UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 2019

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)	(Zip Code)

760-931-9200

(Registrant's telephone number, including area code)

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

Title of each class	Name of each exchange on which registered	Trading symbol
Common Stock, $.001 Par Value	The Nasdaq Stock Market, LLC	"IONS"

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

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, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer	Accelerated filer
Non-accelerated filer	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 May 2, 2019 was 140,322,994.

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TRADEMARKS

"Ionis," the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this report are the property of Ionis Pharmaceuticals, Inc. "Akcea," the Akcea logo, and other trademarks or service marks appearing in this report, including TEGSEDI (inotersen) and WAYLIVRA (volanesorsen), are the property of Akcea Therapeutics, Inc. This report contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this report may appear without the ® or TM symbols.

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

	March 31, 2019 (Unaudited)	December 31, 2018
ASSETS		
Current assets:		
Cash and cash equivalents	$ 375,811	$ 278,820
Short-term investments	1,877,943	1,805,252
Contracts receivable	10,452	12,759
Inventories	11,057	8,582
Other current assets	98,686	102,473
Total current assets	2,373,949	2,207,886
Property, plant and equipment, net	133,519	132,160
Patents, net	25,220	24,032
Long-term deferred tax assets	277,247	290,796
Deposits and other assets	25,954	12,910
Total assets	$ 2,835,889	$ 2,667,784
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 13,332	$ 28,660
Accrued compensation	16,264	29,268
Accrued liabilities	45,130	47,503
Income taxes payable	18,401	858
Current portion of long-term obligations	14,500	13,749
Current portion of deferred contract revenue	144,846	160,256
Total current liabilities	252,473	280,294
Long-term deferred contract revenue	542,416	567,359
1 percent convertible senior notes	577,415	568,215
Long-term obligations, less current portion	16,305	4,914
Long-term mortgage debt	59,860	59,842
Total liabilities	1,448,469	1,480,624
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 139,623,937 and 137,928,828 shares issued and outstanding at March 31, 2019 (unaudited) and December 31, 2018, respectively	140	138
Additional paid-in capital	2,117,969	2,047,250
Accumulated other comprehensive loss	(27,608)	(32,016)
Accumulated deficit	(882,850)	(967,293)
Total Ionis stockholders' equity	1,207,651	1,048,079
Noncontrolling interest in Akcea Therapeutics, Inc.	179,769	139,081
Total stockholders' equity	1,387,420	1,187,160
Total liabilities and stockholders' equity	$ 2,835,889	$ 2,667,784

See accompanying notes.

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

	Three Months Ended March 31,	
	2019	**2018**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 59,711	$ 41,081
TEGSEDI product sales, net	6,754	—
Licensing and other royalty revenue	1,623	942
Total commercial revenue	68,088	42,023
Research and development revenue under collaborative agreements	229,126	102,396
Total revenue	297,214	144,419
Expenses:		
Cost of products sold	1,041	—
Research, development and patent	106,417	104,067
Selling, general and administrative	68,221	43,653
Total operating expenses	175,679	147,720
Income (loss) from operations	121,535	(3,301)
Other income (expense):		
Investment income	12,142	3,610
Interest expense	(11,599)	(10,938)
Other expenses	(147)	(168)
Income (loss) before income tax expense	121,931	(10,797)
Income tax expense	(31,047)	(15)
Net income (loss)	90,884	(10,812)
Net (income) loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	(6,441)	9,392
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 84,443	$ (1,420)
Basic net income (loss) per share	$ 0.63	$ (0.01)
Shares used in computing basic net income (loss) per share	138,582	125,330
Diluted net income (loss) per share	$ 0.62	$ (0.01)
Shares used in computing diluted net income (loss) per share	141,537	125,330

See accompanying notes.

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

	Three Months Ended March 31,	
	2019	**2018**
Net income (loss)	$ 90,884	$ (10,812)
Unrealized gains (losses) on debt securities, net of tax	4,324	(1,530)
Currency translation adjustment	84	55
Comprehensive income (loss)	95,292	(12,287)
Comprehensive (income) loss attributable to noncontrolling interests	6,442	(9,399)
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. stockholders	$ 88,850	$ (2,888)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Three Months Ended March 31, 2018 and 2019
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2017	124,976	$ 125	$ 1,553,681	$ (31,759)	$ (1,241,034)	$ 281,013	$ 84,267	$ 365,280
Net loss	—	—	—	—	(1,420)	(1,420)	—	(1,420)
Change in unrealized gains (losses), net of tax	—	—	—	(1,530)	—	(1,530)	—	(1,530)
Foreign currency translation	—	—	—	55	—	55	—	55
Issuance of common stock in connection with employee stock plans	473	—	5,664	—	—	5,664	—	5,664
Stock-based compensation expense	—	—	28,451	—	—	28,451	—	28,451
Noncontrolling interest in Akcea Therapeutics, Inc	—	—	(10,842)	—	—	(10,842)	1,443	(9,399)
Balance at March 31, 2018	125,449	$ 125	$ 1,576,954	$ (33,234)	$ (1,242,454)	$ 301,391	$ 85,710	$ 387,101
Balance at December 31, 2018	137,929	$ 138	$ 2,047,250	$ (32,016)	$ (967,293)	$ 1,048,079	$ 139,081	$ 1,187,160
Net income	—	—	—	—	84,443	84,443	—	84,443
Change in unrealized gains (losses), net of tax	—	—	—	4,324	—	4,324	—	4,324
Foreign currency translation	—	—	—	84	—	84	—	84
Issuance of common stock in connection with employee stock plans	1,825	2	67,057	—	—	67,059	—	67,059
Stock-based compensation expense	—	—	45,505	—	—	45,505	—	45,505
Payments of tax withholdings related to vesting of employee stock awards	(130)	—	(7,597)	—	—	(7,597)	—	(7,597)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(34,246)	—	—	(34,246)	40,688	6,442
Balance at March 31, 2019	139,624	$ 140	$ 2,117,969	$ (27,608)	$ (882,850)	$ 1,207,651	$ 179,769	$ 1,387,420

See accompanying notes.

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

	Three Months Ended March 31,	
	2019	**2018**
Operating activities:		
Net income (loss)	$ 90,884	$ (10,812)
Adjustments to reconcile net loss to net cash provided by operating activities:		
Depreciation	3,073	2,363
Amortization of patents	470	443
Amortization of premium on investments, net	(2,433)	1,192
Amortization of debt issuance costs	474	441
Amortization of convertible senior notes discount	8,726	8,083
Stock-based compensation expense	45,505	28,451
Non-cash losses related to patents, licensing and property, plant and equipment	14	175
Provision for deferred income taxes	13,549	—
Changes in operating assets and liabilities:		
Contracts receivable	4,908	26,097
Inventories	(2,475)	922
Other current and long-term assets	1,802	11,422
Accounts payable	(17,191)	(13,144)
Accrued compensation	(13,004)	(12,985)
Accrued liabilities and deferred rent	13,756	(1,695)
Deferred contract revenue	(40,353)	(27,788)
Net cash provided by operating activities	107,705	13,165
Investing activities:		
Purchases of short-term investments	(492,781)	(91,157)
Proceeds from the sale of short-term investments	426,868	173,724
Purchases of property, plant and equipment	(3,229)	(2,343)
Acquisition of licenses and other assets, net	(1,032)	(738)
Net cash provided by (used in) investing activities	(70,174)	79,486
Financing activities:		
Proceeds from equity awards	67,057	5,675
Payments of tax withholdings related to vesting of employee stock awards	(7,597)	—
Offering costs paid	—	(451)
Net cash provided by financing activities	59,460	5,224
Net increase in cash and cash equivalents	96,991	97,875
Cash and cash equivalents at beginning of period	278,820	129,630
Cash and cash equivalents at end of period	$ 375,811	$ 227,505
Supplemental disclosures of cash flow information:		
Interest paid	$ 667	$ 644
Supplemental disclosures of non-cash investing and financing activities:		
Right-of-use assets obtained in exchange for lease liabilities	$ 13,557	$ —
Amounts accrued for capital and patent expenditures	$ 1,864	$ 2,091

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three months ended March 31, 2019 and 2018 on the same basis as the audited financial statements for the year ended December 31, 2018. 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, 2018 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 majority owned affiliate, Akcea Therapeutics, Inc. and its wholly owned subsidiaries. We formed Akcea in December 2014. In July 2017, Akcea completed an initial public offering, or IPO, and therefore, beginning in July 2017, we no longer owned 100 percent of Akcea. In the first quarter of 2019, we received 2.8 million shares of Akcea common stock as payment for the sublicense fee Akcea owed us when Novartis licensed AKCEA-APO(a)-L_{Rx}, increasing our ownership to approximately 76 percent at March 31, 2019. We reflected the increase in our ownership in these financial statements. Refer to the section titled “Noncontrolling Interest in Akcea” in Note 2, Significant Accounting Policies, for further information related to our accounting for our investment in Akcea.

Unless the context requires otherwise, “Ionis”, “Company,” “we,” “our,” and “us” refers to Ionis Pharmaceuticals, Inc. and its majority owned affiliate, Akcea Therapeutics, Inc. and its wholly owned subsidiaries.

2. Significant Accounting Policies

Revenue Recognition

Our Revenue Sources

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We earn commercial revenue primarily in the form of royalty payments on net sales of SPINRAZA. We will also recognize as commercial revenue future sales milestone payments and royalties we earn under our partnerships.

Commercial Revenue: TEGSEDI Product Sales, net

We added product sales from TEGSEDI to our commercial revenue in the fourth quarter of 2018. In the U.S., TEGSEDI is distributed through an exclusive distribution agreement with a third-party logistics company, or 3PL, that takes title to TEGSEDI. The 3PL is our sole customer in the U.S. The 3PL then distributes TEGSEDI to a specialty pharmacy and a specialty distributor, which we collectively refer to as wholesalers, who then distribute TEGSEDI to health care providers and patients. In Germany, TEGSEDI is distributed through a non-exclusive distribution model with a 3PL that takes title to TEGSEDI. The 3PL is our sole customer in Germany. The 3PL in Germany then distributes TEGSEDI to hospitals and pharmacies.

Research and development revenue under collaborative agreements

We often enter into collaboration agreements to license and sell our technology on an exclusive or non-exclusive basis. Our collaboration agreements typically contain multiple elements, or performance obligations, including technology licenses or options to obtain technology licenses, research and development, or R&D, services, and manufacturing services.

We provide details about our collaboration agreements in Note 7, Collaborative Arrangements and Licensing Agreements, in our Annual Report on Form 10-K for the year ended December 31, 2018. Under each collaboration note we discuss our specific revenue recognition conclusions, including our significant performance obligations under each collaboration.

Steps to Recognize Revenue

We use a five-step process to determine the amount of revenue we should recognize and when we should recognize it. The five step process is as follows:

1. Identify the contract

Accounting rules require us to first determine if we have a contract with our partner, including confirming that we have met each of the following criteria:

- We and our partner approved the contract and we are both committed to perform our obligations;
- We have identified our rights, our partner's rights and the payment terms;
- We have concluded that the contract has commercial substance, meaning that the risk, timing, or amount of our future cash flows is expected to change as a result of the contract; and
- We believe collectability is probable.

2. Identify the performance obligations

We next identify the distinct goods and services we are required to provide under the contract. Accounting rules refer to these as our performance obligations. We typically have only one performance obligation at the inception of a contract, which is to perform R&D services.

Often times we enter into a collaboration agreement in which we provide our partner with an option to license a medicine in the future. We may also provide our partner with an option to request that we provide additional goods or services in the future, such as active pharmaceutical ingredient, or API. We evaluate whether these options are material rights at the inception of the agreement. If we determine an option is a material right, we will consider the option a separate performance obligation. Historically, we have concluded that the options we grant to license a medicine in the future or to provide additional goods and services as requested by our partner are not material rights. These items are contingent upon future events that may not occur. When a partner exercises its option to license a medicine or requests additional goods or services, then we identify a new performance obligation for that item.

In some cases, we deliver a license at the start of an agreement. If we determine that our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery, then we consider the license to be a separate performance obligation.

3. Determine the transaction price

We then determine the transaction price by reviewing the amount of consideration we are eligible to earn under the collaboration agreement, including any variable consideration. Under our collaboration agreements, consideration typically includes fixed consideration in the form of an upfront payment and variable consideration in the form of potential milestone payments, license fees and royalties. At the start of an agreement, our transaction price usually consists of only the upfront payment. We do not typically include any payments we may receive in the future in our initial transaction price because the payments are not probable and are contingent on certain events. We reassess the total transaction price at each reporting period to determine if we should include additional payments in the transaction price.

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and are usually based on scientific progress. For example, in the first quarter of 2019, we earned $35 million in milestone payments from Roche when it dosed the first patient in the Phase 3 study of IONIS-HTT_{Rx} (RG6042) because we do not have any performance obligations related to these milestone payments as Roche is conducting the Phase 3 study of IONIS-HTT_{Rx}. At December 31, 2018, we determined it was not probable that we could earn these milestone payments. As such, we did not recognize any revenue associated with the milestone payments in 2018.

4. Allocate the transaction price

Next, we allocate the transaction price to each of our performance obligations. When we have to allocate the transaction price to more than one performance obligation, we make estimates of the relative stand-alone selling price of each performance obligation because we do not typically sell our goods or services on a stand-alone basis. We then allocate the transaction price to each performance obligation based on the relative stand-alone selling price.

We may engage a third party, independent valuation specialist to assist us with determining a stand-alone selling price for collaborations in which we deliver a license at the start of an agreement. We estimate the stand-alone selling price of these licenses using valuation methodologies, such as the relief from royalty method. Under this method, we estimate the amount of income, net of taxes, for the license. We then discount the projected income to present value. The significant inputs we use to determine the projected income of a license could include:

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

We typically estimate the selling price of R&D services by using our internal estimates of the cost to perform the specific services. The significant inputs we use to determine the selling price of our R&D services include:

- The number of internal hours we estimate 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 the stand-alone selling price of the R&D services we perform and the API we will deliver, accounting guidance requires us to include a markup for a reasonable profit margin.

We do not reallocate the transaction price after the start of an agreement to reflect subsequent changes in stand-alone selling prices.

5. Recognize revenue

We recognize revenue in one of two ways, over time or at a point in time. We recognize revenue over time when we are executing on our performance obligation over time and our partner receives benefit over time. For example, we recognize revenue over time when we provide R&D services. We recognize revenue at a point in time when our partner receives full use of an item at a specific point in time. For example, we recognize revenue at a point in time when we deliver a license or API to a partner.

For R&D services that we recognize over time, we measure our progress using an input method. The input methods we use are based on the effort we expend or costs we incur toward the satisfaction of our performance obligation. We estimate the amount of effort we expend, including the time we estimate it will take us to complete the activities, or costs we incur in a given period, relative to the estimated total effort or costs to satisfy the performance obligation. This results in a percentage that we multiply by the transaction price to determine the amount of revenue we recognize each period. This approach requires us to make numerous estimates and use significant judgement. If our estimates or judgements change over the course of the collaboration, they may affect the timing and amount of revenue that we recognize in the current and future periods.

The following are examples of when we typically recognize revenue based on the types of payments we receive.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We recognize royalty revenue in the period in which the counterparty sells the related product, which in certain cases may require us to estimate our royalty revenue. We recognize royalties from SPINRAZA sales in the period Biogen records the sale of SPINRAZA.

Commercial Revenue: TEGSEDI Product Sales, net

We recognize TEGSEDI product sales in the period when our customer obtains control of TEGSEDI, which occurs at a point in time upon transfer of title to the customer. We classify payments to customers or other parties in the distribution channel for services that are distinct and priced at fair value as selling, general and administrative expenses in our condensed consolidated statements of operations. Otherwise payments to customers or other parties in the distribution channel that do not meet those criteria are classified as a reduction of revenue, as discussed further below. We exclude from revenues, taxes collected from customers relating to product sales and remitted to governmental authorities.

Reserves for TEGSEDI Product Sales

We record TEGSEDI product sales at our net sales price, or transaction price. We include in our transaction price estimated reserves for discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that we offer within contracts between us and our customers, wholesalers, health care providers and other indirect customers. We estimate our reserves using the amounts we have earned or what we can claim on the associated sales. We classify our reserves as reductions of accounts receivable when the amount is payable to our customer or a current liability when the amount is payable to a party other than our customer in our condensed consolidated balance sheet. In certain cases, our estimates include a range of possible outcomes that are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, our reserves reflect our best estimates under the terms of our respective contracts. When calculating our reserves and related product sales, we only recognize amounts to the extent that we consider it probable that we would not have to reverse in a future period a significant amount of the cumulative sales we previously recognized. The actual amounts we receive may ultimately differ from our reserve estimates. If actual amounts in the future vary from our estimates, we will adjust these estimates, which would affect our net TEGSEDI product sales in the respective period.

The following are the components of variable consideration related to TEGSEDI product sales:

Chargebacks: In the U.S., we estimate obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers at prices lower than the list prices charged to our U.S. customer. Our U.S. customer charges us for the difference between what it pays for the product and the selling price to the qualified healthcare providers. We record reserves for these chargebacks related to TEGSEDI product sales to our U.S. customer during the reporting period. We also estimate the amount of product remaining in the distribution channel at the end of the reporting period that we expect our customer to sell to healthcare providers in future periods.

Government rebates: We are subject to discount obligations under government programs, including Medicaid programs and Medicare in the U.S. and we record reserves for government rebates based on statutory discount rates and estimated utilization. We estimate Medicaid and Medicare rebates based on a range of possible outcomes that are probability-weighted for the estimated payer mix. We record these reserves as an accrued liability on our condensed consolidated balance sheet with a corresponding offset reducing our TEGSEDI product sales in the same period we recognize the related sale. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. On a quarterly basis, we update our estimates and record any adjustments in the period that we identify the adjustments.

Trade discounts and allowances: We provide customary invoice discounts on TEGSEDI product sales to our U.S. customer for prompt payment. We record this discount as a reduction of TEGSEDI product sales in the period in which we recognize the related product revenue. In addition, we receive and pay for various distribution services from our U.S. customer and wholesalers in our U.S. distribution channel. For services we receive that are either not distinct from the sale of TEGSEDI or for which we cannot reasonably estimate the fair value, we classify such fees as a reduction of TEGSEDI product sales.

Product Returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the TEGSEDI's expiration date. We estimate the amount of TEGSEDI product sales that our customer may return. We record our return estimate as an accrued refund liability on our condensed consolidated balance sheet with a corresponding offset reducing our TEGSEDI product sales, in the same period we recognize the related sale. Based on our distribution model for TEGSEDI, contractual inventory limits with our customer and wholesalers and the price of TEGSEDI, we believe we will have minimal returns. Our customer in Germany only takes title to the product once it receives an order from a hospital or pharmacy and therefore does not maintain any inventory of TEGSEDI, as such we do not estimate returns in Germany.

Other incentives: In the U.S., we estimate reserves for other incentives including co-payment assistance we provide to patients with commercial insurance who have coverage and reside in states that allow co-payment assistance. We record a reserve for the amount we estimate we will pay for co-payment assistance. We base our reserve on the number of estimated claims and our estimate of the cost per claim related to TEGSEDI product sales that we have recognized as revenue. We record our other incentive reserve estimates as an accrued liability on our condensed consolidated balance sheet with a corresponding offset reducing our TEGSEDI product sales, in the same period we recognize the related sale.

Research and development revenue under collaboration agreements:

Upfront Payments

When we enter into a collaboration agreement with an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services. For example, under our collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases, we received a $75 million upfront payment in the fourth quarter of 2018. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $75 million upfront payment using an input method over the estimated period of time we are providing R&D services.

Milestone Payments

We are required to include additional consideration in the transaction price when it is probable. We typically include milestone payments for R&D services in the transaction price when they are achieved. We include these milestone payments when they are achieved because there is considerable uncertainty in the research and development processes that trigger these payments under our collaboration agreements. Similarly, we include approval milestone payments in the transaction price once the medicine is approved by the applicable regulatory agency. We will recognize sales based milestone payments in the period we achieve the milestone under the sales-based royalty exception allowed under accounting rules.

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the third quarter of 2017, we initiated a Phase 1/2a clinical study of IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease. We earned a $10 million milestone payment from Biogen related to the initiation of this study. We added this payment to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue from this milestone payment over our estimated period of performance.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation. For example, in the first quarter of 2019, we recognized $35 million in milestone payments when Roche dosed the first patient in a Phase 3 study for IONIS-HTT$_{Rx}$. We concluded that the milestone payments were not related to our R&D services performance obligation. Therefore, we recognized these milestone payments in full in the first quarter of 2019.

License Fees

We generally recognize as revenue the total amount we determine to be the stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery. For example, in the first quarter of 2019, we earned a $150 million license fee when Novartis licensed AKCEA-APO(a)-L_{Rx} from us.

Amendments to Agreements

From time to time we amend our collaboration agreements. When this occurs, we are required to assess the following items to determine the accounting for the amendment:

1) If the additional goods and/or services are distinct from the other performance obligations in the original agreement; and
2) If the goods and/or services are at a stand-alone selling price.

If we conclude the goods and/or services in the amendment are distinct from the performance obligations in the original agreement and at a stand-alone selling price, we account for the amendment as a separate agreement. If we conclude the goods and/or services are not distinct and at their stand-alone selling price, we then assess whether the remaining goods or services are distinct from those already provided. If the goods and/or services are distinct from what we have already provided, then we allocate the remaining transaction price from the original agreement and the additional transaction price from the amendment to the remaining goods and/or services. If the goods and/or services are not distinct from what we have already provided, we update the transaction price for our single performance obligation and recognize any change in our estimated revenue as a cumulative adjustment.

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 $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of 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 $75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, to provide R&D services and to deliver API. We allocated the $75 million transaction price to these performance obligations. Refer to Note 7, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our accounting treatment for our Bayer collaboration.

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 we should account for them individually as distinct arrangements or whether the separate agreements should be combined and accounted for together. We evaluate the following to determine the accounting for the agreements:

- Whether the agreements were negotiated together with a single objective;
- Whether the amount of consideration in one contract depends on the price or performance of the other agreement; or
- Whether the goods and/or services promised under the agreements are a single performance obligation.

Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that accounting guidance requires us to account for them as a combined arrangement.

For example, in the second quarter of 2018, we entered into two separate agreements with Biogen at the same time: a new strategic neurology collaboration agreement and a stock purchase agreement, or SPA. We evaluated the Biogen agreements to determine whether we should treat the agreements separately or combine them. We considered that the agreements were negotiated concurrently and in contemplation of one another. Based on these facts and circumstances, we concluded that we should evaluate the provisions of the agreements on a combined basis.

Contracts Receivable

Our contracts receivable balance represents the amounts we have billed our partners or customers and that are due to us unconditionally for goods we have delivered or services we have performed. When we bill our partners or customers with payment terms based on the passage of time, we consider the contract receivable to be unconditional. We typically receive payment within one quarter of billing our partner or customer.

Unbilled SPINRAZA Royalties

Our unbilled SPINRAZA royalties represent our right to receive consideration from Biogen in advance of when we are eligible to bill Biogen for SPINRAZA royalties. We include these unbilled amounts in other current assets on our condensed consolidated balance sheet.

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our condensed consolidated balance sheet. During the three months ended March 31, 2019 and 2018, we recognized $40.3 million and $34.9 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Products Sold

Our cost of products sold includes manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of TEGSEDI. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of products sold. Prior to obtaining regulatory approval in July 2018, we expensed a significant portion of the costs we incurred to produce the TEGSEDI supply we are using in the commercial launch as research and development expense. We previously recognized $0.3 million of costs to produce TEGSEDI related to the TEGSEDI commercial revenue we recognized in the three months ended March 31, 2019.

Noncontrolling Interest in Akcea Therapeutics, Inc.

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In the second, third and fourth quarters of 2018, we received additional shares of Akcea's stock related to our license of TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea, increasing our ownership percentage to approximately 75 percent. In the first quarter of 2019, we received 2.8 million shares of Akcea common stock as payment for the sublicense fee Akcea owed us when Novartis licensed AKCEA-APO(a)-L_{Rx}, increasing our ownership to approximately 76 percent at March 31, 2019. We reflected this increase in our ownership percentage in these financial statements as an adjustment to noncontrolling interest. The shares third parties own represent an interest in Akcea's equity that is not controlled by us. However, as we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our condensed consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our condensed consolidated balance sheet. In addition, we record a noncontrolling interest adjustment to account for the stock options Akcea grants, which if exercised, will dilute our ownership in Akcea. This adjustment is a reclassification within stockholders' equity from additional paid-in capital to noncontrolling interest in Akcea equal to the amount of stock-based compensation expense Akcea had recognized.

Cash, cash equivalents and 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 debt investments as "available-for-sale" and carry them at fair market value based upon prices on the last day of the fiscal period for identical or similar items. We record unrealized gains and losses on debt securities 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 also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At March 31, 2019, we held equity investments in two publicly held companies, ProQR Therapeutics N.V., or ProQR, and Antisense Therapeutics Limited, or ATL. We also held equity investments in four privately-held companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd.

Inventory valuation

We reflect our inventory on our condensed consolidated balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We capitalize the costs of raw materials that we purchase for use in producing our medicines because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for medicines 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 medicine. For example, if one of our medicines failed, we could use the raw materials for that medicine to manufacture our other medicines. We expense these costs as R&D expenses when we begin to manufacture API for a particular medicine if the medicine has not been approved for marketing by a regulatory agency.

We obtained the first regulatory approval for TEGSEDI in July 2018. At March 31, 2019 and December 31, 2018, our physical inventory for TEGSEDI included API that we produced prior to when we obtained regulatory approval and accordingly has no cost basis as we had previously expensed the costs as R&D expenses.

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. We did not record any inventory write-offs for the three months ended March 31, 2019 and 2018. Total inventory was $11.1 million and $8.6 million as of March 31, 2019 and December 31, 2018, respectively.

Leases

Topic 842 Adoption

In February 2016, the FASB issued amended accounting guidance related to lease accounting. This guidance supersedes the lease requirements we previously followed in Accounting Standards Codification, or ASC, Topic 840, *Leases*, or Topic 840, and created a new lease accounting standard, Topic 842, *Leases*, or Topic 842. Under Topic 842, an entity will record on its balance sheet all leases with a term longer than one year. Further, an entity will record a liability with a value equal to the present value of payments it will make over the life of the lease (lease liability) and an asset representing the underlying leased asset (right-of-use asset). The new accounting guidance requires entities to determine if its leases are operating or financing leases. Entities will recognize expense for operating leases on a straight-line basis as an operating expense. If an entity determines a lease is a financing lease, it will record

both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease. We adopted Topic 842 on January 1, 2019 and adjusted our opening balance sheet on that date for our right-of-use operating lease assets and operating lease liabilities. At adoption, we recorded $13.5 million in right-of-use operating lease assets and $18.5 million in operating lease liabilities, of which we classified $2 million as a current liability. We adopted Topic 842 using the available practical expedients permitted under the transition guidance within the new standard, which among other things, allowed us to carry forward the historical lease classification of those leases we had in place as of January 1, 2019. The adoption did not have an impact on our condensed consolidated statement of operations.

Leases

We determine if an arrangement contains a lease at inception. We currently only have operating leases. We recognize a right-of-use operating lease asset and associated short- and long-term operating lease liability on our condensed consolidated balance sheet for operating leases greater than one year. Our right-of-use assets represent our right to use an underlying asset for the lease term and our lease liabilities represent our obligation to make lease payments arising from the lease arrangement. We recognize our right-of-use operating lease assets and lease liabilities based on the present value of the future minimum lease payments we will pay over the lease term. We determined the lease term at the commencement date of the lease, and in certain cases our lease term could include renewal options if we concluded we were reasonably certain that we will exercise the renewal option.

As our current leases do not provide an interest rate implicit in the lease, we used our or Akcea's incremental borrowing rate, based on the information available on the date we adopted Topic 842 in determining the present value of future payments. Our right-of-use operating lease asset also includes any lease payments we made and excludes any tenant improvement allowances we received. We recognize rent expense for our minimum lease payments on a straight-line basis over the expected term of our lease. We recognize period expenses, such as common area maintenance expenses, in the period we incur the expense.

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.

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in our financial statements or tax returns. In addition, deferred tax assets are recorded for the future benefit of utilizing net operating losses and research and development credit carryforwards. We record a valuation allowance when necessary to reduce our net deferred tax assets to the amount expected to be realized.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Tax Act. The Tax Act created a new requirement on global intangible low-taxed income, or GILTI, earned by foreign subsidiaries for tax years beginning on or after January 1, 2018. The GILTI provisions require foreign subsidiary earnings in excess of an allowable return on the foreign subsidiary's assets to be included in our U.S. income tax return. Under U.S. GAAP, we are permitted to make an accounting policy election to either treat taxes due on future inclusions in U.S. taxable income related to GILTI as a current-period expense when incurred or to factor such amounts into our measurement of deferred taxes. We have made the election to account for GILTI as a component of current taxes incurred rather than as a component of deferred taxes.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment, right-of-use operating lease assets 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 us to make estimates and assumptions that affect the amounts reported in our condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Basic and diluted net income (loss) per share

Basic net income (loss) per share

We compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period.

The calculation of total net income (loss) attributable to our common stockholders for the three months ended March 31, 2019 and 2018 considered our net income for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in the condensed consolidated statements of operations.

Our basic net income per share for the three months ended March 31, 2019, was calculated as follows (in thousands, except per share amounts):

Three months ended March 31, 2019	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Income Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	68,582	$ 0.35	$ 23,846
Akcea's net income attributable to our ownership			$ 23,846
Ionis' stand-alone net income			63,697
Net income available to Ionis common stockholders			$ 87,543
Weighted average shares outstanding			138,582
Basic net income per share			$ 0.63

Our basic net loss per share for the three months ended March 31, 2018, was calculated as follows (in thousands, except per share amounts):

Three months ended March 31, 2018	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Loss Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	45,448	$ (0.44)	$ (19,997)
Akcea's net loss attributable to our ownership			$ (19,997)
Ionis' stand-alone net income			18,785
Net loss available to Ionis common stockholders			$ (1,212)
Weighted average shares outstanding			125,330
Basic net loss per share			$ (0.01)

Dilutive net income (loss per share)

For the three months ended March 31, 2019, we had net income available to Ionis common stockholders. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period.

We calculated our diluted net income per share for the three months ended March 31, 2019 as follows (in thousands except per share amounts):

Three months ended March 31, 2019	**Income (Numerator)**	**Shares (Denominator)**	**Per-Share Amount**
Net income available to Ionis common stockholders	$ 87,543	138,582	$ 0.63
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	2,252	
Shares issuable upon restricted stock award issuance	—	665	
Shares issuable related to our ESPP	—	38	
Income available to Ionis common stockholders	$ 87,543	141,537	$ 0.62

For the three months ended March 31, 2019, the calculation excluded the 1 percent notes because the effect on diluted earnings per share was anti-dilutive.

For the three months ended March 31, 2018, 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;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

Convertible debt

We account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. To determine the fair value of the debt component we are required to use 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 majority-owned affiliate. Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with rare and serious diseases. 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 allocate a portion of Ionis' development, R&D support and general and administrative expenses to Akcea for work Ionis performs on behalf of Akcea.

Stock-based compensation expense

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

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. For the three months ended March 31, 2019 and 2018, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	Three Months Ended March 31,	
	2019	**2018**
Risk-free interest rate	2.4%	2.2%
Dividend yield	0.0%	0.0%
Volatility	60.3%	63.2%
Expected life	4.6 years	4.6 years

Ionis ESPP:

	Three Months Ended March 31,	
	2019	**2018**
Risk-free interest rate	2.5%	1.6%
Dividend yield	0.0%	0.0%
Volatility	45.5%	44.4%
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 three months ended March 31, 2019 was $58.26 per share.

In addition to our stock plans, Akcea has its own stock plan under which it grants options and RSUs and under which it derives its stock-based compensation expense. The following are the weighted-average Black-Scholes assumptions Akcea used under its plan for the three months ended March 31, 2019 and March 31, 2018:

Akcea Employee Stock Options:

	Three Months Ended March 31,	
	2019	**2018**
Risk-free interest rate	2.5%	2.6%
Dividend yield	—	—
Volatility	76.4%	77.1%
Expected life	6.1 years	6.1 years

Akcea ESPP:

	Three Months Ended March 31,	
	2019	**2018**
Risk-free interest rate	2.5%	1.6%
Dividend yield	—	—
Volatility	64.1%	62.3%
Expected life	6 months	6 months

The following table summarizes stock-based compensation expense for the three months ended March 31, 2019 and 2018 (in thousands). Our non-cash stock-based compensation expense includes $18.6 million and $6.4 million of stock-based compensation expense for Akcea employees for the three months ended March 31, 2019 and 2018, respectively.

	Three Months Ended March 31,	
	2019	**2018**
Cost of products sold	$ 118	$ —
Research, development and patent	24,435	19,682
Selling, general and administrative	20,952	8,769
Total	$ 45,505	$ 28,451

As of March 31, 2019, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $192.2 million and $68.7 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 2.0 years, respectively.

Impact of recently issued accounting standards

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. The new guidance requires us to remeasure 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 plan to adopt this guidance on January 1, 2020. We are currently assessing the effects it will have on our condensed consolidated financial statements and disclosures.

In August 2018, the FASB issued clarifying guidance on how to account for implementation costs related to cloud-servicing arrangements. The guidance states that if these fees qualify to be capitalized and amortized over the service period, they need to be expensed in the same line item as the service expense and recognized in the same balance sheet category. The update can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. The updated guidance is effective for fiscal years beginning after December 31, 2019, and interim periods within those fiscal years. Early adoption is permitted in any interim period. We are currently assessing the effects this updated guidance could have on our condensed consolidated financial statements and timing of adoption.

In August 2018, the FASB updated its disclosure requirements related to Level 1, 2 and 3 fair value measurements. The update included deletion and modification of certain disclosure requirements and additional disclosure related to Level 3 measurements. The guidance is effective for fiscal years beginning after December 31, 2019 and early adoption is permitted. We adopted this updated guidance on January 1, 2019 and it did not have a significant impact on our disclosures.

In November 2018, the FASB issued clarifying guidance of the interaction between the collaboration accounting guidance and the new revenue recognition guidance we adopted on January 1, 2018 (Topic 606). Below is the clarifying guidance and how we will implement it (in italics):

1) When a participant is considered a customer in a collaborative arrangement, all of the associated accounting under Topic 606 should be applied
   - *We will apply all of the associated accounting under Topic 606 when we determine a participant in a collaborative arrangement is a customer*
2) Adds "unit of account" concept to collaboration accounting guidance to align with Topic 606. The "unit of account" concept is used to determine if revenue is recognized or if a contra expense is recognized from consideration received under a collaboration
   - *We will use the "unit of account" concept when we receive consideration under a collaboration to determine when we recognize revenue or a contra expense*
3) The clarifying guidance precludes us from recognizing revenue under Topic 606 when we determine a transaction with a collaborative partner is not a customer and is not directly related to the sales to third parties
   - *When we conclude a collaboration partner is not a customer and is not directly related to the sales to third parties, we will not recognize revenue for the transaction*

The updated guidance is effective for public entities for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted. We plan to adopt this guidance on January 1, 2020. We are currently assessing the effects it will have on our condensed consolidated financial statements and disclosures.

3. Investments

As of March 31, 2019, we had invested our excess cash primarily in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or S&P, or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2019:

One year or less	74%
After one year but within two years	21%
After two years but within three years	5%
Total	100%

As illustrated above, at March 31, 2019, 95 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

At March 31, 2019, we had an ownership interest of less than 20 percent in four private companies and two public companies with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd. The publicly-traded companies are ProQR and ATL.

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

		Gross Unrealized		
March 31, 2019	**Cost** (1)	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities:				
Corporate debt securities (2)	$ 869,483	$ 326	$ (531)	$ 869,278
Debt securities issued by U.S. government agencies	124,744	71	(15)	124,800
Debt securities issued by the U.S. Treasury (2)	328,340	110	(12)	328,438
Debt securities issued by states of the U.S. and political subdivisions of the states	63,366	10	(203)	63,173
Other municipal debt securities	2,931	1	—	2,932
Total securities with a maturity of one year or less	1,388,864	518	(761)	1,388,621
Corporate debt securities	360,976	1,236	(336)	361,876
Debt securities issued by U.S. government agencies	120,341	279	(112)	120,508
Debt securities issued by the U.S. Treasury	33,569	12	(22)	33,559
Debt securities issued by states of the U.S. and political subdivisions of the states	15,615	—	(125)	15,490
Total securities with a maturity of more than one year	530,501	1,527	(595)	531,433
Total available-for-sale securities	$ 1,919,365	$ 2,045	$ (1,356)	$ 1,920,054
Equity securities:				
Total equity securities included in other current assets (3)	$ 1,212	$ —	$ (244)	$ 968
Total available-for-sale and equity securities	$ 1,920,577	$ 2,045	$ (1,600)	$ 1,921,022

December 31, 2018	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities	$ 956,879	$ 13	$ (1,858)	$ 955,034
Debt securities issued by U.S. government agencies	168,839	3	(104)	168,738
Debt securities issued by the U.S. Treasury	244,640	15	(77)	244,578
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	63,572	—	(323)	63,249
Total securities with a maturity of one year or less	1,433,930	31	(2,362)	1,431,599
Corporate debt securities	299,018	194	(1,286)	297,926
Debt securities issued by U.S. government agencies	107,789	194	(109)	107,874
Debt securities issued by the U.S. Treasury	15,600	—	(24)	15,576
Debt securities issued by states of the U.S. and political subdivisions of the states	16,980	—	(287)	16,693
Total securities with a maturity of more than one year	439,387	388	(1,706)	438,069
Total available-for-sale securities	$ 1,873,317	$ 419	$ (4,068)	$ 1,869,668
Equity securities:				
Total equity securities included in other current assets (3)	1,212	137	—	1,349
Total available-for-sale and equity securities	$ 1,874,529	$ 556	$ (4,068)	$ 1,871,017

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

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

(3) We recognize our equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer on our condensed consolidated balance sheet.

The following is a summary of our investments we consider to be temporarily impaired at March 31, 2019. 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.

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
(In thousands)	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	275	$ 530,786	$ (306)	$ 102,815	$ (561)	$ 633,601	$ (867)
Debt securities issued by U.S. government agencies	24	91,005	(81)	16,534	(46)	107,539	(127)
Debt securities issued by the U.S. Treasury	15	94,603	(34)	—	—	94,603	(34)
Debt securities issued by states of the U.S. and political subdivisions of the states	39	11,254	(9)	51,579	(319)	62,833	(328)
Total temporarily impaired securities	353	$ 727,648	$ (430)	$ 170,928	$ (926)	$ 898,576	$ (1,356)

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.

The following tables present the major security types we held at March 31, 2019 and December 31, 2018 that we regularly measure and carry at fair value. At March 31, 2019 and December 31, 2018, our ProQR investment was subject to trading restrictions that extend through the fourth quarter of 2019, as a result we included a lack of marketability discount in valuing this investment,

which is a Level 3 input. The amount we owned in ProQR did not change from December 31, 2018 to March 31, 2019. 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 March 31, 2019	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 146,542	$ 146,542	$ —	$ —
Corporate debt securities (2)	1,231,154	—	1,231,154	—
Debt securities issued by U.S. government agencies (3)	245,308	—	245,308	—
Debt securities issued by the U.S. Treasury (4)	361,997	361,997	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	78,663	—	78,663	—
Other municipal debt securities (3)	2,932	—	2,932	—
Investment in ProQR Therapeutics N.V. (5)	968	—	—	968
Total	$ 2,067,564	$ 508,539	$ 1,558,057	$ 968

	At December 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 146,281	$ 146,281	$ —	$ —
Corporate debt securities (6)	1,252,960	—	1,252,960	—
Debt securities issued by U.S. government agencies (3)	276,612	—	276,612	—
Debt securities issued by the U.S. Treasury (7)	260,154	260,154	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	79,942	—	79,942	—
Investment in ProQR Therapeutics N.V. (5)	1,349	—	—	1,349
Total	$ 2,017,298	$ 406,435	$ 1,609,514	$ 1,349

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

(2) $27.1 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) $15.0 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) Included in other current assets on our condensed consolidated balance sheet.

(6) $50.2 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.

(7) $14.2 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.

Convertible Notes

Our 1 percent notes had a fair value of $928.4 million at March 31, 2019. 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. Operating Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease with an initial term ending in June 2021 and an option to extend the lease for up to two five-year periods.

We also lease additional office space and we sublease a portion of this space to Akcea. We lease this space under a non-cancelable operating lease with an initial term ending in June 2023 and an option to extend the lease for one five-year period. The sublease with Akcea is eliminated in our condensed consolidated financial statements.

Akcea entered into an operating lease agreement for office space located in Boston, Massachusetts for its new corporate headquarters in the second quarter of 2018. The lease commencement date was in August 2018 and Akcea took occupancy in September 2018. Akcea is leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. Under the lease agreement, Akcea received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million. Akcea provided the lessor with a letter of credit to secure its obligations under the lease in the initial amount of $2.4 million, to be reduced to $1.8 million on the third anniversary of the rent commencement date and to $1.2 million on the fifth anniversary of the rent commencement date if Akcea meets certain conditions set forth in the lease at each such time.

When we determined our lease term for our operating lease right-of-use assets and lease liabilities for these leases we did not include the extension options for these leases.

Amounts related to our operating leases were as follows (dollar amounts in millions):

	At March 31, 2019
Right-of-use operating lease assets (1)	$ 13.1
Operating lease liabilities (2)	$ 18.0
Weighted average remaining lease term	9 years
Weighted average discount rate	7.6%

(1) Included in deposits and other assets on our condensed consolidated balance sheet.

(2) Current portion of $2.0 million was included in current portion of long-term obligations on our condensed consolidated balance sheet, with the difference included in long-term obligations.

We paid cash of $1.0 million for rent payments we made during the three months ended March 31, 2019, which was included in the measurement of our lease liabilities in our net cash provided by operating activities in our condensed consolidated statement of cash flows.

As of March 31, 2019, the payments for our operating lease liabilities are as follows (in thousands):

	Operating Leases
Remainder of 2019	$ 2,341
Years ending December 31,	
2020	3,008
2021	2,725
2022	2,539
2023	2,505
Thereafter	11,862
Total minimum lease payments	24,980
Less:	
Imputed interest	(7,020)
Total operating lease liabilities	$ 17,960

Rent expense was $0.9 million for the three months ended March 31, 2019 and was negligible for the three months ended March 31, 2018.

6. Income Taxes

Our effective tax rate may vary from the U.S. federal statutory tax rate due to the change in the mix of earnings in tax jurisdictions with different statutory rates, benefits related to tax credits, and the tax impact of non-deductible expenses and other permanent differences between income before income taxes and taxable income. Our effective income tax rate of 25.5 percent for the three months ended March 31, 2019 differed from the U.S. federal statutory rate of 21 percent primarily due to state taxes, partially offset by the tax benefit related to estimated research & development and orphan drug credits and the excess tax benefit related to share-based compensation.

We recorded income tax expense of $31 million for the three months ended March 31, 2019, compared to $15,000 for the same period in 2018. The increase in our income tax expense was primarily due to our expectation that we will generate U.S. federal and state taxable income in 2019. Our 2019 income tax expense has two components. The first component relates to federal income taxes. We expect to utilize our deferred tax assets to offset our U.S. federal taxable income. We are recording non-cash income tax expense as we utilize our federal deferred tax assets. The other component of our income tax expense relates to the estimated cash taxes we will pay for our state income taxes. Although we are recording the expense for our state income taxes in 2019, we will not have to make the majority of the payment for this liability until the first quarter of 2020.

7. Collaborative Arrangements and Licensing Agreements

Below, we have included our collaborations with substantive changes during the first three months of 2019 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, 2018.

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 medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. In December 2017, we entered into a collaboration with Biogen to identify new antisense medicines for the treatment of SMA. Additionally, we and Biogen are currently developing six other medicines to treat neurodegenerative diseases under these collaborations, including tofersen (formerly IONIS-SOD1$_{Rx}$) for ALS patients with SOD1 mutations, or SOD1-ALS, which Biogen moved into a Phase 3 study in the first quarter of 2019, IONIS-MAPT$_{Rx}$ for Alzheimer's disease, IONIS-C9$_{Rx}$ for ALS patients with C9ORF72 mutations, and IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these medicines, we and Biogen are evaluating numerous additional targets to develop medicines to treat neurological diseases. In April 2018, we entered into a new strategic collaboration for the treatment of neurological diseases with Biogen. From inception through March 2019, we have received over $2.1 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 for our 2018 strategic neurology collaboration.

During the three months ended March 31, 2019 and 2018, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended March 31,	
	2019	2018
SPINRAZA royalties (commercial revenue)	$ 59.7	$ 41.1
R&D revenue	24.5	10.8
Total revenue from our relationship with Biogen	$ 84.2	$ 51.9
Percentage of total revenue	28%	36%

During the first quarter of 2019, we did not have any changes to our performance obligations or the timing in which we expect to recognize revenue under our Biogen collaborations.

In April 2019, we achieved a $7.5 million milestone payment from Biogen, when we advanced a new target for an unidentified neurological disease under the 2018 strategic neurology collaboration. We will achieve the next payment of up to $10 million if Biogen designates a target under our 2018 strategic neurology collaboration.

Our condensed consolidated balance sheet at March 31, 2019 and December 31, 2018 included deferred revenue of $556.4 million and $580.9 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

Roche

We have two collaborations with Roche, one to develop treatments for Huntington's disease, or HD, and one to develop IONIS-FB-L$_{Rx}$ for the treatment of complement-mediated diseases. In December 2017, upon completion of the Phase 1/2 study of IONIS-HTT$_{Rx}$, Roche exercised its option to license IONIS-HTT$_{Rx}$ and is now responsible for the global development, regulatory and commercialization activities for IONIS-HTT$_{Rx}$. In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L$_{Rx}$ for the treatment of complement-mediated diseases. The first indication we plan to pursue is the treatment of patients with geographic atrophy, or GA, the advanced stage of dry age-related macular degeneration, or AMD. We are responsible for conducting a Phase 2 study in patients with dry AMD. In addition, we plan to evaluate the medicine for a severe and rare renal indication. Roche has the option to license IONIS-FB-L$_{Rx}$ at the completion of these studies. Upon licensing, Roche will be responsible for all further global development, regulatory and commercialization activities and costs. From inception through March 2019, we have received over $220 million from our Roche collaborations, including $35 million in milestone payments we earned in the first quarter of 2019 when Roche dosed the first patient in a Phase 3 study for IONIS-HTT$_{Rx}$. We will achieve the next payment of $15 million if Roche advances IONIS-HTT$_{Rx}$.

During the three months ended March 31, 2019 and 2018, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Three Months Ended March 31,	
	2019	2018
R&D revenue	$ 41.2	$ 2.0
Percentage of total revenue	14%	1%

Our revenue in the first quarter of 2019, included $35 million of milestone payments we earned when Roche dosed the first patient in the Phase 3 study of IONIS-HTT$_{Rx}$. We recognized these milestone payments in full in the first quarter of 2019 because we do not have any performance obligations related to these milestone payments as Roche is conducting the Phase 3 study of IONIS-HTT$_{Rx}$.

During the first quarter of 2019, we did not have any changes to our performance obligations or the timing in which we expect to recognize revenue under our Roche collaborations.

Our condensed consolidated balance sheet at March 31, 2019 and December 31, 2018 included deferred revenue of $67.5 million and $72.6 million, respectively, related to our relationship with Roche.

Akcea Collaboration

The following collaboration agreement relates to Akcea, our majority owned affiliate. Our consolidated results include all the revenue earned and cash received under this collaboration agreement. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our condensed consolidated balance sheet.

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 further 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 initial quantities of API for each medicine. If Novartis exercises an option for either of these medicines, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such medicine. In the first quarter of 2019, Novartis licensed AKCEA-APO(a)-L$_{Rx}$. Novartis is responsible for conducting and funding all future development, regulatory and commercialization activities for AKCEA-APO(a)-L$_{Rx}$, including a global pivotal cardiovascular outcomes study, for which planning and initiation activities are underway. From inception through March 2019, we have received over $330 million from our Novartis collaboration, including $150 million we earned from Novartis in the first quarter of 2019 for the license of AKCEA-APO(a)-L$_{Rx}$. Akcea paid us $75 million as a sublicense fee in 2.8 million shares of Akcea common stock.

We identified a new performance obligation when we granted Novartis the license of AKCEA-APO(a)-L$_{Rx}$ in the first quarter of 2019 because the license is distinct from our other performance obligations. We recognized the $150 million license fee for AKCEA-APO(a)-L$_{Rx}$ as revenue at that time because Novartis had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Novartis.

Akcea is responsible for the development activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations, and we reflect all of Akcea's revenue in our consolidated results. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue in our Ionis Core operating segment results and Akcea recognizes the fees as R&D expense. In our consolidated results, we eliminate this sublicense revenue and expense. Any cash Akcea receives is included in our condensed consolidated balance sheet.

During the three months ended March 31, 2019 and 2018, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	Three Months Ended March 31,	
	2019	**2018**
R&D revenue	$ 157.1	$ 17.1
Percentage of total revenue	53%	12%

During the first quarter of 2019, we did not have any changes to our performance obligations, except as noted above, or the timing in which we expect to recognize revenue under our Novartis collaboration.

Our condensed consolidated balance sheet at March 31, 2019 and December 31, 2018 included deferred revenue of $23.3 million and $28.8 million, respectively, related to our relationship with Novartis.

8. Segment Information

We have two reportable segments Ionis Core and Akcea Therapeutics. At March 31, 2019 we owned approximately 76 percent of Akcea. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting our antisense technology to generate a broad pipeline of first-in-class and/or best-in-class medicines 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 medicines to treat patients with rare and serious diseases. Akcea generates revenue from TEGSEDI product sales and from its collaborations with Novartis and PTC Therapeutics.

The following tables show our segment revenue and income (loss) from operations for the three months ended March 31, 2019 and March 31, 2018 (in thousands), respectively.

Three Months Ended March 31, 2019	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 59,711	$ —	$ —	$ 59,711
TEGSEDI product sales, net	—	6,754	—	6,754
Licensing and other royalty revenue	1,623	—	—	1,623
Total commercial revenue	$ 61,334	$ 6,754	$ —	$ 68,088
R&D revenue under collaborative agreements	$ 160,556	$ 157,062	$ (88,492)	$ 229,126
Total segment revenue	$ 221,890	$ 163,816	$ (88,492)	$ 297,214
Total operating expenses	$ 114,515	$ 137,610	$ (76,446)	$ 175,679
Income from operations	$ 107,375	$ 26,206	$ (12,046)	$ 121,535

Three Months Ended March 31, 2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 41,081	$ —	$ —	$ 41,081
Licensing and other royalty revenue	942	—	—	942
Total commercial revenue	$ 42,023	$ —	$ —	$ 42,023
R&D revenue under collaborative agreements	$ 90,517	$ 17,108	$ (5,229)	$ 102,396
Total segment revenue	$ 132,540	$ 17,108	$ (5,229)	$ 144,419
Total operating expense	$ 105,544	$ 47,435	$ (5,259)	$ 147,720
Income (loss) from operations	$ 26,996	$ (30,327)	$ 30	$ (3,301)

The following table shows our total assets by segment at March 31, 2019 and December 31, 2018 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
March 31, 2019	$ 3,112,235	$ 458,717	$ (735,063)	$ 2,835,889
December 31, 2018	$ 2,975,491	$ 365,261	$ (672,968)	$ 2,667,784

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 majority owned affiliate, Akcea Therapeutics, Inc.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, the Report includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority-owned affiliate. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report and described in additional detail in our annual report on Form 10-K for the year ended December 31, 2018, which is on file with the U.S. Securities and Exchange Commission and is available from us, and those identified within Part II Item 1A. Risk Factors of this Report. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

Overview

We are a leader in discovering and developing RNA-targeted therapeutics with sustained and growing revenues. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics that we believe has fundamentally changed medicine and transformed the lives of people with devastating and often deadly diseases. Our large, diverse and advanced pipeline of over 40 first-in-class and/or best-in-class medicines addresses diseases across a broad range of therapeutic areas, targeting small, medium and large patient populations.

We have three commercial medicines approved in major markets around the world, SPINRAZA, TEGSEDI and WAYLIVRA. We have two medicines in Phase 3 studies, IONIS-HTT$_{Rx}$, for Huntington's disease, and tofersen, for SOD1-ALS. We also have the potential for two more medicines to begin Phase 3 studies this year and the potential for a total of 10 medicines in Phase 3 studies by the end of 2020. These medicines, along with the more than 30 additional medicines in our pipeline, represent multiple potential drivers of value for years to come. We believe our efficient drug discovery platform, coupled with our innovation-centric business model, provides us with the flexibility to determine the optimal development and commercialization strategy to maximize the commercial opportunity for each of our medicines and ensure that we continue to produce transformative medicines for patients who need them. We believe we are positioned to drive substantial value for patients and shareholders.

As of March 2019, SPINRAZA was approved in over 40 countries around the world, and our partner Biogen, who is responsible for global SPINRAZA commercial activities, reported that more than 7,500 patients are now on SPINRAZA therapy. In addition, Biogen plans to continue to pursue regulatory filings in additional countries. SPINRAZA is the first and only approved medicine for the treatment of SMA. SPINRAZA is the established standard-of-care for all people with this progressive, debilitating and often fatal genetic disease. In November 2018, SPINRAZA was recognized with the 2018 International Prix Galien award as Best Biotechnology Product. This prestigious honor marks the seventh Prix Galien award for SPINRAZA. To date, we have earned more than $410 million in commercial revenues from royalties on sales of SPINRAZA.

TEGSEDI, a once weekly, self-administered subcutaneous medicine, was approved in 2018 in the U.S., EU and Canada for the treatment of polyneuropathy caused by hATTR in adult patients. hATTR is a debilitating, progressive, and fatal disease. Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat patients with rare and serious diseases, launched TEGSEDI globally in late 2018. Our aim is to make TEGSEDI available globally. We plan to achieve this in part through Akcea's exclusive license agreement with PTC to commercialize TEGSEDI in Latin America. In January 2019, PTC filed an application for regulatory approval in Brazil with ANVISA, the Brazilian regulatory authority. ANVISA granted priority review for TEGSEDI. We have earned $9 million in TEGSEDI product sales since launching late last year.

WAYLIVRA, a self-administered, subcutaneous medicine, received conditional marketing authorization from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis in May 2019. We and Akcea are preparing to commercialize WAYLIVRA in the EU and we are also focused on regulatory discussions in the U.S and Canada. Akcea plans to leverage its existing commercial infrastructure in Europe to market WAYLIVRA. Akcea is continuing to conduct open-label extension and early access programs. We are also developing WAYLIVRA for the treatment of people with familial partial lipodystrophy, or FPL. People with FPL lack subcutaneous adipose tissue and have abnormal subcutaneous fat distribution causing increased incidence of potentially life-threatening pancreatitis, diabetes, extreme insulin resistance and increased liver fat.

In addition to commercializing TEGSEDI and preparing to commercialize WAYLIVRA, Akcea is developing four other clinical-stage medicines: AKCEA-APO(a)-L$_{Rx}$ (TQJ230), AKCEA-ANGPTL3-L$_{Rx}$, AKCEA-APOCIII-L$_{Rx}$ and AKCEA-TTR-L$_{Rx}$, each of which could potentially treat multiple patient populations. Moving these medicines into Akcea allows us to retain substantial value from these medicines and ensures our core focus remains on innovation. As of March 2019, we owned approximately 76 percent of Akcea.

We are continuously advancing our technology and pipeline to provide the most value to patients. We have a pipeline of over 40 medicines that, like SPINRAZA, TEGSEDI and WAYLIVRA, have the potential to transform the treatment of diseases with no adequate treatment today. These medicines range from treatments for rare diseases with small patient populations to more common diseases afflicting millions of patients. Our pipeline covers a broad spectrum of therapeutic areas, such as cardiometabolic diseases, neurodegenerative diseases, cancer, severe and rare diseases and others. We believe our large and diverse pipeline contains many near-, mid- and longer-term growth drivers for the company.

The depth of our knowledge and expertise with antisense technology together with our strong financial position provides us the flexibility to partner our medicines at what we believe is the optimal time to maximize the value of our medicines. We have a distinct partnering strategy based on each specific medicine and the expertise and resources we and our potential partners may bring to a collaboration. We may develop and commercialize some medicines through affiliates. In general, these are medicines, like TEGSEDI and WAYLIVRA, that can benefit from our internal expertise and infrastructure, have manageable development plans and costs, and have the potential for initial rare disease indications. For other medicines, we may establish collaborations to advance the medicine. We have alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our medicines, advancing our technology, preparing to commercialize our medicines and selling our medicines. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis and Roche. Our partners bring resources and expertise that augment and build upon our internal capabilities. We have the potential to earn over $20 billion in future milestone payments and licensing fees from our existing partnerships.

Financial Highlights

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

	Three Months Ended March 31,	
	2019	**2018**
Total revenue	$ 297,214	$ 144,419
Total operating expenses	$ 175,679	$ 147,720
Income (loss) from operations	$ 121,535	$ (3,301)
Net income (loss)	$ 90,884	$ (10,812)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 84,443	$ (1,420)

Our revenue for the three months ended March 31, 2019 of $297.2 million increased significantly compared to the same period in 2018, primarily from the $150 million license fee we earned from Novartis when it licensed AKCEA-APO(a)-L_{Rx} and a more than 45 percent increase in commercial revenue from SPINRAZA royalties.

Our operating expenses for the first quarter of 2019 of $175.7 million increased over the same period in 2018. The increase in operating expenses was principally due to our investments in the global launch of TEGSEDI.

During the first quarter of 2019 we received more than $270 million in payments from our partners, including $150 million from Novartis, $78 million from Biogen and $35 million from Roche. This is compared to more than $155 million received in the first quarter of 2018. We believe our strong financial position should enable us to continue to execute on our corporate goals throughout 2019 and beyond.

Recent Business Highlights *(Q1 2019 and subsequent activities)*

- *SPINRAZA – the worldwide standard-of-care for the treatment of people with all forms of spinal muscular atrophy*
  - Biogen reported worldwide sales of SPINRAZA of $518 million in the first quarter of 2019, a 42 percent increase compared to Q1 2018, driven primarily by increased penetration in existing markets, new country launches and continued uptake in the U.S. by children and adult patients.
  - There were more than 7,500 SMA patients from over 40 countries on SPINRAZA treatment at the end of the first quarter of 2019, including commercial patients and patients in the expanded access program and clinical trials.
  - SPINRAZA data from the ongoing NURTURE and SHINE open-label extension studies demonstrated continued durable efficacy and reinforced the safety profile of SPINRAZA in patients treated for up to 6 years, as presented by Biogen at the 2019 AAN Annual Meeting.

- *TEGSEDI – launch underway in multiple markets for the treatment of polyneuropathy of hATTR in adult patients*
  - TEGSEDI product sales were $7 million in its first full quarter on the market and $9 million since launching in Q4 2018.
  - TEGSEDI received a positive Final Evaluation Document, or FED, from the National Institute for Health and Care Excellence, or NICE, authorizing reimbursement for the treatment of patients with polyneuropathy due to hATTR amyloidosis in England.
  - Data presented at AAN from the TEGSEDI NEURO-TTR open-label extension study demonstrated long-term efficacy and safety in patients with hATTR.

- *WAYLIVRA – approved in the EU for the treatment of adults with genetically confirmed FCS at high risk for pancreatitis*
  - Akcea's preparations to launch in the EU are underway, beginning in Germany in Q3 2019.
  - Launch in additional EU countries is planned in 2020.
  - Earned a $6 million milestone payment from PTC Therapeutics for the EU approval of WAYLIVRA.

- Roche presented nine-month data from the ongoing Phase 1/2 open-label extension study of IONIS-HTT_{Rx} in patients with Huntington's disease at AAN, demonstrating continued and sustained reductions in mutant huntingtin protein with bi-monthly dosing.
  - Based on these data, Roche amended the dosing regimen in the Phase 3 study of IONIS-HTT_{Rx} in patients with Huntington's disease to replace the monthly dosing regimen with a tri-annual (every four months) dosing regimen.

- Biogen presented data from the Phase 1/2 study of tofersen in SOD1-ALS patients at AAN, demonstrating improvements in clinical measures of ALS disease progression after three months of treatment.
  - Tofersen is in a Phase 3 clinical study that could support a rapid path to patients.
  - Biogen is collaborating with regulators to further define the scope of the clinical data package required to support registration.

- We generated a $7.5 million milestone payment for advancing a new target for an unidentified neurological disease under our 2018 strategic neurology collaboration with Biogen.

- Brett P. Monia, Ph.D., our chief operating officer was appointed to our board of directors.

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;
- Valuing premiums received under our collaborations;
- Determining the proper valuation of investments in marketable securities;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Accounting for income taxes.

There have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” included in our Annual Report on Form 10-K for the year ended December 31, 2018.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2019 was $297.2 million compared to $144.4 million for the same period in 2018 and was comprised of the following (amounts in thousands):

	Three Months Ended March 31,	
	2019	**2018**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 59,711	$ 41,081
TEGSEDI product sales, net	6,754	—
Licensing and other royalty revenue	1,623	942
Total commercial revenue	68,088	42,023
R&D revenue:		
Amortization from upfront payments	35,851	28,011
Milestone payments	40,017	6,329
License fees	150,000	61,678
Other services	3,258	6,378
Total R&D revenue	229,126	102,396
Total revenue	$ 297,214	$ 144,419

In the first quarter of 2019, we significantly increased both commercial revenue and R&D revenue. Commercial revenue from SPINRAZA royalties increased over 45 percent. We also added growing TEGSEDI product sales to our commercial revenue.

Our R&D revenue substantially increased in the first quarter of 2019 due to the $150 million license fee we earned from Novartis when it licensed AKCEA-APO(a)-L_{Rx} and $35 million we earned from Roche when it enrolled the first patient in the Phase 3 study of IONIS-HTT_{Rx} in patients with Huntington’s disease.

In the second quarter of 2019, Alnylam announced it licensed our technology to Regeneron. Once the transaction closes, we expect to earn $20 million in sublicensing revenue.

Operating Expenses

Operating expenses for the three months ended March 31, 2019 were $175.7 million, and increased compared to $147.7 million for the same period in 2018. Our operating expenses increased year over year principally due to our investment in the global launch of TEGSEDI. Stock-based compensation expense increased year over year primarily due to the increase in the grant date fair value of Akcea options granted and from stock option grants made to new employees as Akcea continued to build out its organization.

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

	Three Months Ended March 31,	
	2019	2018
Ionis Core	$ 78,514	$ 83,476
Akcea Therapeutics	128,106	41,052
Elimination of intercompany activity	(76,446)	(5,259)
Subtotal	130,174	119,269
Non-cash compensation expense related to equity awards	45,505	28,451
Total operating expenses	$ 175,679	$ 147,720

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.

Cost of Products Sold

Our cost of products sold consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and certain associated period costs. We do not expect our fixed costs will increase in direct correlation to TEGSEDI product sales. We expensed a significant portion of the cost of producing TEGSEDI that Akcea is using in the commercial launch as R&D expense prior to the regulatory approval of TEGSEDI. We expect cost of products sold to increase as we deplete these inventories.

Our cost of products sold by segment were as follows (in thousands):

	Three Months Ended March 31,
	2019
Ionis Core	$ —
Akcea Therapeutics	2,326
Elimination of intercompany activity	(1,403)
Subtotal	923
Non-cash compensation expense related to equity awards	118
Total cost of products sold	$ 1,041

For the three months ended March 31, 2019, our cost of products sold was $0.9 million. We began recognizing cost of products sold in the third quarter of 2018 when TEGSEDI was approved. We previously recognized $0.3 million of costs we incurred to produce the amount of TEGSEDI we sold in the first quarter of 2019. We recognized these costs prior to the first quarter of 2019 because we incurred these costs before we obtained regulatory approval. We did not have cost of products sold in the first quarter of 2018. Akcea includes the amortization for milestone payments it made to us related to the U.S. and European approvals of TEGSEDI in its cost of products sold. Akcea is recognizing this amortization over TEGSEDI's remaining estimated patent life. We eliminate this amortization in our consolidated results. All amounts exclude non-cash compensation expense related to equity awards.

Research, Development and Patent Expenses

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

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

	Three Months Ended March 31,	
	2019	2018
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 81,982	$ 84,385
Non-cash compensation expense related to equity awards	24,435	19,682
Total research, development and patent expenses	$ 106,417	$ 104,067

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

	Three Months Ended March 31,	
	2019	2018
Ionis Core	$ 61,327	$ 63,988
Akcea Therapeutics	95,698	25,657
Elimination of intercompany activity	(75,043)	(5,259)
Subtotal	81,982	84,386
Non-cash compensation expense related to equity awards	24,435	19,682
Total research, development and patent expenses	$ 106,417	$ 104,068

For the three months ended March 31, 2019, our total research, development and patent expenses were $82.0 million compared to $84.4 million for the same period in 2018. 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. Our antisense drug discovery expenses are part of our Ionis Core business segment.

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

	Three Months Ended March 31,	
	2019	2018
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 14,632	$ 13,905
Non-cash compensation expense related to equity awards	5,493	4,376
Total antisense drug discovery expenses	$ 20,125	$ 18,281

Antisense drug discovery expenses for the three months ended March 31, 2019 were $14.6 million, and were slightly higher compared to $13.9 million for the same period in 2017, due to expenses we incurred related to advancing our early stage research programs. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth drug development expenses, including the breakdown for medicines in Phase 3 development and/or commercialization for which we have incurred significant costs (in thousands):

	Three Months Ended March 31,	
	2019	2018
WAYLIVRA	$ 1,971	$ 6,401
TEGSEDI	4,691	5,836
Other antisense development projects	22,310	20,653
Development overhead expenses	18,944	17,110
Total antisense drug development, excluding non-cash compensation expense related to equity awards	47,916	50,000
Non-cash compensation expense related to equity awards	12,234	8,858
Total antisense drug development expenses	$ 60,150	$ 58,858

Antisense drug development expenses were $47.9 million for the three months ended March 31, 2019, and decreased slightly compared to $50.0 million for the same period in 2018. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended March 31,	
	2019	2018
Ionis Core	$ 29,070	$ 30,972
Akcea Therapeutics	93,846	19,028
Elimination of intercompany activity	(75,000)	—
Subtotal	47,916	50,000
Non-cash compensation expense related to equity awards	12,234	8,858
Total antisense drug development expenses	$ 60,150	$ 58,858

In the first quarter of 2019, we received 2.8 million shares of Akcea common stock as payment for the $75 million sublicense fee Akcea owed us when Novartis licensed AKCEA-APO(a)-L_{Rx}. Akcea recognized the $75 million sublicense fee in its R&D development expenses. We eliminated this expense in our consolidated results.

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 medicines in preclinical and early stage clinical research, the fluctuations in expenses from medicine to medicine, in large part, offset one another. If we partner a medicine, 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 March 31,	
	2019	2018
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 10,154	$ 12,309
Non-cash compensation expense related to equity awards	2,057	2,402
Total manufacturing and operations expenses	$ 12,211	$ 14,711

Manufacturing and operations expenses were $10.2 million for the three months ended March 31, 2019 and decreased compared to $12.3 million for the same period in 2018. Manufacturing and operations expenses decreased primarily related to manufacturing costs we expensed for TEGSEDI in the first quarter of 2018 that did not recur in the first quarter of 2019 because upon approval in mid-2018, we now capitalize all TEGSEDI manufacturing costs into inventory and recognize these expenses into cost of products sold as we sell TEGSEDI. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended March 31,	
	2019	2018
Ionis Core	$ 8,799	$ 11,642
Akcea Therapeutics	1,355	5,896
Elimination of intercompany activity	—	(5,229)
Subtotal	10,154	12,309
Non-cash compensation expense related to equity awards	2,057	2,402
Total manufacturing and operations expenses	$ 12,211	$ 14,711

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 March 31,	
	2019	2018
Personnel costs	$ 3,910	$ 3,103
Occupancy	2,177	1,759
Patent expenses	523	701
Depreciation and amortization	121	101
Insurance	411	470
Other	2,138	2,038
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	9,280	8,172
Non-cash compensation expense related to equity awards	4,651	4,046
Total R&D support expenses	$ 13,931	$ 12,218

R&D support expenses for the three months ended March 31, 2019 were $9.3 million, and increased slightly compared to $8.2 million for the same period in 2018. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended March 31,	
	2019	2018
Ionis Core	$ 8,826	$ 7,470
Akcea Therapeutics	497	732
Elimination of intercompany activity	(43)	(30)
Subtotal	9,280	8,172
Non-cash compensation expense related to equity awards	4,651	4,046
Total R&D support expenses	$ 13,931	$ 12,218

Selling, General and Administrative Expenses

Selling, general and administrative expenses include personnel and outside costs associated with the pre-commercialization and commercialization activities for our medicines and costs to support our company, our employees and our stockholders including, 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 fees we owe under our in-licensing agreements related to SPINRAZA.

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

	Three Months Ended March 31,	
	2019	2018
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 47,269	$ 34,884
Non-cash compensation expense related to equity awards	20,952	8,769
Total selling, general and administrative expenses	$ 68,221	$ 43,653

Selling, general and administrative expenses were $47.3 million for the three months ended March 31, 2019, and increased compared to $34.9 million for the same period in 2018. The increase in SG&A expenses was principally due to the cost of commercializing TEGSEDI. 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 March 31,	
	2019	2018
Ionis Core	$ 17,187	$ 19,488
Akcea Therapeutics	30,082	15,396
Subtotal	47,269	34,884
Non-cash compensation expense related to equity awards	20,952	8,769
Total selling, general and administrative expenses	$ 68,221	$ 43,653

Akcea Therapeutics, Inc.

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

	Three Months Ended March 31,	
	2019	2018
Cost of products sold	$ 2,326	$ —
Development and patent expenses	95,698	25,656
Selling, general and administrative expenses	30,082	15,396
Profit/loss share for TEGSEDI commercialization activities	(9,056)	—
Total operating expenses, excluding non-cash compensation expense related to equity awards	119,050	41,052
Non-cash compensation expense related to equity awards	18,560	6,383
Total Akcea Therapeutics operating expenses	$ 137,610	$ 47,435

Operating expenses for Akcea were $119.1 million for the three months ended March 31, 2019, and increased compared to $41.1 million for the same period in 2018.

In the third quarter of 2018, Akcea began recognizing cost of products sold expenses after the approval of TEGSEDI.

Akcea's development and patent expenses increased for the three months ended March 31, 2019, compared to the same period in 2018 as a result of the one-time $75 million sublicense fee it paid to Ionis in Akcea common stock for Ionis' portion of the license fee Akcea received from Novartis in the first quarter of 2019.

Akcea's SG&A expenses increased in the three months ended March 31, 2019 compared to the same period in 2018, primarily because Akcea was continuing to build its commercial infrastructure and advance commercialization activities necessary to successfully launch TEGSEDI and WAYLIVRA. For each period presented, we allocated a portion of Ionis' SG&A expenses to Akcea for work we performed on Akcea's behalf. We include these allocated expenses in Akcea's SG&A expenses in the table above. All amounts exclude non-cash compensation expense related to equity awards.

In the first quarter of 2019, we began sharing profits and losses for TEGSEDI with Akcea under our TTR licensing agreement. As Akcea is the principal for all commercial activities related to the TTR License Agreement, Akcea records all activities related to TEGSEDI on a gross basis in its statement of operations based on the nature of the activity, including revenues, cost of products sold and sales and marketing expenses. Ionis' share of the net profit/loss from commercializing TEGSEDI is separately presented on Akcea's statement of operations on the line titled "Profit/loss share for TEGSEDI commercialization activities". This represents the amount Ionis owes Akcea under the licensing agreement for its share of the net profit/loss of TEGSEDI commercialization activities during the period. For the three months ended March 31, 2019, profit/loss share for TEGSEDI commercialization activities was $9.1 million. We eliminate this amount in our consolidated results.

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

Investment Income

Investment income for the three months ended March 31, 2019 was $12.1 million compared to $3.6 million for 2018. The increase in investment income was primarily due to a higher average cash balance and an improvement in the market conditions during the three months ended March 31, 2019 compared to the same period in 2018.

Interest Expense

Interest expense for the three months ended March 31, 2019 was $11.6 million and increased slightly compared to $10.9 million for the same period in 2018.

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

	Three Months Ended March 31,	
	2019	**2018**
Convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 9,200	$ 8,524
Interest expense payable in cash	1,714	1,714
Interest on mortgage for primary R&D and manufacturing facilities	582	594
Other	103	106
Total interest expense	$ 11,599	$ 10,938

Income Tax Expense

We recorded income tax expense of $31 million for the three months ended March 31, 2019, compared to $15,000 for the same period in 2018. The increase in our income tax expense was primarily due to our expectation that we will generate U.S. federal and state taxable income in 2019. Our 2019 income tax expense has two components. The first component relates to federal income taxes. We expect to utilize our deferred tax assets to offset our U.S. federal taxable income. We are recording non-cash income tax expense as we utilize our federal deferred tax assets. The other component of our income tax expense relates to the estimated cash taxes we will pay for our state income taxes. Although we are recording the expense for our state income taxes in 2019, we will not have to make the majority of the payment for this liability until the first quarter of 2020.

Net Income (Loss)

We reported net income of $90.9 million for the three months ended March 31, 2019, compared to a net loss of $10.8 million for the same period in 2018. Our net income was primarily due to increased revenue year-over-year.

Net (Income) Loss Attributable to Noncontrolling Interest in Akcea Therapeutics, Inc.

At March 31, 2019, we owned approximately 76 percent of Akcea. The shares of Akcea third parties own represent an interest in Akcea's equity that we do not control. However, because we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line called "Net loss attributable to noncontrolling interest in Akcea" on our statement of operations. Our noncontrolling interest in Akcea on our statement of operations for the three months ended March 31, 2019, was income of $6.4 million, compared to a loss of $9.4 million for same period in 2018.

Net Income (Loss) Attributable to Ionis Pharmaceuticals, Inc. Common Stockholders and Net Income (Loss) per Share

We had net income attributable to our common stockholders' of $84.4 million for the three months ended March 31, 2019, compared to a net loss of $1.4 million for the same period in 2018. Basic and diluted net income per share for the three months ended March 31, 2019 was $0.63 and $0.62, respectively. Our basic and diluted net loss per share for the three months ended March 31, 2018 were both $0.01.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. Beginning in December 2016 we added commercial revenue from SPINRAZA royalties and in the third quarter of 2018 we added product sales from TEGSEDI. From our inception through March 31, 2019, we have earned approximately $3.5 billion in revenue. We also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through March 31, 2019, we have raised net proceeds of approximately $1.8 billion from the sale of our equity securities, not including the $182.4 million Akcea received in net proceeds from its IPO in July 2017. Additionally, we have borrowed approximately $1.4 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

At March 31, 2019, we had cash, cash equivalents and short-term investments of $2.3 billion and stockholders' equity of $1.4 billion. In comparison, we had cash, cash equivalents and short-term investments of $2.1 billion and stockholders' equity of $1.2 billion at December 31, 2018. Our cash, cash equivalents and short-term investments increased in the first quarter of 2019 primarily from payments we received from Novartis and Roche.

At March 31, 2019, we had consolidated working capital of $2.1 billion compared to $1.9 billion at December 31, 2018. As of March 31, 2019, our debt and other obligations totaled $776.1 million compared to $763.9 million at December 31, 2018. The increase in our debt and other obligations is from the operating lease liability we added to our balance sheet when we adopted the new accounting guidance for leases on January 1, 2019.

The following table summarizes our contractual obligations as of March 31, 2019. 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)	$ 706.0	$ 6.9	$ 699.1	$ —	$ —
Building mortgage payments	80.2	2.4	4.8	6.4	66.6
Financing arrangements (principal and interest payable)	12.7	12.7	—	—	—
Other obligations (principal and interest payable)	1.0	0.1	0.1	0.1	0.7
Operating leases	25.3	3.2	5.8	5.1	11.2
Total	$ 825.2	$ 25.3	$ 709.8	$ 11.6	$ 78.5

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility mortgages, facility leases, equipment financing arrangements and other obligations. Due to the uncertainty with respect to the timing of future cash flows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded our gross unrecognized tax benefits from our contractual obligations table above.

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 March 31, 2019, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At March 31, 2019, we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share and interest rate 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. 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 March 31, 2019, 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 and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million. We purchased our manufacturing facility in July 2017 for $14.0 million. We financed the purchase of our primary R&D facility and manufacturing facility, with mortgage debt of $51.3 million and $9.1 million, respectively. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages we are only required to make interest payments. Both mortgages mature in August 2027.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2019 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

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, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

We are also exposed to changes in foreign currency exchange rates as we have foreign subsidiaries with functional currencies other than the U.S. dollar. We translate our subsidiaries' functional currencies into our reporting currency, the U.S. dollar. As a result, our financial position, results of operations and cash flows can be affected by market fluctuations in the foreign currencies to U.S. dollar exchange rate, which are difficult to predict. A hypothetical 10 percent change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements. Our business strategy incorporates potentially significant international expansion, particularly related to TEGSEDI and WAYLIVRA, therefore we expect that the impact of foreign currency exchange rate fluctuations may become more substantial in the future.

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 March 31, 2019. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2019.

We also performed an evaluation of any changes in our internal controls over financial reporting that occurred during our last fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls 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 changes in our internal controls over financial reporting that occurred during our latest fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Not applicable.

ITEM 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. 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, 2018.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

If the market does not accept our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, we are not likely to generate revenues or become consistently profitable.

Even if our medicines are authorized for marketing, including SPINRAZA, TEGSEDI and WAYLIVRA, our success will depend upon the medical community, patients and third-party payors accepting our medicines as medically useful, cost-effective and safe. Even when the FDA or foreign regulatory authorities authorize our or our partners' medicines for commercialization, doctors may not prescribe our medicines to treat patients. We and our partners may not successfully commercialize additional medicines.

Additionally, in many of the markets where we may sell our medicines in the future, if we cannot agree with the government regarding the price we can charge for our medicines, then we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third-party payors could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, unaffordable.

The degree of market acceptance for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, 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 medicines and their potential advantages over competing products;
- cost and effectiveness of our medicines compared to other available therapies;
- patient convenience of the dosing regimen for our medicines; and
- reimbursement policies of government and third-party payors.

Based on the profile of our medicines, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any medicines that we may develop.

For example, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is ONPATTRO (patisiran), marketed by Alnylam Pharmaceuticals, Inc. Although ONPATTRO requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. Additionally, in the clinical studies with WAYLIVRA, declines in platelet counts were observed in many patients and some patients discontinued the studies because of platelet declines. The product label for WAYLIVRA requires periodic blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these medicines. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we and Akcea can better maintain patients on TEGSEDI and WAYLIVRA through patient-centric commercial approaches where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on TEGSEDI or WAYLIVRA, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If we or our partners fail to compete effectively, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, 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 medicines that are:

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

These competitive developments could make our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other medicines 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 medicines and, as a result, could delay or otherwise negatively affect the commercialization of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

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, in obtaining FDA and other regulatory authorizations of such products and in commercializing 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 medicines, and we will primarily 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, Zolgensma (AVXS-101), Risdiplam (RG7916), reldesemtiv and firdapse could compete with SPINRAZA, and ONPATTRO (approved in the U.S. and Europe for a similar indication as TEGSEDI), Tafamadis, AG10, CRX-1008 and vutrisiran could compete with TEGSEDI. Also, metreleptin and gemcabene could compete with WAYLIVRA, while laquinimod, OMS823, selistat, VX15, WVE-120101 and WVE-120102 could compete with IONIS-HTT_{Rx}. Furthermore, arimoclomol could potentially compete with tofersen.

Following approval, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA could be subject to regulatory limitations. *

Following approval of a medicine, 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, TEGSEDI and WAYLIVRA.

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:

- In the U.S., TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis;
- TEGSEDI requires periodic blood and urine monitoring; and
- in the U.S. TEGSEDI is available only through a Risk Evaluation and Mitigation Strategy, or REMS, program.

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. For example, in connection with the conditional marketing approval for WAYLIVRA in the EU, we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. 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, TEGSEDI and WAYLIVRA.

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 or spend additional funding, and SPINRAZA's commercialization may be harmed or delayed.

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

If Akcea cannot optimize and maintain effective marketing and sales capabilities or enter into agreements with third parties to market and sell TEGSEDI and WAYLIVRA, we may not generate significant product revenue from TEGSEDI or WAYLIVRA.*

To successfully commercialize TEGSEDI Akcea must successfully manage its marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. Akcea may not be successful in doing so. To commercialize TEGSEDI and WAYLIVRA in the initial indications Akcea is pursuing, Akcea will need to optimize and maintain a specialty sales force in each global region it expects to market TEGSEDI and WAYLIVRA, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine blood and urine monitoring and a medical affairs team. Akcea may seek to further penetrate markets by expanding its sales force or through strategic partnerships with other pharmaceutical or biotechnology companies or third-party sales organizations.

Even though certain members of Akcea's management team and other employees have experience commercializing drug products, Akcea has no prior experience marketing, selling or distributing drug products, and there are significant risks involved in building and managing a commercial infrastructure. It will be expensive and time consuming for Akcea to maintain its own sales force and related compliance protocols to market TEGSEDI. Akcea may never successfully optimize or manage this capability and any failure could preclude the successful commercialization of TEGSEDI. Akcea and its partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel.

Akcea incurred expenses prior to the launch of TEGSEDI and WAYLIVRA to integrate and manage the associated marketing and sales infrastructure. If regulatory requirements or other factors cause the commercial launch of TEGSEDI or WAYLIVRA to be less successful than expected, Akcea will have incurred expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI or WAYLIVRA. Akcea's sales force and marketing teams may not successfully commercialize TEGSEDI or WAYLIVRA.

To the extent we and Akcea decide to rely on third parties to commercialize TEGSEDI or WAYLIVRA in a particular geographic market, such as the collaboration Akcea has with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America, we may receive less revenue than if Akcea commercialized TEGSEDI or WAYLIVRA by itself. Further we would have less control over the sales efforts of any other third parties involved in commercializing TEGSEDI or WAYLIVRA.

If Akcea cannot effectively build and manage its distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable third party to perform such functions, the commercial launch and sales of TEGSEDI may be delayed, less successful or precluded. Such events may result in decreased sales and lower revenue, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

If government or other third-party payors fail to provide adequate coverage and payment rates for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, 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 people in the U.S. who would fit within our target patient populations for our medicines 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 medicines 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 U.S., 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 U.S. and in international markets. For example, in the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several 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 medicines may not be available or adequate in either the U.S. 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 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 maintain commercial success, which will harm our ability to generate revenue.

If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for SPINRAZA, TEGSEDI and WAYLIVRA, we or our partners cannot sell them in the applicable markets.*

We cannot guarantee that any of our medicines will be considered safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA, TEGSEDI and WAYLIVRA 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 medicines 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 medicines. It is possible that regulatory agencies will not approve our medicines for marketing or additional marketing authorizations for SPINRAZA, TEGSEDI or WAYLIVRA. 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 medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, the agency will not approve the specific medicine or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the medicine. For example, Akcea received a CRL from the FDA and a preliminary notice of noncompliance withdrawal letter from Health Canada for WAYLIVRA. As result, Akcea may need to submit additional data to the FDA and Health Canada or conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays.

Failure to receive marketing authorization for our medicines, or failure to receive additional marketing authorizations for SPINRAZA, TEGSEDI or WAYLIVRA, or delays in these authorizations could prevent or delay commercial introduction of the medicine, 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 medicines 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 medicines are a relatively new approach to therapeutics. If we cannot demonstrate that our medicines 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 medicines that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our medicines, including the study of WAYLIVRA in patients with FPL, the study of IONIS-HTT_{Rx} in patients with Huntington's disease and the study of tofersen in adults with SOD1-ALS. If any of our medicines in clinical studies, including WAYLIVRA, IONIS-HTT_{Rx} and tofersen do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

Even if our medicines are successful in preclinical and human clinical studies, the medicines 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 medicines in development, may not predict the results of subsequent clinical studies, including the Phase 3 study of WAYLIVRA in patients with FPL, the study of IONIS-HTT_{Rx} in patients with Huntington's disease and the study of tofersen in adults with SOD1-ALS. 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 medicine 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;
- people 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 medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

In addition, our current medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine 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 medicines 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 medicines: 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 WAYLIVRA in patients with FPL, an ongoing open-label extension study of WAYLIVRA in patients with FCS, an ongoing open-label extension study of TEGSEDI and expanded access programs for each medicine. Adverse events or results from these studies could negatively impact our current or planned marketing approval applications for WAYLIVRA in patients with FCS or the commercial opportunity for each product.

Any failure or delay in the clinical studies, including the Phase 3 study for WAYLIVRA in patients with FPL, the study of IONIS-HTT_{Rx} in patients with Huntington's disease and the study of tofersen in adults with SOD1-ALS, could reduce the commercial potential or viability of our medicines.

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

To successfully commercialize any of our medicines, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. We and Akcea will rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAYLIVRA. 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 medicines, called oligonucleotides, on a commercial scale for the systemic administration of a medicine. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our medicines, 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 medicines 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 medicines, including authorizations for SPINRAZA, TEGSEDI and WAYLIVRA, or result in enforcement action after authorization that could limit the commercial success of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

We depend on third parties to conduct our clinical studies for our medicines 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 medicines 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 medicines, including TEGSEDI and WAYLIVRA. 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 medicines or additional authorizations for SPINRAZA, TEGSEDI and WAYLIVRA.

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2019, we had an accumulated deficit of approximately $0.9 billion and stockholders' equity of approximately $1.4 billion. Most of our historical 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 income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. If we do not continue to earn substantial revenue, we may incur additional operating losses in the future. We may not successfully develop any additional products or achieve or sustain future profitability.

Our ability to use our net operating loss carryovers and certain other tax attributes may be limited.

Under the Internal Revenue Code of 1986, as amended, or the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under that provision, we can carryforward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits.

Under the Tax Cut and Jobs Act of 2017, or the Tax Act, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the newly enacted federal tax law.

In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percent change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations.

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 medicines. 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 medicines could suffer.

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

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, as part of a reprioritization of its pipeline and strategic review of its rare disease business, GSK declined its option on TEGSEDI and IONIS-FB-L_{Rx}.

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 and commercial 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 medicines.

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, Janssen, Novartis and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we first anticipated.

For example, a collaborator such as AstraZeneca, Bayer, Biogen, GSK, Janssen, 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 medicine 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 medicines than it does for its own medicines.

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 medicines, including SPINRAZA.

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 medicine will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, 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, TEGSEDI and WAYLIVRA, 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 U.S. 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 parties 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 U.S. 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.

If a third party claims that our medicines 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 U.S. 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 medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of March 31, 2019, we had cash, cash equivalents and short-term investments equal to approximately $2.3 billion. If we do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license our medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- successful commercialization for SPINRAZA, TEGSEDI and WAYLIVRA;
- additional marketing approvals for WAYLIVRA and TEGSEDI;
- the profile and launch timing of our medicines, including TEGSEDI and WAYLIVRA;
- 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; and
- competing technological and market developments, including the introduction by others of new therapies that address our markets.

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 medicines.

If our planned management transition is not successful our business could suffer.

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, plans to transition from Chief Executive Officer to Executive Chairman of our Board of Directors. As Executive Chairman, Dr. Crooke will continue to be responsible for the activities of the board and will remain active in the company, providing strategic advice and continuing to participate in the scientific activities. Our board has selected Dr. Monia, who has been our Chief Operating Officer for the last year and a member of our team since our founding nearly 30 years ago, to serve as our Chief Executive Officer starting in January 2020. If this transition is not successful, our business could suffer.

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2019, the market price of our common stock ranged from $39.07 to $81.59 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 medicines 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, TEGSEDI and WAYLIVRA. 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, product 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 most of 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 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 medicines.

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

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

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

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

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

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 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.

Changes in tax laws, regulations and treaties could affect our future taxable income.

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us. For example, the Tax Act represented a substantial change to tax laws in the U.S. and although it did not have a material impact on our financial statements any future changes or interpretation to this or any other tax laws could have a material effect on our business.

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and sales taxes in the U.S. and foreign income taxes, withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value-added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.

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.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

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

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Amended and Restated Strategic Advisory Services Agreement by and between the Registrant and B. Lynne Parshall, dated March 22, 2019. – Filed as an exhibit to the Registrant's Current Report on Form 8-K filed March 26, 2019 and incorporated herein by reference.
10.2	Registrant's Amended and Restated 2000 Employee Stock Purchase Plan. – Filed as an exhibit to the Registrant's Current Report on Form 8-K filed March 26, 2019 and incorporated herein by reference.
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 March 31, 2019, 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 stockholders' equity, (v) condensed consolidated statements of cash flows and (vi) 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)	May 9, 2019
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 9, 2019

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

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

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 9, 2019

/s/ STANLEY T. CROOKE

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

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

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

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 9, 2019

/s/ ELIZABETH L. HOUGEN
Elizabeth L. Hougen
Chief Financial Officer

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Ionis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2019, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 9, 2019

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

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