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 June 30, 2017

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 ☐
	Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act. ☐

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 August 2, 2017 was 124,354,692.

IONIS PHARMACEUTICALS, INC.
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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.

SPINRAZA™ is a trademark of Biogen, Inc.

KYNAMRO® is a registered trademark of Kastle Therapeutics LLC

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

	June 30, 2017 (Unaudited)	December 31, 2016
ASSETS		
Current assets:		
Cash and cash equivalents	$ 132,991	$ 84,685
Short-term investments	722,718	580,538
Contracts receivable	50,615	108,043
Inventories	6,504	7,489
Other current assets	51,531	17,177
Total current assets	964,359	797,932
Property, plant and equipment, net	99,677	92,845
Patents, net	21,362	20,365
Deposits and other assets	5,433	1,325
Total assets	$ 1,090,831	$ 912,467
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 13,268	$ 21,120
Accrued compensation	10,298	24,186
Accrued liabilities	35,878	36,013
Current portion of long-term obligations	21,476	1,185
Current portion of deferred contract revenue	110,840	51,280
Total current liabilities	191,760	133,784
Long-term deferred contract revenue	100,843	91,198
1 percent convertible senior notes	516,539	500,511
Long-term obligations, less current portion	15,095	15,050
Long-term financing liability for leased facility	51,023	72,359
Total liabilities	875,260	812,902
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 124,146,356 and 120,351,480 shares issued and outstanding at June 30, 2017 and December 31, 2016, respectively	124	122
Additional paid-in capital	1,434,986	1,311,229
Accumulated other comprehensive loss	(30,372)	(30,358)
Accumulated deficit	(1,189,167)	(1,181,428)
Total stockholders' equity	215,571	99,565
Total liabilities and stockholders' equity	$ 1,090,831	$ 912,467

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	**2016**	**2017**	**2016**
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 22,366	$ —	$ 27,577	$ —
Licensing and other royalty revenue	557	16,015	4,103	17,675
Total commercial revenue	22,923	16,015	31,680	17,675
Research and development revenue under collaborative agreements	81,229	22,455	182,776	57,670
Total revenue	104,152	38,470	214,456	75,345
Expenses:				
Research, development and patent	83,506	77,573	166,144	158,536
Selling, general and administrative	22,317	9,824	35,994	20,386
Total operating expenses	105,823	87,397	202,138	178,922
Income (loss) from operations	(1,671)	(48,927)	12,318	(103,577)
Other income (expense):				
Investment income	2,465	1,466	4,744	2,921
Interest expense	(11,778)	(9,625)	(23,141)	(19,115)
Other expense	—	—	(1,438)	—
Loss before income tax expense	(10,984)	(57,086)	(7,517)	(119,771)
Income tax (expense) benefit	(222)	231	(222)	(1)
Net loss	$ (11,206)	$ (56,855)	$ (7,739)	$ (119,772)
Basic and diluted net loss per share	$ (0.09)	$ (0.47)	$ (0.06)	$ (0.99)
Shares used in computing basic and diluted net loss per share	123,989	120,798	123,428	120,698

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	**2016**	**2017**	**2016**
Net loss	$ (11,206)	$ (56,855)	$ (7,739)	$ (119,772)
Unrealized gains (losses) on securities, net of tax	130	(10,738)	396	(13,288)
Reclassification adjustment for realized gains included in net loss	—	—	(374)	—
Currency translation adjustment	(42)	—	(36)	—
Comprehensive loss	$ (11,118)	$ (67,593)	$ (7,753)	$ (133,060)

See accompanying notes.

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

	Six Months Ended June 30,	
	2017	**2016**
Operating activities:		
Net loss	$ (7,739)	$ (119,772)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:		
Depreciation	3,990	3,715
Amortization of patents	802	775
Amortization of premium on investments, net	3,558	3,793
Amortization of debt issuance costs	797	601
Amortization of convertible senior notes discount	15,163	11,709
Amortization of long-term financing liability for leased facility	3,352	3,345
Stock-based compensation expense	42,170	39,364
Gain on investment in Regulus Therapeutics, Inc.	(374)	—
Non-cash losses related to patents, licensing and property, plant and equipment	129	464
Changes in operating assets and liabilities:		
Contracts receivable	57,428	10,610
Inventories	985	(769)
Other current and long-term assets	(39,371)	(2,576)
Accounts payable	(10,030)	(12,436)
Accrued compensation	(13,888)	(8,624)
Accrued liabilities and deferred rent	(1,149)	(9,032)
Deferred contract revenue	69,205	(30,719)
Net cash provided by (used in) operating activities	125,028	(109,552)
Investing activities:		
Purchases of short-term investments	(347,916)	(81,814)
Proceeds from the sale of short-term investments	202,475	180,158
Purchases of property, plant and equipment	(9,453)	(3,263)
Acquisition of licenses and other assets, net	(1,593)	(2,195)
Proceeds from the sale of Regulus Therapeutics stock	2,507	—
Net cash (used in) provided by investing activities	(153,980)	92,886
Financing activities:		
Proceeds from equity awards	9,927	4,120
Proceeds from sale of stock to Novartis	71,640	—
Offering costs paid	(1,031)	—
Principal payments on debt and capital lease obligations	(3,278)	(3,717)
Net cash provided by financing activities	77,258	403
Net increase (decrease) in cash and cash equivalents	48,306	(16,263)
Cash and cash equivalents at beginning of period	84,685	128,797
Cash and cash equivalents at end of period	$ 132,991	$ 112,534
Supplemental disclosures of cash flow information:		
Interest paid	$ 3,607	$ 3,414
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,705	$ 1,662
Unpaid deferred offering costs	$ 473	$ 379

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and six months ended June 30, 2017 and 2016 on the same basis as the audited financial statements for the year ended December 31, 2016. We included all normal recurring adjustments in the financial statements, which we considered 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, 2016 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In the condensed consolidated financial statements we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our subsidiary, Akcea Therapeutics, Inc., which we formed in December 2014. In July 2017, Akcea completed an initial public offering, or IPO, and therefore beginning in July 2017, we no longer own 100 percent of Akcea. As of July 19, 2017, the closing of the IPO, we retained a 68 percent ownership of Akcea. Refer to Note 8, *Subsequent Events*, for further information related to Akcea's IPO. Unless the context requires otherwise, "Ionis", "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals, Inc. and its majority owned subsidiary, Akcea Therapeutics, Inc.

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.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We often enter into agreements to license and sell our proprietary patent rights on an exclusive or non-exclusive basis in exchange for upfront fees, milestone payments and/or royalties. We generally recognize as revenue immediately license payments with stand-alone value when the license is delivered and for which we are reasonably assured of collecting the resulting receivable. We recognize royalty revenue in the period in which the counterparty sells the related product, unless we are unable to obtain information to estimate the royalty. For example, for the first half of 2017 we recorded SPINRAZA royalty revenue of $27.6 million.

Research and development revenue under collaborative agreements

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.

Amendments to agreements

From time to time we amend our collaboration agreements. For these agreements, before we identify our deliverables and allocate consideration to each unit of accounting, we must determine if the amendment should be accounted for as a separate agreement, or if the amendment and any undelivered elements for the original agreement should be accounted for as a single new arrangement.

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 $100 million upfront payment in the second quarter of 2015. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis and for providing an initial supply of active pharmaceutical ingredient, or API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. As part of the 2017 amendment, Bayer paid us $75 million, which we received in April 2017. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$.

We concluded that the February 2017 amendment should be evaluated with the undelivered elements of the original agreement as a single new arrangement. Under the amendment, there was a substantial increase in the consideration we are eligible to receive and a significant change in the deliverables we will provide to Bayer. As a result, we evaluated our original and 2017 amended agreements with Bayer together to determine our deliverables. We concluded that the 2017 amendment did not impact the items we already delivered to Bayer.

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, our 2017 amended agreement with Bayer has multiple elements. We evaluated the deliverables in this arrangement when we entered into the 2017 amended agreement and determined that certain deliverables have stand-alone value. Below is a list of the three units of accounting under our 2017 amended agreement:

- The exclusive license we granted to Bayer to develop and commercialize IONIS-FXI-L_{Rx} for the treatment of thrombosis;
- The development services we agreed to perform for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx}; and
- The remaining undelivered IONIS-FXI_{Rx} API that was part of the original agreement.

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-L_{Rx} or to sublicense its rights. The development services and the remaining undelivered 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 2017 amended agreement was $76.3 million, comprised of the $75 million we received as part of the amendment and the remaining amount of the $100 million upfront payment we had not yet recognized into revenue, related to the undelivered API. We allocated the consideration based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation specialist to assist us with determining BESP. We estimated the selling price of the license granted for IONIS-FXI-L_{Rx} by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for IONIS-FXI-L_{Rx}. We then discounted the projected income to present value. The significant inputs we used to determine the projected income of the license included:

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

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

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

For purposes of determining BESP of the services we will perform and the API we will deliver in our 2017 amended Bayer transaction, accounting guidance required us to include a markup for a reasonable profit margin.

Based on the units of accounting under the 2017 amended agreement, we allocated the $76.3 million of allocable consideration as follows:

- $64.9 million to the IONIS-FXI-L_{Rx} exclusive license;
- $11.0 million for development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx}; and
- $0.4 million for the remaining delivery of IONIS-FXI_{Rx} 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-L_{Rx} license, we determined that the revenue we would have allocated to the IONIS-FXI-L_{Rx} license would change by approximately one percent, or $0.7 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-L_{Rx} in the first quarter of 2017 because that was when we delivered the license. We also recognize revenue over time as we provide services. 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 estimate our period of performance at the inception of the agreement when the agreements we enter into do not clearly define such information. We then recognize revenue from development services ratably over such period. In certain instances, the period of performance may change as the development plans for our drugs progress. 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. Any changes in estimates are recognized on a prospective basis.

The following are the periods over which we are recognizing revenue for each of our units of accounting under our 2017 amended Bayer agreement:

- We recognized the portion of the consideration attributed to the IONIS-FXI-L_{Rx} license in the first quarter of 2017 because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx} over the period of time we are performing the services; and
- We are recognizing the amount attributed to the remaining API supply as we deliver it to Bayer.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same partner. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, in the first quarter of 2017, we and Akcea entered into two separate agreements with Novartis at the same time: a collaboration agreement and a stock purchase agreement, or SPA.

Akcea entered into a collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Akcea received a $75 million upfront payment. For each drug, Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and delivering API. Under the collaboration agreement, Novartis has an exclusive option to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. If Novartis exercises an option for one of these drugs, Novartis will pay Akcea a license fee and will assume all further global development, regulatory and commercialization activities for the licensed drug. Akcea is also eligible to receive a development milestone payment, milestone payments if Novartis achieves pre-specified regulatory milestones, commercial milestones and tiered royalties on net sales from each drug under the collaboration.

Under the SPA, Novartis purchased 1.6 million shares of Ionis' common stock for $100 million in the first quarter of 2017 and paid a premium over the weighted average trading price at the time of purchase. Additionally, the SPA required Novartis to purchase an additional $50 million of common stock in the future, as part of Akcea's IPO in July 2017. The purchase of Akcea's common stock was at the IPO price.

We evaluated the Novartis agreements to determine whether we should treat the agreements separately or as a single arrangement. We considered that the agreements were negotiated concurrently and in contemplation of one another. Additionally, the same individuals were involved in the negotiations of both agreements. Based on these facts and circumstances, we concluded that we should treat both agreements as a single arrangement and evaluate the provisions of the agreements on a combined basis. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the Novartis collaboration.

Milestone payments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Option to license

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

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 received as part of a technology license or partner agreement. At June 30, 2017, we held ownership interests of less than 20 percent in each of the respective companies.

We account for our equity investments in publicly held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock of these publicly-held companies as a separate component of comprehensive income (loss). At June 30, 2017, we held equity investments in one publicly held company, Antisense Therapeutics Limited. We account for equity investments in privately held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. At June 30, 2017, we held cost method investments in four companies, Atlantic Pharmaceuticals Limited, Kastle Therapeutics, Dynacure SAS and Suzhou Ribo Life Science CO. Realization of our equity position in these private companies is uncertain. When realization of our investment is uncertain, we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs. We did not record any inventory write-offs for the six months ended June 30, 2017 and 2016. Total inventory was $6.5 million and $7.5 million as of June 30, 2017 and December 31, 2016, 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.

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.

For the three and six months ended June 30, 2017 and 2016, we incurred a net loss; therefore, 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 loss

We include unrealized gains and losses on investments, net of taxes, in accumulated other comprehensive income (loss) along with adjustments we make to reclassify realized gains and losses on investments from other accumulated comprehensive income (loss) to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income (loss) for the three and six months ended June 30, 2017 and 2016 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Beginning balance accumulated other comprehensive loss	$ (30,460)	$ (16,115)	$ (30,358)	$ (13,565)
Unrealized gains (losses) on securities (1)	130	(10,738)	396	(13,288)
Amounts reclassified from accumulated other comprehensive income (loss)	—	—	(374)	—
Currency translation adjustment	(42)	—	(36)	—
Net current period other comprehensive income (loss)	88	(10,738)	(14)	(13,288)
Ending balance accumulated other comprehensive loss	$ (30,372)	$ (26,853)	$ (30,372)	$ (26,853)

(1) There was no tax expense or benefit related to elements of other comprehensive income (loss) for the three and six months ended June 30, 2017 and 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 assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing our debt issuance costs and debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method.

Segment information

We have two operating segments, our Ionis Core segment and Akcea Therapeutics, our subsidiary. In July 2017, Akcea completed an IPO and therefore, beginning in July 2017, we no longer own 100 percent of Akcea. We have retained approximately 68 percent ownership of Akcea. Refer to Note 8, *Subsequent Events*, for further information related to Akcea's IPO. Our reportable segments remain unchanged as a result of Akcea's IPO. Akcea is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. We provide segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments.

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 six months ended June 30, 2017 and 2016, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2017	**2016**
Risk-free interest rate	1.8%	1.5%
Dividend yield	0.0%	0.0%
Volatility	66.1%	58.4%
Expected life	4.5 years	4.5 years

ESPP:

	Six Months Ended June 30,	
	2017	**2016**
Risk-free interest rate	0.7%	0.5%
Dividend yield	0.0%	0.0%
Volatility	66.5%	69.4%
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 six months ended June 30, 2017 was $47.85 per share.

We did not grant stock options or RSUs to our Board of Directors during the six months ended June 30, 2017 and 2016.

The following table summarizes stock-based compensation expense for the three and six months ended June 30, 2017 and 2016 (in thousands). Our consolidated non-cash stock-based compensation expense includes $3.9 million and $3.1 million of stock-based compensation expense for Akcea employees for the three months ended June 30, 2017 and 2016, respectively, and $7.1 million and $6.3 million of stock-based compensation expense for Akcea employees for the six months ended June 30, 2017 and 2016, respectively.

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	**2016**	**2017**	**2016**
Research, development and patent	$ 16,140	$ 14,492	$ 32,262	$ 29,262
Selling, general and administrative	5,118	4,768	9,908	10,102
Total non-cash stock-based compensation expense	$ 21,258	$ 19,260	$ 42,170	$ 39,364

As of June 30, 2017, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $85.9 million and $21.7 million, respectively. We will adjust total unrecognized compensation cost for future 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 1.4 years and 1.6 years, respectively.

Amendment to equity plan

In May 2017, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan to increase the total number of shares reserved for issuance under the plan from 11 million to 16 million shares.

Income taxes

In interim periods when a small change in forecasted information results in a significant change to our estimated annual effective tax rate and our income tax expense or benefit for an interim period, a discrete effective tax rate method may provide a more reliable estimate. The discrete method of calculating our estimated effective tax rate and our income tax expense or benefit uses actual results for the interim period(s), instead of forecasted information.

For the second quarter of 2017, we used the discrete effective tax rate method to calculate our income tax expense. We determined that using the discrete effective tax rate method would provide a more reliable estimate than applying the annual effective tax rate method to our year-to-date loss.

Impact of recently issued accounting standards

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. Under the current accounting guidance, we recognize revenue from milestone payments we earn under the milestone method. Under the new guidance, the milestone method of revenue recognition is eliminated. This new guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance as originally issued is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. In July 2015, the FASB issued updated accounting guidance to allow for an optional one year deferral from the original effective date. As a result, we will adopt this guidance beginning on January 1, 2018. We plan to adopt this guidance under the full retrospective approach, meaning we will apply the guidance to all periods presented. We have a significant number of collaborations that we will present in our financial statements upon adoption. We are currently assessing the impact the adoption will have on our consolidated financial statements and disclosures. Although we have completed this assessment for some agreements, we will not be able to conclude on the overall impact to our consolidated financial statements until we have reviewed every agreement, as the impact to each agreement may be different.

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

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

In May 2017, the FASB issued clarifying guidance related to the accounting for modifications of share-based payment awards. The new guidance is meant to clarify when modification accounting is required. We early adopted this guidance in these financial statements for the quarter ended June 30, 2017 and it did not have an effect on our consolidated financial statements and disclosures.

3. Investments

As of June 30, 2017, 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 June 30, 2017:

One year or less	69%
After one year but within two years	20%
After two years but within three and a half years	11%
Total	100%

As illustrated above, at June 30, 2017, 89 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 June 30, 2017, we had an ownership interest of less than 20 percent in four private companies and one public company with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Kastle Therapeutics, Dynacure SAS and Suzhou Ribo Life Science CO and the publicly-traded company is Antisense Therapeutics Limited. We account for equity investments in the privately-held companies under the cost method of accounting and we account for equity investments in the publicly-traded company 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):

		Gross Unrealized		
June 30, 2017	**Cost** (1)	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities:				
Corporate debt securities (2)	$ 369,416	$ 27	$ (360)	$ 369,083
Debt securities issued by U.S. government agencies	63,125	—	(98)	63,027
Debt securities issued by the U.S. Treasury (2)	28,295	—	(25)	28,270
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	43,528	12	(122)	43,418
Other municipal debt securities	3,000	—	(2)	2,998
Total securities with a maturity of one year or less	507,364	39	(607)	506,796
Corporate debt securities	159,233	42	(674)	158,601
Debt securities issued by U.S. government agencies	19,181	—	(108)	19,073
Debt securities issued by the U.S. Treasury	—	—	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states	49,957	—	(336)	49,621
Total securities with a maturity of more than one year	228,371	42	(1,118)	227,295
Total available-for-sale securities	$ 735,735	$ 81	$ (1,725)	$ 734,091

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

(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 June 30, 2017 were as follows (in thousands):

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	354	$ 423,899	$ (1,001)	$ 18,197	$ (33)	$ 442,096	$ (1,034)
Debt securities issued by U.S. government agencies	42	81,100	(206)	—	—	81,100	(206)
Debt securities issued by the U.S. Treasury	4	25,772	(25)	—	—	25,772	(25)
Debt securities issued by states of the U.S. and political subdivisions of the states	74	83,078	(385)	2,687	(73)	85,765	(458)
Other municipal debt securities	1	2,998	(2)	—	—	2,998	(2)
Total temporarily impaired securities	475	$ 616,847	$ (1,619)	$ 20,884	$ (106)	$ 637,731	$ (1,725)

We believe that the decline in value of these securities is temporary and is 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 our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' 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. We classify the majority of our securities 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 six months ended June 30, 2017, there were no transfers between our Level 1 and Level 2 investments. When we recognize transfers between levels of the fair value hierarchy, we recognize the transfer on the date the event or change in circumstances that caused the transfer occurs.

The following tables present the major security types we held at June 30, 2017 and December 31, 2016 that are regularly measured and carried at fair value. The tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At June 30, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 113,466	$ 113,466	$ —
Corporate debt securities (2)	527,684	—	527,684
Debt securities issued by U.S. government agencies (3)	82,100	—	82,100
Debt securities issued by the U.S. Treasury (4)	28,270	28,270	—
Debt securities issued by states of the U.S. and political subdivisions of the states (5)	93,039	—	93,039
Other municipal debt securities (3)	2,998	—	2,998
Total	$ 847,557	$ 141,736	$ 705,821

	At December 31, 2016	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 54,137	$ 54,137	$ —
Corporate debt securities (3)	396,221	—	396,221
Debt securities issued by U.S. government agencies (3)	55,179	—	55,179
Debt securities issued by the U.S. Treasury (3)	29,286	29,286	—
Debt securities issued by states of the U.S. and political subdivisions of the states (5)	109,111	—	109,111
Investment in Regulus Therapeutics Inc.	2,414	2,414	—
Total	$ 646,348	$ 85,837	$ 560,511

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

(2) At June 30, 2017, $7.5 million was 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.

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

(4) At June 30, 2017, $2.5 million was 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.

(5) At June 30, 2017 and December 31, 2016, $1.4 million and $9.3 million, respectively, was 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.

Other Fair Value Disclosures

Novartis Future Stock Purchase

In January 2017, we and Akcea entered into a SPA with Novartis. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or in our common stock at a premium if an IPO did not occur by April 2018. Therefore, at the inception of the SPA, we recorded a $5.0 million asset representing the fair value of the potential future premium we could have received if Novartis purchased our common stock. We determined the fair value of the future premium by calculating the value based on the stated premium in the SPA and estimating the probability of an Akcea IPO. We also included a lack of marketability discount when we determined the fair value of the premium because we would have issued unregistered shares to Novartis if they had purchased our common stock. We measured this asset using Level 3 inputs and recorded it in other assets on our condensed consolidated balance sheet. At the end of the first and second quarters of 2017 prior to Akcea's IPO, we reassessed the fair value of this asset. We recorded an adjustment to other income/expense on our condensed consolidated statement of operations for the change in value. As a result of Akcea's IPO closing in July 2017, we will write-off the remaining balance to other expense on our third quarter 2017 condensed consolidated statement of operations.

The following is a reconciliation of the potential premium we would have received if Akcea had not completed its IPO, measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the six months ended June 30, 2017 (in thousands):

Beginning balance of Level 3 asset (at December 31, 2016)	$ —
Value of the potential premium we will receive from Novartis at inception of the SPA (January 2017)	5,035
Recurring fair value adjustment during the six months ended June 30, 2017	(1,438)
Ending balance of Level 3 asset (at June 30, 2017)	$ 3,597

At December 31, 2016 we did not have any financial instruments that were valued using Level 3 inputs.

Convertible Notes

Our 1 percent notes had a fair value of $730.4 million at June 30, 2017. 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. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, we can borrow up to a maximum of $30 million of revolving credit for general working capital purposes. Under the credit agreement interest is payable monthly in arrears on the outstanding principal at a borrowing 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 pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of June 30, 2017 we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which we used to fund our capital equipment needs consistent with our historical practice to finance these costs.

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

6. Collaborative Arrangements and Licensing Agreements

Below, we have included our collaborations with substantive changes during the first half of 2017 from those included in Note 6 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2016.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved drug to treat pediatric and adult patients with SMA. Additionally, we and Biogen are currently developing five other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$ for ALS, IONIS-MAPT$_{Rx}$ (formerly IONIS-BIIB4$_{Rx}$) for Alzheimer's disease and IONIS-BIIB5$_{Rx}$, IONIS-BIIB6$_{Rx}$ and IONIS-BIIB7$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. From inception through June 2017, we have received over $560 million from our Biogen collaborations.

During the three and six months ended June 30, 2017, we earned revenue of $79.1 million and $99.4 million from our relationship with Biogen, respectively. Our revenue for the six months ended June 30, 2017 included $27.6 million in royalties for sales of SPINRAZA, a $50 million milestone payment we earned in the second quarter of 2017 from the EU approval of SPINRAZA and a $5 million milestone payment we earned in the first quarter of 2017 for validation of an undisclosed neurological disease target. Additionally, in July 2017 we earned a $10 million milestone payment for validating an undisclosed neurological disease target under our Strategic Neurology collaboration. As a result of earning these milestone payments, our next potential milestone payment has changed for our SPINRAZA and Strategic Neurology collaborations. Under our SPINRAZA collaboration, we will earn the next milestone payment of $40 million upon determination of pricing in Japan. Under our Strategic Neurology collaboration, we will earn the next milestone payment of up to $2 million if we advance a program under this collaboration. Our revenue from Biogen represented 76 percent and 46 percent of our total revenue for the three and six months ended June 30, 2017, respectively. In comparison, we earned revenue of $9.4 million and $30.7 million for the same periods in 2016, which represented 25 percent and 41 percent of our total revenue for those periods. Our condensed consolidated balance sheet at June 30, 2017 included deferred revenue of $52.1 million related to our relationship with Biogen.

Research, Development and Commercialization Partners

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. We were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis. Under the terms of the agreement, we received a $100 million upfront payment in the second quarter of 2015. We recorded revenue of $91.2 million related to the license for IONIS-FXI$_{Rx}$ in June 2015 and we recognized the majority of the remaining amount related to development activities for IONIS-FXI$_{Rx}$ through November 2016.

In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. In conjunction with the decision to advance these programs, we received a $75 million payment from Bayer. We recorded revenue of $64.9 million related to the license for IONIS-FXI-L$_{Rx}$ in February 2017 and we are recognizing the remaining amount over the period we are performing the ongoing development activities for IONIS-FXI-L$_{Rx}$ and IONIS-FXI$_{Rx}$ through May 2019. We plan to conduct a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to rapidly develop IONIS-FXI-L$_{Rx}$ through Phase 1. Following these studies and Bayer's decision to further advance these programs, Bayer will be responsible for all global development, regulatory and commercialization activities for both drugs. We are eligible to receive additional milestone payments as each drug advances toward the market. In total over the term of our collaboration, we are eligible to receive up to $385 million in license fees, substantive milestone payments and other payments, including up to $125 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both drugs combined. From inception through June 2017, we have received over $175 million from our Bayer collaboration. We will earn the next milestone payment of $10 million if we advance a program under this collaboration.

During the three and six months ended June 30, 2017, we earned revenue of $1.2 million and $66.7 million from our relationship with Bayer, respectively, which represented one percent and 31 percent of our total revenue for those periods, respectively. In comparison, we earned revenue of $3.7 million and $5.0 million for the same periods in 2016, which represented ten percent and 7 percent of our total revenue for those periods, respectively. Our condensed consolidated balance sheet at June 30, 2017 included $9.7 million of deferred revenue related to our relationship with Bayer.

Novartis

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

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it retained $60 million and paid us $15 million as a sublicense fee. If Novartis exercises its option for a drug, Novartis will pay Akcea a license fee equal to $150 million for each drug it licenses. In addition, for AKCEA-APO(a)-L_{Rx}, Akcea is eligible to receive up to $600 million in substantive milestone payments, including $25 million for the achievement of a development milestone, up to $290 million for the achievement of regulatory milestones and up to $285 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx}, Akcea is eligible to receive up to $530 million in substantive milestone payments, including $25 million for the achievement of a development milestone, up to $240 million for the achievement of regulatory milestones and up to $265 million for the achievement of commercialization milestones. Akcea plans to co-commercialize any licensed drug commercialized by Novartis in selected markets, under terms and conditions that it plans to negotiate with Novartis in the future, through the specialized sales force Akcea is building to commercialize volanesorsen. Following Novartis' exercise of its option for either drug, Akcea will earn the next milestone payment of $25 million if Novartis advances the Phase 3 study for either drug. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee.

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

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

In conjunction with this collaboration, we and Akcea entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for $100 million in the first quarter of 2017. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or in our common stock at a premium if an IPO did not occur by April 2018.

To determine the amount of revenue to recognize under our agreements with Novartis, we first concluded that we would account for the collaboration and SPA agreements as a single multiple element arrangement. We next identified four separate units of accounting under the arrangement, each with stand-alone value:

- Development services for AKCEA-APO(a)-L_{Rx};
- Development services for AKCEA-APOCIII-L_{Rx};
- API for AKCEA-APO(a)-L_{Rx}; and
- API for AKCEA-APOCIII-L_{Rx}.

We then determined the total consideration under the arrangement was $180.0 million, which included the following:

- $75 million from the upfront payment;
- $100 million from our common stock Novartis purchased under the SPA, including $28.4 million for the premium paid by Novartis for its purchase of our common stock at a premium in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future.

We first allocated $71.6 million of the consideration to equity based on the fair value of our common stock Novartis purchased. Next, we allocated the remaining consideration of $108.4 million based on the relative stand-alone selling price of each unit of accounting as follows:

- $64.0 million for the development services for AKCEA-APO(a)-L_{Rx};
- $40.1 million for the development services for AKCEA-APOCIII-L_{Rx};
- $1.5 million for the delivery of AKCEA-APO(a)-L_{Rx} API; and
- $2.8 million for the delivery of AKCEA-APOCIII-L_{Rx} API.

We are recognizing the amount attributed to the development services for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} over the period of time we are performing the services, currently estimated to be through November 2018 and June 2019, respectively. We will recognize the amount attributed to the API supply as we deliver it to Novartis. We determined at the inception that all milestones under its Novartis collaboration are substantive milestones and we will recognize any future exercise of an option to license a drug under the Novartis agreement in full in the period the option is exercised. Akcea is responsible for the development activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue and Akcea recognizes the fees as R&D expense. On a consolidated basis, the sublicense fees are eliminated.

During the three and six months ended June 30, 2017, we earned revenue of $14.1 million and $23.7 million from our relationship with Novartis, respectively, which represented 14 percent and 11 percent of our total revenue for that period, respectively. Our condensed consolidated balance sheet at June 30, 2017 included deferred revenue of $84.7 million related to our relationship with Novartis.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics, our subsidiary. In July 2017, Akcea completed an IPO and therefore beginning in July 2017, we no longer own 100 percent of Akcea. We have retained approximately 68 percent ownership of Akcea. Refer to Note 8, *Subsequent Events*, for further information related to Akcea's IPO. Our reportable segments remain unchanged as a result of Akcea's IPO. Segment income (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 and/or best-in-class drugs for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders.

The following table shows our segment revenue and income (loss) from operations for the three and six months ended June 30, 2017 (in thousands), respectively.

Three Months Ended June 30, 2017	**Ionis Core**	**Akcea Therapeutics**	**Elimination of Intercompany Activity**	**Total**
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 22,366	$ —	$ —	$ 22,366
Licensing and other royalty revenue	557	—	—	557
Total commercial revenue	22,923	—	—	22,923
R&D revenue under collaborative agreements	70,031	14,128	(2,930)	81,229
Total segment revenue	$ 92,954	$ 14,128	$ (2,930)	$ 104,152
Total operating expenses	$ 83,381	$ 25,402	$ (2,960)	$ 105,823
Income (loss) from operations	$ 9,573	$ (11,274)	$ 30	$ (1,671)

Three Months Ended June 30, 2016	**Ionis Core**	**Akcea Therapeutics**	**Elimination of Intercompany Activity**	**Total**
Revenue:				
R&D revenue under collaborative agreements	$ 22,455	$ —	$ —	$ 22,455
Licensing and other royalty revenue	16,015	—	—	16,015
Total segment revenue	$ 38,470	$ —	$ —	$ 38,470
Total operating expenses	$ 72,622	$ 14,805	$ (30)	$ 87,397
Loss from operations	$ (34,152)	$ (14,805)	$ 30	$ (48,927)

Six Months Ended June 30, 2017	**Ionis Core**	**Akcea Therapeutics**	**Elimination of Intercompany Activity**	**Total**
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 27,577	$ —	$ —	$ 27,577
Licensing and other royalty revenue	4,103	—	—	4,103
Total commercial revenue	31,680	—	—	31,680
R&D revenue under collaborative agreements	213,457	23,725	(54,406)	182,776
Total segment revenue	$ 245,137	$ 23,725	$ (54,406)	$ 214,456
Total operating expenses	$ 161,733	$ 94,872	$ (54,467)	$ 202,138
Income (loss) from operations	$ 83,405	$ (71,147)	$ 60	$ 12,318

Six Months Ended June 30, 2016	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
R&D revenue under collaborative agreements	$ 57,670	$ —	$ —	$ 57,670
Licensing and other royalty revenue	17,675	—	—	17,675
Total segment revenue	$ 75,345	$ —	$ —	$ 75,345
Total operating expenses	$ 148,135	$ 30,847	$ (60)	$ 178,922
Loss from operations	$ (72,790)	$ (30,847)	$ 60	$ (103,577)

The following table shows our total assets by segment at June 30, 2017 and December 31, 2016 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
June 30, 2017	$ 1,227,050	$ 124,104	$ (260,323)	$ 1,090,831
December 31, 2016	$ 1,067,770	$ 10,684	$ (165,987)	$ 912,467

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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Partner A	76 %	25 %	46 %	41 %
Partner B	14 %	0 %	11 %	0 %
Partner C	1 %	10 %	31 %	7 %
Partner D	0 %	39 %	0 %	20 %

Contracts receivables from one significant partner comprised approximately 99 percent of our contracts receivables at June 30, 2017. Contracts receivables from two significant partners comprised approximately 92 percent of our contracts receivables at December 31, 2016.

8. Subsequent Events

In July 2017, Akcea completed an IPO. Akcea raised $193.8 million of aggregate gross proceeds from the IPO, including $50 million from a private placement by Novartis. Akcea's net proceeds were $182.4 million. As part of Akcea's IPO, we invested $25.0 million. In conjunction with the IPO, our series A convertible preferred stock converted into common stock. Additionally, Akcea's borrowings under its line of credit with us converted into common stock. As a result, we retained approximately 68 percent ownership in Akcea. Beginning in our third quarter of 2017, we will adjust our financial statements to reflect the non-controlling interest that we no longer own in Akcea.

Additionally, in July 2017, we purchased the building that houses our primary R&D facility and the building that houses our primary manufacturing facility for $79.4 million and $14.0 million, respectively. In conjunction with the purchase of the buildings we obtained a $51.3 million mortgage for our primary R&D facility with an interest rate of 3.88 percent and a $9.1 million mortgage for our primary manufacturing facility with an interest rate of 4.2 percent. Both mortgages mature in August 2027. We will record the impact of these transactions in our third quarter results.

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 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 financial position and outlook, our business, the business of Akcea Therapeutics, Inc., and the therapeutic and commercial potential of our technologies and products in development, including SPINRAZA, inotersen 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. 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. These and other risks concerning our programs are described in additional detail in our annual report on Form 10-K for the year ended December 31, 2016, 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.

Overview

We are leaders in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform. Using this platform, we have developed a large, diverse and advanced pipeline of potentially first-in-class and/or best-in-class drugs that we believe can provide high value for patients with significant unmet medical needs. In this way, we believe we are fundamentally changing medicine with the goal to transform the lives of those suffering from severe, often life-threatening, diseases. The recent U.S. approval and commercial launch of SPINRAZA for pediatric and adult patients with SMA highlights our progress toward this goal. Our pipeline also contains two near-term potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential, volanesorsen and inotersen. In the first half of 2017, we reported positive Phase 3 data in patients with familial chylomicronemia, or FCS. In July 2017, Akcea, working closely with us, filed for marketing authorization for volanesorsen to treat patients with FCS in the EU. Akcea and we plan to file for marketing authorization in the U.S. and Canada in September 2017. We also reported positive data from our Phase 3 study of inotersen in patients with hereditary transthyretin amyloidosis with polyneuropathy, or hATTR-PN, in the second quarter of 2017. We and our partner, GSK, are preparing to file for marketing authorization for inotersen to treat patients with hATTR-PN in the U.S. and EU by the end of 2017.

With FDA approval in December 2016, SPINRAZA injection became the first and only approved drug to treat pediatric and adult patients with SMA. SMA is a leading genetic cause of death in infants and toddlers that is marked by progressive, debilitating muscle weakness. In June 2017, SPINRAZA was approved in the EU and was approved in Japan and Canada during the third quarter, and is under review in several other key countries with additional filings planned in 2017. In the first half of 2017, we earned $27.6 million in commercial revenue from SPINRAZA royalties. We also earned a $50 million milestone payment for the EU approval of SPINRAZA in the second quarter of 2017.

Akcea Therapeutics, Inc. is focused on developing and commercializing volanesorsen and three other clinical-stage drugs for serious cardiometabolic diseases caused by lipid disorders, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Each of these four drugs could potentially treat multiple patient populations. Moving these drugs into a company that we own allows us to retain substantial value from them and ensures our core focus remains on innovation. Akcea completed its IPO in July 2017. Akcea received $182.4 million in net proceeds from the IPO and the Novartis concurrent private placement in the third quarter of 2017. We retained approximately 68 percent ownership in Akcea and we plan to continue to consolidate Akcea's financial results in our third quarter 2017 financial statements. Akcea plans to use proceeds from its IPO to further advance its drugs and commercialization efforts. Akcea is continuing to assemble the global infrastructure to continue developing the drugs in its pipeline, to commercialize them with a focus on lipid specialists as the primary call point and to provide the specialized patient and physician support required to address rare disease patient populations.

Akcea, working closely with us, is developing volanesorsen to treat two severe and rare, genetically defined diseases, FCS and familial partial lipodystrophy, or FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. The clinical development program for volanesorsen consists of three Phase 3 studies called APPROACH, BROADEN and COMPASS. In the first quarter of 2017, we reported positive Phase 3 data from the APPROACH study in patients with FCS. In December 2016, we and Akcea reported positive results from the Phase 3 COMPASS study in patients with triglycerides above 500 mg/dL. In July 2017, Akcea, working closely with us, filed for marketing authorization for volanesorsen in the EU and we are on track to file in the U.S. and Canada in September 2017. We estimate that FCS and FPL each affect 3,000 to 5,000 patients globally. If approved, Akcea plans to commercialize volanesorsen for both FCS and FPL.

Inotersen is potentially a first-in-class and best-in-class drug for the treatment of hereditary transthyretin amyloidosis, or hATTR, a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body. We reported positive top-line data from our Phase 3 study of inotersen, NEURO-TTR, in patients with hATTR polyneuropathy, or hATTR-PN, in May 2017. More than half of these patients also have cardiomyopathy. As part of the NEURO-TTR study, we are evaluating cardiomyopathy in this subset of patients by cardiac imaging and biomarkers. We and our partner, GSK, are preparing to file for marketing authorization for inotersen to treat patients with hATTR-PN in the U.S. and EU by the end of 2017. GSK has the option to license inotersen following a review of data from the NEURO-TTR study and prior to regulatory submissions.

In addition to our Phase 3 programs, we have a pipeline of drugs with the potential to be first-in-class and/or best-in-class drugs to treat patients with diseases that have inadequate treatment options. We are addressing a broad spectrum of diseases from common diseases affecting millions, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease, to rare diseases, such as amyotrophic lateral sclerosis and Huntington's disease. Our pipeline has over a dozen drugs in Phase 2 development, many of which we believe have the potential to be significant commercial opportunities. In particular, IONIS-FXI_{Rx} and AKCEA-APO(a)-L_{Rx} represent the value we have created. IONIS-FXI_{Rx} is the first antithrombotic drug in development that has shown it can decrease the risk of blood vessel obstruction caused by a blood clot without increasing bleeding risk. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI_{Rx} and to initiate development of IONIS-FXI-L_{Rx}, which Bayer licensed. AKCEA-APO(a)-L_{Rx} is the first and only drug in clinical development designed to selectively and robustly lower Lp(a), a key driver of cardiovascular disease. We believe that addressing Lp(a) is the next important horizon in lipid-focused cardiovascular disease treatment. In March 2017, Akcea and we initiated a Phase 2b study of AKCEA-APO(a)-L_{Rx} in patients with elevated Lp(a).

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our products. Our partners bring substantial resources and expertise that augment and build upon our internal capabilities. We have strategic partnerships with Biogen and AstraZeneca through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas for which our partners can provide expertise, tools and resources to complement our drug discovery efforts. We also have partnerships with Bayer, GSK, Janssen, Novartis and Roche. Each of these companies brings significant expertise and global resources to develop and potentially commercialize the drugs under each partnership. We also form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas. Lastly, we also work with a consortium of companies that can exploit our drugs and technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Financial Highlights

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	**2016**	**2017**	**2016**
Total revenue	$ 104,152	$ 38,470	$ 214,456	$ 75,345
Total operating expenses	$ 105,823	$ 87,397	$ 202,138	$ 178,922
Income (loss) from operations	$ (1,671)	$ (48,927)	$ 12,318	$ (103,577)
Net loss	$ (11,206)	$ (56,855)	$ (7,739)	$ (119,772)

For the first half of 2017 we had a net loss of $7.8 million, compared to net loss of $119.8 million for the same period in 2016. Our net loss declined significantly due to the substantial revenue we earned. In the first half of 2017, we added $27.6 million of commercial revenue from SPRINRAZA royalties. These royalties were primarily from sales in the U.S. Additionally, we earned R&D revenue of $182.8 million, including a $50 million milestone payment we earned for the EU approval of SPINRAZA.

Our operating expenses for the three and six months ended June 30, 2017 were $105.8 million and $202.1 million, respectively, and increased compared to $87.4 million and $178.9 million for the same periods in 2016. The increase in operating expenses was primarily due to higher SG&A expenses as Akcea prepares to commercialize volanesorsen globally next year and from fees we owe under our in-licensing agreements related to SPINRAZA.

Recent Events

Our Drug and Corporate Development Highlights *(Q2 2017 and subsequent activities)*

Recent SPINRAZA Accomplishments:

- Biogen reported more than $200 million from sales of SPINRAZA in the second quarter.
- The European Commission granted marketing authorization for SPINRAZA for the treatment of 5q SMA in the EU, representing approximately 95% of all SMA cases in the EU.
- SPINRAZA has begun selling in Germany and the Nordics, with additional country rollouts planned through 2018.
- We earned a $50 million milestone payment from Biogen for the approval of SPINRAZA in the EU.
- SPINRAZA was also approved in Japan, for which we are eligible to receive a $40 million milestone payment upon determination of pricing in Japan.
- SPINRAZA was approved in Canada.

Recent Corporate and Pipeline Accomplishments:

- Inotersen met both co-primary endpoints with a high degree of statistical significance in the Phase 3 NEURO-TTR study.
- Our Phase 1/2a study of IONIS-HTT_{Rx}, which is partnered with Roche, completed enrollment, with data anticipated around year-end 2017 or early 2018. We also announced that we plan to initiate an open-label extension study for IONIS-HTT_{Rx} in the second half of 2017.
- We initiated Phase 1 studies for three LICA drugs, including IONIS-GHR-L_{Rx}, IONIS-AGT-L_{Rx} and IONIS-TMPRSS6-L_{Rx}.
- IONIS-$BIIB7_{Rx}$ marked the seventh neurological disease program under our Biogen collaboration for neurodegenerative diseases to enter development.
- We entered a collaboration and license agreement with Suzhou Ribo Life Science Co., Ltd. (Ribo) to develop and commercialize RNA-targeted therapeutics in China.
- We advanced two wholly owned drugs in our neurological disease franchise.
- We, in collaboration with Dynacure, published in *Nature Communications* preclinical results evaluating antisense drugs targeting DNM2 for the treatment of centronuclear myopathy.
- Preclinical data demonstrating the potential of IONIS-KRAS-2.5_{Rx} in cancer were published in *Science Translational Medicine.*
- We purchased the buildings that house our research and development activities and our manufacturing suites, which should allow us to realize significant cash and interest expense savings.

Recent Akcea Accomplishments:

- Akcea, working closely with Ionis, filed for marketing authorization for volanesorsen for the treatment of FCS in the EU.
- Akcea raised over $190 million in its IPO and the concurrent strategic investment by Novartis.
  - The underwriters for Akcea's IPO exercised their full overallotment option to purchase additional shares.
- Akcea and we published key preclinical findings with angiopoietin-like 3 (ANGPTL3)-targeting drugs and Phase 1/2 clinical study results with AKCEA-ANGPTL3-L_{Rx} in the *New England Journal of Medicine*.

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 and clinical development activities; and
- Estimating our net deferred income tax asset valuation allowance.

These critical accounting policies and estimates are included in our Annual Report on Form 10-K for the year ended December 31, 2016 in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations". There have been no material changes to these critical accounting policies and estimates.

For the first quarter of 2017, we added the following additional critical accounting policy:

- Valuing premiums under our and Akcea's Novartis collaboration.

During the first quarter of 2017, we valued the premiums under the SPA agreement with Novartis. These premiums included the premium Novartis paid related to the $100 million purchase of our stock in the first quarter of 2017 and the premium we could have received related to Novartis' potential purchase of our stock. These valuations required us to use level 3 inputs, which we consider to be a critical accounting policy for our results in the first half of 2017.

For valuation purposes, 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; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions.

We determined the fair value of the premium we received and future premium we could have received by calculating the value based on the stated premium in the SPA. We also included a lack of marketability discount when we determined the fair value of the premiums because we initially issued unregistered shares as part of the $100 million purchase and we would have issued unregistered shares to Novartis if they purchase our common stock. Additionally, for the future potential stock purchase, we estimated the probability of an Akcea IPO. At the inception of the agreements, we concluded the following fair values:

- $28.4 million for the premium paid by Novartis for its purchase of our common stock in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future at a premium.

At the end of the first and second quarter of 2017, we reassessed the fair value of this asset and as necessary, we recorded an adjustment to other income/expense on our condensed consolidated statement of operations for the change in value. See further discussion about our valuation of the potential premium in Note 4, *Fair Value Measurements*, in the Notes to the Consolidated Financial Statements.

Results of Operations

Revenue

Total revenue for the three and six months ended June 30, 2017 was $104.2 million and $214.5 million, compared to $38.5 million and $75.3 million for the same periods in 2016.

Commercial Revenue

SPINRAZA Royalties

The first quarter of 2017 was the first full quarter in which we earned commercial revenue from SPINRAZA royalties. Commercial revenue from SPINRAZA royalties for the three and six months ended June 30, 2017 was $22.4 million and $27.6 million, respectively.

Licensing and Other Royalty Revenue

Our revenue from licensing activities and other royalties for the three and six months ended June 30, 2017 was $0.6 million and $4.1 million, respectively, compared to $16.0 million and $17.7 million for 2016. During the second quarter of 2016 we earned $15 million from Kastle when it acquired the global rights to develop and commercialize Kynamro.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2017 was $81.2 million and $182.8 million, respectively, compared to $22.5 million and $57.7 million for the same periods in 2016. The change in our R&D revenue was primarily due to revenue from the license fee from Bayer and Akcea's collaboration with Novartis. Our R&D revenue for the first half of 2017 primarily consisted of the following:

- $66.7 million from Bayer primarily for the license of IONIS-FXI-L_{Rx};
- $57.0 million in milestone payments from Biogen, including $50 million for the approval of SPINRAZA in the EU and $5 million for validating an undisclosed neurological disease target;
- $52.4 million from the amortization of upfront fees; and
- $6.7 million primarily from services we performed for our partners.

Our R&D 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.

Operating Expenses

Operating expenses for the three and six months ended June 30, 2017 were $105.8 million and $202.1 million, respectively, and increased compared to $87.4 million and $178.9 million for the same periods in 2016. Our operating expenses increased year over year principally due to higher SG&A expenses as Akcea prepares to commercialize volanesorsen globally next year and from fees we owe under our in-licensing agreements related to SPINRAZA. As this year progresses, we expect selling, general and administrative expenses to increase as Akcea continues to prepare to launch volanesorsen and we continue to incur fees under our in-licensing agreements related to SPINRAZA sales.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Ionis Core	$ 66,065	$ 56,439	$ 126,685	$ 115,037
Akcea Therapeutics	21,460	11,728	87,750	24,581
Elimination of intercompany activity	(2,960)	(30)	(54,467)	(60)
Subtotal	84,565	68,137	159,968	139,558
Non-cash compensation expense related to equity awards	21,258	19,260	42,170	39,364
Total operating expenses	$ 105,823	$ 87,397	$ 202,138	$ 178,922

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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Research, development and patent expenses	$ 67,366	$ 63,081	$ 133,882	$ 129,274
Non-cash compensation expense related to equity awards	16,140	14,492	32,262	29,262
Total research, development and patent expenses	$ 83,506	$ 77,573	$ 166,144	$ 158,536

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Ionis Core	$ 53,758	$ 53,478	$ 108,587	$ 108,747
Akcea Therapeutics	16,568	9,633	79,762	20,587
Elimination of intercompany activity	(2,960)	(30)	(54,467)	(60)
Subtotal	67,366	63,081	133,882	129,274
Non-cash compensation expense related to equity awards	16,140	14,492	32,262	29,262
Total research, development and patent expenses	$ 83,506	$ 77,573	$ 166,144	$ 158,536

For the three and six months ended June 30, 2017, our total research, development and patent expenses were $67.4 million and $133.9 million, and increased slightly compared to $63.1 million and $129.3 million for the same periods in 2016. Our research, development and patent expenses increased primarily from the initiation of a Phase 2b dose-ranging study of AKCEA-APO(a)-L_{Rx}. 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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Antisense drug discovery expenses	$ 13,162	$ 11,408	$ 25,760	$ 23,006
Non-cash compensation expense related to equity awards	3,746	3,549	7,709	7,046
Total antisense drug discovery expenses	$ 16,908	$ 14,957	$ 33,469	$ 30,052

Antisense drug discovery expenses for the three and six months ended June 30, 2017 were $13.2 million and $25.8 million, compared to $11.4 million and $23.0 million for the same periods in 2016. Expenses were slightly higher because we conducted more research activities to support our partnerships during the first half of 2017 compared to the same period in 2016. 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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
SPINRAZA	$ 5,154	$ 9,246	$ 10,802	$ 18,649
Volanesorsen	5,944	4,552	10,203	9,966
Inotersen	5,324	5,028	12,110	9,515
Other antisense development projects	11,011	9,501	21,428	19,414
Development personnel and overhead expenses	11,635	9,786	22,838	20,139
Total antisense drug development, excluding non-cash compensation expense related to equity awards	39,068	38,113	77,381	77,683
Non-cash compensation expense related to equity awards	7,000	5,925	14,012	12,012
Total antisense drug development expenses	$ 46,068	$ 44,038	$ 91,393	$ 89,695

Antisense drug development expenses were $39.1 million and $77.4 million for the three and six months ended June 30, 2017, respectively, compared to $38.1 million and $77.7 million for the same periods in 2016. Expenses for the three and six months ended June 30, 2017 were flat compared to the same periods in 2016. We are winding down two of our Phase 3 programs. Specifically, we have transitioned all further development of SPINRAZA to Biogen and we are closing out our Phase 3 volanesorsen trial in patients with FCS and our Phase 3 inotersen trial in patients with hATTR-PN. Akcea is conducting a Phase 3 trial of volanesorsen in patients with FPL. 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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Ionis Core	$ 26,422	$ 29,349	$ 54,133	$ 58,605
Akcea Therapeutics	12,646	8,764	71,642	19,078
Elimination of intercompany activity	—	—	(48,394)	—
Subtotal	39,068	38,113	77,381	77,683
Non-cash compensation expense related to equity awards	7,000	5,925	14,012	12,012
Total antisense drug development expenses	$ 46,068	$ 44,038	$ 91,393	$ 89,695

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, Akcea 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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Manufacturing and operations expenses	$ 8,288	$ 7,233	$ 17,093	$ 15,228
Non-cash compensation expense related to equity awards	1,745	1,584	3,450	3,186
Total manufacturing and operations expenses	$ 10,033	$ 8,817	$ 20,543	$ 18,414

Manufacturing and operations expenses were $8.3 million and $17.1 million for the three and six months ended June 30, 2017, compared to $7.2 million and $15.2 million for the same periods in 2016. 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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Ionis Core	$ 7,728	$ 6,750	$ 15,832	$ 14,439
Akcea Therapeutics	3,490	483	7,274	789
Elimination of intercompany activity	(2,930)	—	(6,013)	—
Subtotal	8,288	7,233	17,093	15,228
Non-cash compensation expense related to equity awards	1,745	1,584	3,450	3,186
Total manufacturing and operations expenses	$ 10,033	$ 8,817	$ 20,543	$ 18,414

R&D Support

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Personnel costs	$ 2,714	$ 2,509	$ 5,566	$ 5,383
Occupancy	2,076	1,875	3,954	3,727
Patent expenses	495	494	994	1,253
Depreciation and amortization	57	58	124	115
Insurance	327	339	673	678
Other	1,179	1,052	2,337	2,201
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	6,848	6,327	13,648	13,357
Non-cash compensation expense related to equity awards	3,649	3,434	7,091	7,018
Total R&D support expenses	$ 10,497	$ 9,761	$ 20,739	$ 20,375

R&D support expenses for the three and six months ended June 30, 2017 were $6.8 million and $13.6 million, and were essentially flat compared to $6.3 million and $13.4 million for the same periods in 2016. 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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Ionis Core	$ 6,446	$ 5,971	$ 12,862	$ 12,697
Akcea Therapeutics	432	386	846	720
Elimination of intercompany activity	(30)	(30)	(60)	(60)
Subtotal	6,848	6,327	13,648	13,357
Non-cash compensation expense related to equity awards	3,649	3,434	7,091	7,018
Total R&D support expenses	$ 10,497	$ 9,761	$ 20,739	$ 20,375

Selling, General and Administrative Expenses

Selling, general and administrative expenses include costs associated with the pre-commercialization activities for our drugs and costs to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of pre-commercialization, legal, human resources, investor relations, and finance. Additionally, we include in selling, 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. We also include nominal fees we owe under our in-licensing agreements related to SPINRAZA in these costs.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Selling, general and administrative expenses	$ 17,199	$ 5,056	$ 26,086	$ 10,284
Non-cash compensation expense related to equity awards	5,118	4,768	9,908	10,102
Total selling, general and administrative expenses	$ 22,317	$ 9,824	$ 35,994	$ 20,386

Selling, general and administrative expenses were $17.2 million and $26.1 million for the three and six months ended June 30, 2017, respectively, and increased compared to $5.1 million and $10.3 million for the same periods in 2016. The increase in SG&A expenses was principally due to Akcea preparing to commercialize volanesorsen globally next year and from fees we owe under our in-licensing agreements related to SPINRAZA. Expenses for Akcea will increase as it continues to prepare to launch volanesorsen. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Ionis Core	$ 12,307	$ 2,961	$ 18,098	$ 6,290
Akcea Therapeutics	4,892	2,095	7,988	3,994
Non-cash compensation expense related to equity awards	5,118	4,768	9,908	10,102
Total selling, general and administrative expenses	$ 22,317	$ 9,824	$ 35,994	$ 20,386

Akcea Therapeutics, Inc.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Research and development expenses	$ 16,568	$ 9,633	$ 79,762	$ 20,587
General and administrative expenses	4,892	2,095	7,988	3,994
Total operating expenses, excluding non-cash compensation expense related to equity awards	21,460	11,728	87,750	24,581
Non-cash compensation expense related to equity awards	3,942	3,077	7,122	6,266
Total Akcea Therapeutics operating expenses	$ 25,402	$ 14,805	$ 94,872	$ 30,847

Expenses for Akcea were $21.5 million and $87.8 million for the three and six months ended June 30, 2017, and increased compared to $11.7 million and $24.6 million for the same periods in 2016. $48.4 million of the increase for the six months ended June 30, 2017 in Akcea's development expenses was for one-time sublicensing expenses related to entering into the Novartis collaboration recorded in the first quarter of 2017. $33.4 million of these expenses were non-cash. In the second quarter of 2017, Akcea paid us the remaining $15 million of these expenses. For future payments received under the Novartis collaboration, Akcea will pay 50 percent of all license fees, milestone payments and royalties to us as a sublicense fee. Additionally, Akcea is continuing to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen. During the first quarter of 2017, we and Akcea reported positive results from its Phase 3 study of volanesorsen in patients with FCS. In July 2017, Akcea, working closely with us, filed for marketing approval in the EU. We plan to file in for marketing approval in the U.S. and Canada in September 2017. 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. Additionally, for each period presented, we allocated a portion of Ionis' general and administrative expenses, which are included in general and administrative expenses in the table above, to Akcea for work we performed on Akcea's behalf. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three and six months ended June 30, 2017 were $2.5 million and $4.7 million, compared to $1.5 million and $2.9 million for the same periods in 2016. The increase in investment income was primarily due to a higher average cash balance, a gain on the sale of our stock in Regulus Therapeutics and an improvement in the market conditions during the first half of 2017 compared to the same period in 2016.

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 June 30,		Six Months Ended June 30,	
	2017	2016	2017	2016
Convertible notes:				
Non-cash amortization of the debt discount and debt issuance costs	$ 8,058	$ 6,218	$ 15,960	$ 12,310
Interest expense payable in cash	1,946	1,671	3,660	3,342
Non-cash interest expense for long-term financing liability	1,676	1,673	3,352	3,345
Other	98	63	169	118
Total interest expense	$ 11,778	$ 9,625	$ 23,141	$ 19,115

Interest expense for the three and six months ended June 30, 2017 was $11.8 million and $23.1 million, respectively, and increased compared to $9.6 million and $19.1 million for the same periods in 2016. The increase was primarily non-cash expense.

In July 2017, we purchased the building that houses our primary R&D facility and the building that houses our primary manufacturing facility for $79.4 million and $14.0 million, respectively. In conjunction with the purchase of the buildings we obtained a $51.3 million mortgage for our primary R&D facility with an interest rate of 3.88 percent and a $9.1 million mortgage for our primary manufacturing facility with an interest rate of 4.2 percent. Both mortgages mature in August 2027. The non-cash interest expense for our long-term financing liability will be replaced with lower mortgage interest expense. We expect these transactions will result in cash and interest expense savings for us over the next several years.

Net Loss and Net Loss per Share

We had a net loss of $11.2 million for the three months ended June 30, 2017, compared to $56.9 million for the same period in 2016. Basic and diluted net loss per share for the three months ended June 30, 2017 was $0.09, compared to a loss of $0.47 per share for the same period in 2016.

We had a net loss of $7.7 million for the six months ended June 30, 2017, compared to $119.8 million for the same period in 2016. Basic and diluted net loss per share for the six months ended June 30, 2017 was $0.06, compared to a loss of $0.99 per share for the same period in 2016.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, in 2017 we have recently added commercial revenue from SPINRAZA royalties. Additionally, we earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through June 30, 2017, we have earned approximately $2.3 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through June 30, 2017, 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 June 30, 2017, we had cash, cash equivalents and short-term investments of $855.7 million and stockholders' equity of $215.6 million. In comparison, we had cash, cash equivalents and short-term investments of $665.2 million and stockholders' equity of $99.6 million at December 31, 2016. Our cash, cash equivalents and short-term investments increased in the first half of 2017 primarily from the $175 million we received from our collaboration with Novartis, the more than $100 million that we earned in late 2016 and received in 2017 and the $75 million from Bayer for expanding our collaboration.

Already in the third quarter of 2017 we have received $50 million from Biogen for EU approval of SPINRAZA and Akcea raised $182.4 million in net proceeds from closing its IPO and concurrent private placement with Novartis, of which $25 million was from Ionis' participation.

In July 2017, we purchased two buildings that house our primary R&D facility and our primary manufacturing facility for $79.4 million and $14 million, respectively. In conjunction with the purchase of the buildings we obtained a $51.4 million mortgage for our primary R&D facility and a $9.1 million mortgage for our primary manufacturing facility. Both mortgages mature in August 2027. We will record the impact of this transaction in our third quarter results. We expect these transactions will result in cash and interest expense savings for us over the next several years.

At June 30, 2017, we had consolidated working capital of $772.6 million compared to $664.1 million at December 31, 2016. Working capital increased in 2017 primarily due to the increase in our cash, cash equivalents and short-term investments as a result of the substantial payments we received from partners during the first half of 2017.

As of June 30, 2017, our debt and other obligations totaled $773.2 million compared to $774.1 million at December 31, 2016.

The following table summarizes our contractual obligations as of June 30, 2017. 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**
Convertible senior notes (principal and interest payable)	$ 716.5	$ 6.9	$ 13.9	$ 695.7	$ —
Facility rent payments	$ 115.7	$ 6.7	$ 14.1	$ 14.9	$ 80.0
Financing arrangements (principal and interest payable)	$ 13.2	$ 0.3	$ 12.9	$ —	$ —
Other obligations (principal and interest payable)	$ 1.2	$ 0.1	$ 0.1	$ 0.1	$ 0.9
Operating leases	$ 22.9	$ 2.3	$ 3.7	$ 2.9	$ 14.0
Total	$ 869.5	$ 16.3	$ 44.7	$ 713.6	$ 94.9

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

Our contractual obligations table above does not reflect the changes related to the purchase of two of our buildings, which we completed in July 2017. As a result of the purchase of our primary R&D facility and our primary manufacturing facility, the facility rent payments line in the contractual obligations table above will be eliminated. We will replace this line with the contractual obligations related to the new mortgages we obtained in July 2017. Refer to Note 8, *Subsequent Events*, for further information related to our purchase of these buildings and the mortgages we obtained.

1 Percent Convertible Senior Notes

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

In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. At June 30, 2017, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At June 30, 2017, we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

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

Interest is payable semi-annually for the 1 percent notes. The notes are convertible under certain conditions, at the option of the note holders. We settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 1 percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Financing Arrangements

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, Morgan Stanley will provide a maximum of $30 million of revolving credit for general working capital purposes. Any loans under the credit agreement have interest payable monthly in arrears at a borrowing 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 pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of June 30, 2017 we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which we used to fund our capital equipment needs consistent with our historical practice to finance these costs.

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

Research and Development Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed constructed our primary R&D facility in Carlsbad, California. The lease had 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 was 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 applied our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In July 2017, we purchased this building from BioMed for $79.4 million. We will record the impact of this transaction in our third quarter results.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2017 for the purchase of services, capital equipment and materials as part of our normal course of business.

In July 2017, we purchased two buildings that house our primary R&D facility and our primary manufacturing facility for $79.4 million and $14 million, respectively. In conjunction with the purchase of the buildings we obtained a $51.4 million mortgage for our primary R&D facility and a $9.1 million mortgage for our primary manufacturing facility. Both mortgages mature in August 2027. We will record the impact of this transaction in our third quarter results.

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.

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, 2016.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

If the market does not accept our drugs, including SPINRAZA, volanesorsen, inotersen and Kynamro, we are not likely to generate revenues or become consistently profitable.*

Even if our drugs are authorized for marketing, including SPINRAZA, volanesorsen, inotersen, 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. Similarly, cost control initiatives by governments or third party payors could decrease the price received for our drugs or increase patient coinsurance to a level that makes our drugs, including SPINRAZA, volanesorsen, inotersen and Kynamro, unaffordable.

The degree of market acceptance for our drugs, including SPINRAZA, volanesorsen, inotersen and Kynamro, depends upon a number of factors, including the:

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

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. For example, we expect the product label for volanesorsen and inotersen will require periodic platelet monitoring and the product label for inotersen will require periodic renal monitoring, which could negatively affect our ability to attract and retain patients for these drugs. Additionally, in the clinical setting, some patients discontinued treatment with volanesorsen, including five patients who discontinued participation in the APPROACH study due to platelet count declines. While we believe Akcea can better maintain patients on volanesorsen through Akcea’s patient-centric commercial approach where it plans to have greater involvement with physicians and patients, if Akcea cannot effectively maintain patients on volanesorsen, we may not be able to generate substantial revenue from volanesorsen sales.

If we or our partners fail to compete effectively, our drugs, including SPINRAZA, volanesorsen, inotersen and Kynamro, will not contribute significant revenues.

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

- priced lower than our drugs;
- reimbursed more favorably by government and other third-party payors than our drugs;
- safer than our drugs;
- more effective than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our drugs, including SPINRAZA, volanesorsen, inotersen and Kynamro, obsolete or non-competitive.

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

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

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, AVXS-101, RG7800, RG7916, and LMI070 could compete with SPINRAZA and metreleptin could compete with volanesorsen, patisiran, tafamadis, diflunisal, tolcapone and ALN-TTRsc02 could compete with inotersen and lomitapide and evolocumab could compete with Kynamro.

Following approval, our drugs, including SPINRAZA, volanesorsen and inotersen could be subject to regulatory limitations. Kynamro is subject to regulatory limitations.

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

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

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

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

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

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

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

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

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

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

If government or other third-party payors fail to provide adequate coverage and payment rates for our drugs, including SPINRAZA, inotersen, volanesorsen and Kynamro, our revenue will be limited.

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

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

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

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

If we or our partners fail to obtain regulatory approval for our drugs, including volanesorsen, inotersen, and additional approvals for SPINRAZA and Kynamro, we or our partners cannot sell them in the applicable markets.

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

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our drugs. It is possible that regulatory agencies will not approve our drugs including, volanesorsen and inotersen for marketing or additional marketing authorizations for SPINRAZA or Kynamro. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including SPINRAZA, volanesorsen and inotersen, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, the FDA or foreign regulatory authorities could claim that we have not tested volanesorsen in a sufficient number of patients to demonstrate volanesorsen is safe and effective in patients with FCS or FPL to support an application for marketing authorization, especially since a small number of patients in the APPROACH FCS study experienced severe thrombocytopenia, a condition where the patient has severely low platelet levels. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays.

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

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

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

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

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

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our drugs in development, may not predict the results of subsequent clinical studies, including the Phase 3 studies for volanesorsen. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- patients who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

In addition, our current drugs, including SPINRAZA, volanesorsen, inotersen, and Kynamro, are chemically similar to each other. As a result, a safety observation we encounter with one of our drugs could have, or be perceived by a regulatory authority to have, an impact on a different drug we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our drugs or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our drugs: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. Similarly, we have an ongoing Phase 3 study of volanesorsen in patients with FPL, an ongoing open label extension study of volanesorsen in patients with FCS and an ongoing open label extension study of inotersen. Adverse events or results from these studies could negatively impact our planned marketing approval applications for volanesorsen in patients with FCS, for inotersen or the commercial opportunity for each product.

Any failure or delay in the clinical studies, including the Phase 3 studies for volanesorsen and inotersen, could reduce the commercial potential or viability of our drugs.

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

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

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

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

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

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of June 30, 2017, we had an accumulated deficit of approximately $1.2 billion and stockholders' equity of approximately $215.6 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

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

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

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

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

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

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

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

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

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

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

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs, including SPINRAZA, volanesorsen, inotersen and Kynamro.

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for marketing authorization. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' expectations, including milestones related to SPINRAZA, volanesorsen and inotersen 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 June 30, 2017, we had cash, cash equivalents and short-term investments equal to $855.7 million. If we do not meet our goals to successfully commercialize our drugs, including SPINRAZA, volanesorsen, inotersen and Kynamro, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

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

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding June 30, 2017, the market price of our common stock ranged from $23.26 to $57.00 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, marketing authorization, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 10.3 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

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

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

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

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

ITEM 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 design 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 June 30, 2017. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2017.

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 Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, which are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead asked the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents infringes those patents, and requesting monetary damages to compensate for such infringement. In the trial for this case held in March 2016, the jury upheld all ten of the asserted claims of the patents-in-suit. The jury then decided that we and Merck are entitled to four percent of $5 billion in past sales of sofosbuvir. Gilead has stated it would appeal the jury's finding of validity. In the meantime, Gilead asserted two additional non-jury defenses: waiver and unclean hands. Although the judge rejected the waiver defense, she granted Gilead's motion claiming that the patents are unenforceable against it under the doctrine of unclean hands. We believe this ruling is contrary to the relevant law and the facts of the case. Accordingly, in July 2016, together with Merck we appealed the decision. Gilead cross-appealed on the issue of validity. The appeal remains pending before the Court of Appeals for the Federal Circuit and briefing is ongoing. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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

None.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
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 June 30, 2017, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

* This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

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)	August 8, 2017
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	August 8, 2017

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: August 8, 2017

/s/ STANLEY T. CROOKE

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

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this 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: August 8, 2017

/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 June 30, 2017, 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: August 8, 2017

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