the rest of the case. Thus, that issue will be subject to a separate proceeding, the timing of which has yet to be determined.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

Not Applicable.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	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.
10.2	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.
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. Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive loss, (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

SIGNATURES

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)	May 4, 2016
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 4, 2016

EXHIBIT 10.1

FINAL EXECUTION VERSION

AMENDMENT NO.3

This Amendment No.3 ("the "Amendment") to the Collaboration, License and Development Agreement dated December 7th, 2012 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at 151 85 Södertälje, Sweden and with offices at SE-43 183 Mölndal, Sweden ("AstraZeneca")
(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("Ionis")

and is made effective as of the day of January 18th 2016 (the "Amendment Effective Date")

Recitals

WHEREAS, the Parties entered into the Agreement

WHEREAS the Agreement amongst others provides for the Parties to conduct discovery efforts on three targets

WHEREAS these discovery efforts have resulted in the identification of a oligonucleotide drug targeting the [***] gene

WHEREAS the Parties desire to further amend, modify and restate certain terms and conditions of the Agreement with regards to the Parties rights and obligations with regards to the Oncology Research and Development Plan with a view in particular to enable the further development of the [***] targeted drug.

Agreement

NOW, THEREFORE, in consideration of the mutual covenants contained in this Amendment, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, agree as follows:

1. Definitions

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. Modifications

Article 3.3.3 shall be deleted and replaced by the following:

3.3.3 Oncology Development Candidate Selection. Ionis will notify AstraZeneca in writing promptly after designating an Oncology Lead Candidate and, together with such notice, Ionis will provide AstraZeneca the applicable Lead Candidate Data Package. As promptly as possible (but no later than [***] days after AstraZeneca receives such Lead Candidate Data Package) (each such [***]-day deadline, which AstraZeneca has determined is sufficient for AstraZeneca to complete its candidate selection identification criteria analysis, an "***Oncology Development Candidate Decision Deadline***"), AstraZeneca will determine whether to select the Oncology Lead Candidate (or another Oncology Compound) as an Oncology Development Candidate. In addition, during such [***]-day period, AstraZeneca will keep the JSC apprised of AstraZeneca's progress in making a decision regarding which Oncology Compound AstraZeneca may select as the Oncology Development Candidate to enable Ionis to plan as early as possible for manufacturing of the Oncology Development Candidate for IND-Enabling Toxicology Studies. If the JSC determines that any back up Oncology Compound to the proposed Oncology Lead Candidate should be considered alongside the proposed Oncology Lead Candidate, then the JSC may unanimously agree to extend the Oncology Development Candidate Decision Deadline if the JSC determines AstraZeneca should have additional time to consider both candidates before making a decision as to which may be selected as the Oncology Development Candidate. If AstraZeneca selects the Oncology Lead Candidate or any other Oncology Compound as an Oncology Development Candidate, then AstraZeneca will notify Ionis of such selection by the Oncology Development Candidate Decision Deadline and will pay Ionis the Designation of Oncology Development Candidate milestone payment under Section 8.6 within 30 days after AstraZeneca's receipt of an invoice from Ionis. In addition, provided Ionis has supplied the API to AstraZeneca in accordance with Section 4.6.1 (b) (iii) or Section 4.6.1 (b) (iv), as applicable, AstraZeneca will initiate IND-Enabling Toxicology Studies under the applicable Oncology Research and Development Plan no later than [***] days after AstraZeneca pays Ionis the Designation of Oncology Development Candidate milestone payment under Section 8.6. Notwithstanding the foregoing and for the avoidance of doubt, solely for any Oncology Development Candidate targeting [***] ("a [***] Candidate"), the Oncology Development Candidate milestone payment will be due upon the earlier of (i) the completion of [***] and [***] of [***] of the [***] for such [***] Candidate; and (ii) [***], which will be deemed to be the "Oncology Development Candidate Decision Deadline" for any [***] Develpment Candidate. However, the [***] will be extended by one day for every day beyond [***] Ionis delivers API for the GLP toxicology study to AstraZeneca as set forth below (which API will be deemed delivered upon delivery to a carrier designated by AstraZeneca at Ionis manufacturing facility).

If AstraZeneca either (i) does not provide Ionis written notice that AstraZeneca has selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, or (ii), provides Ionis written notice that AstraZeneca has not selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, then such Oncology Collaboration Program will no longer be a part of this Agreement and AstraZeneca's Option for (and Ionis' obligations with respect to) such Oncology Collaboration Program will terminate and no milestone payments for such Oncology Collaboration Program will be payable.

Article 4.6.1 shall be deleted and replaced by the following:

4.6.1 Collaboration Manufacturing and Supply.

Supplies for Activities under the Collaboration Plans.

(a) **Ionis Conducted Activities**. [***], Ionis will supply API and finished Product sufficient to support the Ionis Conducted Activities designated under a given Collaboration Plan, including but not limited to the API to support the IND Enabling Toxicology Studies for the AR Program.

(b) **AstraZeneca Conducted Activities**. In addition, with respect to the AstraZeneca Conducted Activities, Ionis will supply (the "***Initial Supply***"):

(i) ***STAT3 Program Supply***. API and finished Product sufficient to support the [***] that will be conducted by AstraZeneca under the STAT3 Research and Development Plan;

(ii) ***AR Program Supply***. The quantity of API [***] (which will be set forth in the AR Research and Development Plan) to support the [***] for the AR Development Candidate;

(iii) ***[***] Program Supply***. Up to [***] kilograms of API of the [***] Candidate, to be delivered in [***] [***] the [***] of up to [***] kilogram to support the [***], and other [***] to be delivered by [***], provided and released in the same manner Isis releases API for [***] it conducts, and the [***] of up to [***] kilograms to support the [***], to be delivered by [***], and to be provided under cGMP in the same manner as Isis has supplied API for the STAT3 and AR Programs (AstraZeneca will be responsible for formulation and filling of all API so provided by Ionis), and

(iv) ***Other Oncology Programs***. The quantity of API [***] for each Oncology Development Candidate other than the [***] Candidate, and the quantity of API [***] (which will be set forth in the applicable Oncology Research and Development Plan) for each Oncology Development Candidate.

In each of the foregoing cases in this Section 4.6.1 (b), AstraZeneca will pay Ionis for such API and/or finished Product at [***], within 60 days after AstraZeneca's receipt of the applicable invoice. Notwithstanding the foregoing and for the avoidance of doubt, Ionis will provide AstraZeneca the API outlined in Section 4.6.1(b)(iii) [***]. In the event that AstraZeneca does not [***] the [***] for a [***] Development Candidate, then AstraZeneca will [***] $[***] per kilogram, which is equal to [***] for the [***] API provided by Ionis to AstraZeneca, with such [***]. For the avoidance of doubt, if AstraZeneca has [***] the [***] for the [***] Development Candidate, AstraZeneca shall be under no obligation to [***] for the [***].

Other than the finished Product sufficient to support the [***] in patients under the STAT3 Research and Development Plan, AstraZeneca is responsible for supplying finished Product for all AstraZeneca Conducted Activities. In addition, should AstraZeneca require additional API or research-grade Compound for the STAT3 Program or the AR Program for pre-clinical studies in [***] not covered by the STAT3 or AR Research and Development Plan or in connection with the Oncology Research and Development Plans, then, at AstraZeneca's reasonable request, Ionis will use its reasonable endeavors to provide (A) such API to AstraZeneca at [***], or (B) such research-grade Compound for such [***] studies [***] of such Compound (and for any additional quantities of research-grade Compound, at [***].

It is intended that the API lot used for [***] under a given Collaboration Plan will be of sufficient size to also use in the [***] of the relevant Product.

Article 8.4, Table 3, shall be deleted and replaced by the following:

TABLE 3

Oncology Product Milestone Event	**Oncology Product Milestone Event Payment**
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

3. Amendment Effective Date

This Amendment shall become effective on the Amendment Effective Date.

4. Entire Agreement

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreeement. The Agreeemnt together with this Amendment and any prior Amendments thereto supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreeemnet, as amended. Each Party confirms that it is not relying on any representations, warranties or covenants of the other Party except as specifically set out in the Agreement as amended. Nothing in this Agreement is intended to limit or exclude any liability or fraud. All Schedules referred to in this Amendment are intended to be and are hereby specifically incorporated into and made a part of the Agreement. The Parties hereby agree that subject to the modifciations specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

5. Execution

THIS AMENDMENT IS EXECUTED by the authorized representatives of the parties as of the date first written above.

ASTRAZENECA AB		**Ionis Pharmaceuticals, Inc.**	
Signature :	*/s/ Marcus Schindler*	Signature :	*/s/ B. Lynne Parshall*
Name :	Marcus Schindler	Name :	B. Lynne Parshall
Title :	Vice President, Head of CVMD iMed AstraZeneca AB	Title :	Chief Operating Officer

EXHIBIT 10.2

EXECUTION COPY **CONFIDENTIAL**

AMENDMENT #7 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This **AMENDMENT #7 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT** (this "***Amendment No. 7***") is entered into and made effective as of the 4th day of March, 2016 (the "***Amendment No. 7 Effective Date***") by and between **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 (formerly, "Isis Pharmaceuticals, Inc.") ("***Ionis***"), and **GLAXO GROUP LIMITED**, a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("***GGL***"), and **GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED,** a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("***GSK IPDL***"). GGL and GSK IPDL are referred to together as "***GSK***". Ionis and GSK are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Ionis and GGL are parties to the Research, Development and License Agreement dated March 30, 2010, as amended (the "***Agreement***") and (to the extent applicable) GGL has sub-licensed its rights under the Agreement to GSK IPDL;

WHEREAS, Ionis and GSK are Developing the molecule known as [***] under the Collaboration Program focused on hepatitis B virus (the "***HBV Program***"); and

WHEREAS, Ionis and GSK amended the Agreement (Amendment No. 5) to include research and development activities to identify and advance, in addition to the current lead Development Candidate ([***]) work on [***] ASOs discovered by Ionis that bind to HBV and conjugated with Ionis' proprietary Ligand Conjugated Antisense (LICA) technology (the "***HBV LICA Compounds***") and to advance an HBV LICA Compound as a second development candidate;

WHEREAS, Ionis and GSK now desire to further amend the Agreement to allow GSK to assume responsibility for the development activities for the current lead Development Candidate ([***]) (the "***HBV Lead Compound***") in addition to the HBV LICA Compounds (which GSK assumed responsibility for under the terms of Amendment No. 5), on the terms and conditions set forth herein.

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and solely with respect to the HBV Program, the Parties, intending to be legally bound, do hereby agree as follows:

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

1. Amendment of Activities under HBV Program.

a. ***GSK Responsible for All Further Development of HBV Lead Compound; Costs***. As of the Amendment No. 7 Effective Date, except as otherwise expressly stated in this Amendment No. 7, GSK shall be solely responsible for, and will [***] to conduct, all further Development and Manufacturing of the HBV Lead Compound.

GSK will be [***] associated with such further Development and Manufacturing of the HBV Lead Compound, including, without limitation, paying Ionis [***] associated with the activities set forth on Exhibit A, using [***] ([***]) [***] per [***], to be conducted by Ionis, either itself or through its Third Party contractor, with respect to the [***] Study. Ionis will invoice GSK for any such costs and GSK will pay such invoice within [***] days of GSK's receipt of such invoice. If GSK were to request support from Ionis in addition to the activities set forth on Exhibit A that Ionis is responsible for, GSK will pay Ionis to provide such support for [***] ([***]) [***] at the agreed-upon [***], plus any reasonable, agreed out-of-pocket expenses.

b. ***CS3 Study***. On or after the Amendment No. 7 Effective Date, GSK will negotiate and enter into an agreement (the "***Clinical Study Agreement***") with a mutually agreed Third Party contractor (the "***CRO***") currently presumed to be [***], for the conduct of the CS3 Study for the HBV Lead Compound. GSK will provide [***] and will [***] with respect to such draft. As between GSK and Ionis, GSK shall be responsible for, and will [***] to provide the day-to-day oversight and management of the CRO in the performance of its obligations for the CS3 Study, as set forth under the Clinical Study Agreement. Until the Completion of the CS3 Study, Ionis shall remain the study sponsor for the conduct of the CS3 Study, and will maintain all regulatory filings (including the IND) for the CS3 Study in good standing. As the study sponsor, until the Completion of the CS3 Study, Ionis shall be responsible for, and will use Commercially Reasonable Efforts to conduct, [***], including approval of all [***] and all [***] related to the CS3 Study as required by the applicable Regulatory Authorities. GSK, itself or through its Third Party contractor, will prepare and, following approval by Ionis, will make all required regulatory filings and submissions for the CS3 Study with the applicable Regulatory Authorities. The attached Exhibit A, incorporated herein by reference, sets out the specific activities to be conducted by GSK, either itself or through its Third Party contractor, and by Ionis, either itself or through its Third Party contractor, with respect to the CS3 Study.

c. ***HBV Lead Compound IND; HBV Lead Compound Development Plan***. As soon as reasonably practicable following the Completion of the CS3 Study, Ionis shall transfer the IND for the HBV Lead Compound to GSK, and Ionis and GSK will coordinate on the timing and activities required by each Party to transfer to GSK the IND and other regulatory filings for the HBV Lead Compound. For the avoidance of doubt, the foregoing shall not modify or amend the terms of GSK's [***].

As soon as reasonably practicable following the Completion of the CS3 Study, GSK will promptly [***], and thereafter will update such [***] on at least an annual basis until such time as the HBV Option is exercised (or otherwise expires). After Option exercise, GSK will provide updates as required under Section 4.3.2 and Section 4.3.3 of the Agreement.

2. **Safety Reporting; Data Integrity**.

a. ***Safety Reporting.*** GSK will report to Ionis any serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) under any Clinical Study for the HBV Lead Compound being conducted by or on behalf of GSK prior to the date of exercise of its Option to the HBV Program, strictly in accordance with the timelines set out in the Safety Data Exchange Agreement (as set forth below) (such timelines to ensure that each Party is able to meet all applicable legal and regulatory obligations in line with its own respective internal processes). In addition, GSK will provide Ionis with [***] and [***] regarding adverse events and material lab findings under any Clinical Study for the HBV Lead Compound being conducted on behalf of GSK prior to the date of exercise of its Option to the HBV Program.

b. ***Safety Data Exchange Agreement (or equivalent)***. GSK and Ionis entered into a Safety Data Exchange Agreement on 25 January, 2016 to govern the collection, review, assessment, tracking, exchange and filing of information related to adverse events and safety data associated with, *inter alia*, the HBV LICA Compound. Promptly following the Amendment No. 7 Effective Date, the Parties will negotiate and execute a mutually agreed amendment to such Safety Data Exchange Agreement to the extent necessary to govern the collection, review, assessment, tracking, exchange and filing of information related to adverse events and safety data associated with the HBV Lead Compound. After GSK's exercise of its Option to the HBV Program, the Parties will wind-down and discontinue the activities provided for under the Safety Data Exchange Agreement, but GSK will continue to provide Ionis the cooperation and information described in Section 4.4.1 of the Agreement as it relates to the HBV Program.

c. ***Ionis Database***. Notwithstanding the fact that GSK has not exercised its Option for the HBV Program, GSK will provide Ionis the cooperation and information described in Section 4.4.1 of the Agreement as it relates to activities undertaken by GSK in relation to the HBV Lead Compound prior to the date of exercise of its Option to the HBV Program.

d. ***Data Integrity***. GSK agrees that it will carry out its activities under the HBV Program for the HBV Lead Compound and collect and record any data generated therefrom in a manner consistent with Good Data Management Practices. Prior to GSK's exercise of its Option to the HBV Program, GSK will, upon reasonable request by Ionis, permit review of relevant notebooks and records in GSK's possession or control by Ionis during normal business hours.

3. Manufacture and Supply of HBV Lead Compound and Placebo.

a. Ionis has manufactured and shall provide, [***], all [***] of [***] for the HBV Lead Compound and relevant placebo in [***], which is currently estimated to be [***] and [***] [***], respectively (collectively, the "***Ionis HBV Lead Compound Supply***"). Within [***] days after the Amendment No. 7 Effective Date, Ionis will deliver the Ionis HBV Lead Compound Supply in [***] to GSK or if so instructed by GSK, directly to GSK's Third Party contractor, [***] Ionis' facility (Incoterms 2010). GSK will contract with a Third Party contractor to package and label the Ionis HBV Lead Compound Supply to be used in the CS3 Study. IONIS PROVIDES NO WARRANTIES WITH RESPECT TO THE IONIS HBV LEAD COMPOUND SUPPLY HEREUNDER, AND EXPRESSLY DISCLAIMS ALL EXPRESS AND IMPLIED WARRANTIES, INCLUDING ANY WARRANTY OF MERCHANTABILITY, NON-INFRINGEMENT, OR FITNESS FOR A PARTICULAR PURPOSE. THE IONIS HBV LEAD COMPOUND SUPPLY IS PROVIDED TO AND ACCEPTED BY GSK IN ITS "AS IS" CONDITION.

b. Subject to Section 3(c) below, GSK shall be responsible, at its cost, for all further Manufacturing in relation to the HBV Program.

c. Ionis will remain responsible, [***], for [***] of the Ionis HBV Lead Compound Supply through the Completion of the CS3 Study, which [***] is currently conducted by Ionis' Third Party contractor. Ionis will invoice GSK for such [***] costs incurred by Ionis' Third Party contractor on [***] and any associated reasonable, agreed out-of-pocket costs and [***] incurred by Ionis in monitoring such [***], and GSK will pay such invoice within [***] days of GSK's receipt of such invoice.

4. Financial Provisions. The following revised financial provisions will apply solely to the HBV Program:

a. ***Milestone Payments for First Achievement of Development Milestone Event***. Solely with respect to Compounds under the HBV Program that first achieve a Development Milestone Event by or on behalf of GSK or its Affiliates or Sublicensees, TABLE 3 set forth in Section 5.6.1 (Milestone Payments for First Achievement of Development Milestone Event) of the Agreement and TABLE 3A of Section 8(b) (Milestone Payments for First Achievement of Development Milestone Event) of Amendment No. 5 to the Agreement are hereby deleted in their entirety and replaced with Table 3B below.

TABLE 3B		
Development Milestone Events for the HBV Program	**Milestone Payment 1st Indication**	**Milestone Payment 2nd Indication**
[***]	**$[***] ([***])**	**$[***]**
[***]	**$[***] ([***])**	**$[***]**
[***]	**$[***] ([***])**	**$[***]**
[***]	**$[***] ([***])**	**$[***]**
Initiation of a Phase 1 Trial with the HBV LICA DC	**$1,500,000**	**$[***]**
[***]	**$[***]**	**$[***]**
[***]	**$[***]**	**$[***]**
[***]	**$[***]**	**$[***]**
[***]†	**$[***]**	**$[***]**
[***]†	**$[***]**	**$[***]**
[***]††	**$[***]**	**$[***]**
[***]†† ([***])	**$[***]**	**$[***]**
Total Development Milestone Payments for the HBV Program	**$[***]**	**$[***]**

† For clarity with respect to this Milestone Event, "[***]" by the applicable Regulatory Authority in [***] (or any other [***] such as [***] or the [***]) of the equivalent of [***] in [***] (or any other [***] such as [***] or the [***]) will satisfy the requirements for achievement of this Development Milestone Event.

†† For clarity with respect to this Milestone Event, "[***]" by the applicable Regulatory Authority in [***] (or any other [***] such as [***] or the [***]) of the equivalent of [***] in [***] (or any other [***] such as [***] or the [***]) will satisfy the requirements for achievement of this Development Milestone Event.

Except as expressly set forth in Section 5.6.2 of the Agreement (as Section 5.6.2 of the Agreement relates to Compounds that are not the HBV Lead Compound or the HBV LICA DC), each milestone set forth in TABLE 3B above will be paid only once for the HBV Program upon the first achievement of the Milestone Event, regardless of the number of Licensed Compounds, Follow-On Compounds or Licensed Products resulting under the HBV Program.

For avoidance of doubt, except as expressly amended by this Amendment No. 7, the terms and conditions of Section 5.6.2 of the Agreement continue to apply to the HBV Program with respect to Compounds that are not the HBV Lead Compound or the HBV LICA DC.

b. ***Milestone Payments for First Achievement of Sales Milestone Event for HBV Lead Compound***. GSK will pay to Ionis the applicable one-time milestone payments as set forth in TABLE 4C below after a Licensed Product that includes the HBV Lead Compound first achieves the listed events (as set forth in TABLE 4C) as a result of sales by or on behalf of GSK, its Affiliates or Sublicensees:

TABLE 4C

Sales Milestones for each Licensed Product that includes the HBV Lead Compound	**Milestone Payment**
$[***] in worldwide Annual Net Sales	$[***]
$[***] in worldwide Annual Net Sales	$[***]
$[***] in worldwide Annual Net Sales	$[***]
Total Sales Milestone Payments for the Licensed Products that include the HBV Lead Compound	**$[***]**

TABLE 4C above replaces the milestone payments set forth in Section 5.7.1 of the Agreement solely with respect to the Licensed Products that include the HBV Lead Compound. For the avoidance of doubt, TABLE 4B set forth in Amendment No. 5 remains in full force and effect and this Amendment No. 7 does not amend such TABLE 4B.

5. **HBV Lead Compound Royalties**. Solely with respect to Licensed Products that include the HBV Lead Compound sold by GSK, its Affiliates or Sublicensees, TABLE 5 set forth in Section 5.9.1 (GSK Patent Royalty) of the Agreement is deleted in its entirety and replaced with TABLE 5C below:

TABLE 5C	
Worldwide Annual Net Sales of each Licensed Product that includes the HBV Lead Compound	**Royalty Rate**
For the portion up to and including $[***]	[***]%
For the portion above $[***] and up to and including $[***]	[***]%
For the portion above $[***]	[***]%

6. **No Impact on Other Collaboration Programs**. Except as otherwise expressly amended by this Amendment No. 7, the Agreement (including Amendment No. 5 as amended by this Amendment No. 7) remains in full force and effect in accordance with its terms, as amended. For the avoidance of doubt, this Amendment No. 7 is solely intended to modify certain terms of the Agreement regarding the HBV Program, and does not amend the Agreement in any way with respect to the other Collaboration Programs.

7. **Termination by Ionis of Rights to the HBV Lead Compound**. (a) If GSK, in Ionis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 1 of this Amendment No. 7, Ionis will notify GSK and within [***] days thereafter, Ionis and GSK will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to GSK's use of Commercially Reasonable Efforts in Section 1 of this Amendment No. 7. Following such meeting, if GSK fails to use Commercially Reasonable Efforts as contemplated by Section 1 of this Amendment No. 7, then, subject to Section 7(b) below and Sections 9.2.3(c) and 9.2.4 of the Agreement, Ionis will have the right, at its sole discretion, to terminate GSK's rights under this Amendment No. 7 and the Agreement with respect to the HBV Lead Compound. In the case of such a termination, the HBV Lead Compound will be excluded from the HBV Program, including GSK's Option and licenses to the HBV Program under Section 3.1 and Section 4.1 under the Agreement.

(b) This Section 7 and Section 8 below of this Amendment No. 7 set forth Ionis' sole and exclusive remedy for GSK's breach of its obligation to use Commercially Reasonable Efforts under Section 1 of this Amendment No. 7.

8. **Special Consequences for Termination by Ionis or Voluntary Termination by GSK**. In addition to the consequences set forth in Section 9.3.2 of the Agreement (as applicable), in the event of (i) a termination of the Agreement either in its entirety or with respect to the HBV Program by Ionis pursuant to Section 9.2.2 of the Agreement or by GSK pursuant to Section 9.2.1 of the Agreement, or (ii) a termination by Ionis pursuant to Section 7 above of this Amendment No. 7, in each case ((i) and (ii)) prior to GSK's exercise of its Option for the HBV Program by GSK or upon the unexercised expiration of GSK's Option for the HBV Program and solely with respect to the HBV Lead Compound:

a. GSK will [***] of the Agreement, as though such obligations under Section 4.2.1 were obligations owed by GSK to Ionis, *mutatis mutandis*, with respect to the HBV Lead Compound, except for such information as is already in Ionis' possession at the date of termination;

b. GSK will, at GSK's election and [***], either (i) complete any ongoing Clinical Study for the HBV Lead Compound or (ii) subject to applicable law and regulatory consents, transfer sponsorship of any ongoing Clinical Study for the HBV Lead Compound to Ionis together with the transfer of all of the rights and responsibilities thereunder, except as described in Section 8(c) below;

c. If, as part of terminating the HBV Program, GSK terminates a Clinical Study for the HBV Lead Compound due to safety reasons as confirmed by GSK's Global Product Safety Board, then GSK cannot elect to complete such Clinical Study under Section 8(b)(i) above but will: (i) take such action consistent with its internal policies and applicable regulatory requirements to close out such Clinical Study (including, without limitation, notification to the FDA and withdrawal of the IND), and (ii) provide to Ionis all data and information contained within or referenced in the IND and such other data and information within GSK's possession or control generated under the HBV Program (except for such information as is already in Ionis' possession at the date of termination or as a result of the technology transfer under Section 8(b)(ii) above), at GSK's sole cost and expense. For clarity, in the circumstances described in this Section 8(c), GSK will not be required to transfer sponsorship of such terminated Clinical Study pursuant to Section 8(b)(ii) above.

d. If GSK elects to transfer sponsorship to Ionis under Section 8(b)(ii) above, the Parties agree to, as soon as practicable following the date of such termination or expiration according to this Section 8, negotiate in good faith a separate agreement to effect such transfer consistent with industry standards under similar circumstances and in accordance with each Party's respective internal policies.

9. **Governing Law; Counterparts**. This Amendment No. 7 and any dispute arising from the performance or breach hereof will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles. This Amendment No. 7 may be signed in counterparts, each and every one of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Amendment No. 7 from separate computers or printers. Facsimile signatures and signatures transmitted via PDF will be treated as original signatures.

10. **Definitions**. Capitalized terms used in this Amendment No. 7 will have the meaning set forth in Appendix A attached hereto.

* - * - * - *

[Signature page follows]

IN WITNESS WHEREOF, the Parties have caused this Amendment No. 7 to be executed by their duly authorized representatives as of the Amendment No. 7 Effective Date.

IONIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: Chief Operating Officer

Date:

GLAXO GROUP LIMITED

By: */s/ Paul Williamson*

Name: Paul Williamson

Title: Authorised Signatory for and on behalf

of Edinburgh Pharmaceutical Industries Limited

Date: March 3, 2016

GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED

By: */s/ Paul Williamson*

Name: Paul Williamson

Title: Authorised Signatory for and on behalf

of Edinburgh Pharmaceutical Industries Limited

Date: March 3, 2016

APPENDIX A

DEFINED TERMS

Capitalized terms used in this Amendment No. 7 but not otherwise defined herein will have the meanings given in the Agreement. For purposes of this Amendment No. 7, the following capitalized terms will have the following meanings:

a. "***Complete***", "***Completed***", or "***Completion***" means, with respect to a Clinical Study, the point in time at which the primary database lock for the study data for such Clinical Study has occurred and the data generated based on that primary database lock has been analyzed under the statistical analysis plan for such Clinical Study and such analysis is available.

b. ***CS3 Study***" means ISIS-505358 CS3, A Phase 2, Double-Blinded, Randomized, Placebo-Controlled, Dose-Escalation Study to Examine the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of ISIS 505358 in Treatment-Naïve Patients with Chronic Hepatitis B Virus Infection

c. "[*******]" means [***]. [***] is a global contract research organization providing comprehensive, integrated drug development, laboratory and lifecycle management services.

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Ionis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly 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 quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly 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: May 4, 2016

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Ionis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly 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 quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly 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: May 4, 2016

/s/ ELIZABETH L. HOUGEN

Elizabeth L. Hougen
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 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 Quarterly Report on Form 10-Q for the period ended March 31, 2016, to which this Certification is attached as Exhibit 32.1 (the "Periodic 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 Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 4, 2016

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Ionis Pharmaceuticals, Inc. and will be retained by Ionis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.