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 September 30, 2018

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
Common Stock, $.001 Par Value	The Nasdaq Stock Market, LLC

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 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 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 ☐ (Do not check if a smaller reporting company)	Smaller reporting company ☐
	Emerging growth company ☐

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

The number of shares of voting common stock outstanding as of October 31, 2018 was 137,571,510.

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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)
(Unaudited)

	September 30, 2018	December 31, 2017 (as revised*)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 479,891	$ 129,630
Short-term investments	1,479,098	893,085
Contracts receivable	14,732	62,955
Inventories	8,378	9,982
Other current assets	97,125	73,082
Total current assets	2,079,224	1,168,734
Property, plant and equipment, net	132,003	121,907
Patents, net	24,027	22,004
Deposits and other assets	12,659	10,129
Total assets	$ 2,247,913	$ 1,322,774
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 13,576	$ 24,886
Accrued compensation	24,259	25,151
Accrued liabilities	50,786	66,618
Current portion of long-term obligations	14,472	1,621
Current portion of deferred contract revenue	157,145	125,336
Total current liabilities	260,238	243,612
Long-term deferred contract revenue	523,384	108,026
1 percent convertible senior notes	559,184	533,111
Long-term obligations, less current portion	5,138	12,974
Long-term mortgage debt	59,825	59,771
Total liabilities	1,407,769	957,494
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 137,506,203 and 124,976,373 shares issued and outstanding at September 30, 2018 and December 31, 2017, respectively	138	125
Additional paid-in capital	2,030,313	1,553,681
Accumulated other comprehensive loss	(32,532)	(31,759)
Accumulated deficit	(1,287,369)	(1,241,034)
Total Ionis stockholders' equity	710,550	281,013
Noncontrolling interest in Akcea Therapeutics, Inc.	129,594	84,267
Total stockholders' equity	840,144	365,280
Total liabilities and stockholders' equity	$ 2,247,913	$ 1,322,774

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017 (as revised*)	2018	2017 (as revised*)
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 70,010	$ 32,890	$ 167,743	$ 60,467
Licensing and other royalty revenue	12,746	1,727	14,232	5,639
Total commercial revenue	82,756	34,617	181,975	66,106
Research and development revenue under collaborative agreements	62,639	83,697	225,584	280,281
Total revenue	145,395	118,314	407,559	346,387
Expenses:				
Research, development and patent	95,255	80,214	301,153	246,358
Selling, general and administrative	68,712	26,788	178,563	62,782
Total operating expenses	163,967	107,002	479,716	309,140
Income (loss) from operations	(18,572)	11,312	(72,157)	37,247
Other income (expense):				
Investment income	9,963	2,811	18,711	7,504
Interest expense	(11,282)	(10,825)	(33,332)	(33,966)
Loss on extinguishment of financing liability for leased facility	—	(7,689)	—	(7,689)
Other income (expenses)	(22)	(2,141)	(145)	(3,528)
Loss before income tax expense	(19,913)	(6,532)	(86,923)	(432)
Income tax expense	(452)	(961)	(824)	(1,184)
Net loss	(20,365)	(7,493)	(87,747)	(1,616)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	15,806	4,882	41,412	4,882
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (4,559)	$ (2,611)	$ (46,335)	$ 3,266
Basic net income (loss) per share	$ (0.03)	$ (0.02)	$ (0.33)	$ 0.13
Shares used in computing basic net income (loss) per share	143,314	124,370	132,518	123,746
Diluted net income (loss) per share	$ (0.03)	$ (0.02)	$ (0.33)	$ 0.13
Shares used in computing diluted net income (loss) per share	143,314	124,370	132,518	125,858

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017 (as revised*)	2018	2017 (as revised*)
Net loss	$ (20,365)	$ (7,493)	$ (87,747)	$ (1,616)
Unrealized gains (losses) on debt securities, net of tax	133	215	(834)	610
Reclassification adjustment for realized gains included in net income (loss)	—	—	—	(374)
Currency translation adjustment	(28)	(42)	61	(77)
Comprehensive loss	(20,260)	(7,320)	(88,520)	(1,457)
Comprehensive loss attributable to noncontrolling interests	15,797	3,952	41,455	3,952
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. stockholders	$ (4,463)	$ (3,368)	$ (47,065)	$ 2,495

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Nine Months Ended September 30,	
	2018	**2017**
Operating activities:		**(as revised*)**
Net loss	$ (87,747)	$ (1,616)
Adjustments to reconcile net loss to net cash provided by operating activities:		
Depreciation	7,650	6,138
Amortization of patents	1,356	1,216
Amortization of premium on investments, net	791	5,227
Amortization of debt issuance costs	1,343	1,202
Amortization of convertible senior notes discount	24,781	22,963
Amortization of long-term financing liability for leased facility	—	3,659
Stock-based compensation expense	97,210	63,642
Gain on investment in Regulus Therapeutics, Inc.	—	(374)
Loss on extinguishment of financing liability for leased facility	—	7,689
Non-cash losses related to patents, licensing and property, plant and equipment	482	(403)
Changes in operating assets and liabilities:		
Contracts receivable	48,223	65,119
Inventories	1,604	(962)
Other current and long-term assets	(26,573)	(34,866)
Accounts payable	(13,606)	(1,707)
Accrued compensation	(892)	(8,999)
Accrued liabilities and deferred rent	(14,392)	(5,251)
Deferred contract revenue	447,168	31,071
Net cash provided by operating activities	487,398	153,748
Investing activities:		
Purchases of short-term investments	(1,156,335)	(589,655)
Proceeds from the sale of short-term investments	568,517	313,860
Purchases of property, plant and equipment	(12,221)	(26,502)
Acquisition of licenses and other assets, net	(3,317)	(4,289)
Proceeds from the sale of Regulus Therapeutics stock	—	2,507
Net cash used in investing activities	(603,356)	(304,079)
Financing activities:		
Proceeds from equity awards	18,254	17,672
Proceeds from the issuance of common stock from Akcea Therapeutics, Inc.'s initial public offering, net of underwriters' discount	—	110,438
Proceeds from building mortgage debt, net of issuance costs	—	59,750
Proceeds from the issuance of common stock to Novartis	—	71,737
Proceeds from the issuance of common stock to Biogen	447,965	—
Offering costs paid	—	(1,057)
Proceeds from the sale of Akcea Therapeutics, Inc. common stock to Novartis in a private placement	—	50,000
Payment to settle financing liability for leased facility	—	(80,133)
Principal payments on debt and capital lease obligations	—	(3,577)
Net cash provided by financing activities	466,219	224,830
Net increase in cash and cash equivalents	350,261	74,499
Cash and cash equivalents at beginning of period	129,630	84,685
Cash and cash equivalents at end of period	$ 479,891	$ 159,184
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,434	$ 4,020
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 2,296	$ 3,475
Purchases of property, plant and equipment included in long-term obligations	$ 3,596	$ —
Unpaid deferred offering costs	$ —	$ 638

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and nine months ended September 30, 2018 and 2017 on the same basis as the audited financial statements for the year ended December 31, 2017. 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, 2017 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, which we formed in December 2014. Prior to Akcea's initial public offering, or 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 and third 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. We reflected the increase in our ownership in these financial statements. In October 2018, we received an additional 1.7 million shares of Akcea's stock when TEGSEDI received marketing authorization in the U.S., increasing our ownership to approximately 76 percent. 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

Adoption of New Revenue Recognition Accounting Standard (Topic 606)

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. This guidance supersedes the revenue recognition requirements we previously followed in Accounting Standards Codification, or ASC, Topic 605, *Revenue Recognition*, or Topic 605, and created a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. Under Topic 606, an entity will recognize revenue when it transfers control of promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. Further, an entity will recognize revenue upon satisfying the performance obligation(s) under the related contract. We adopted Topic 606 on January 1, 2018 under the full retrospective approach, which required us to revise our prior period revenue. Under Topic 606, we were required to review all of our ongoing collaboration agreements in which we recognized revenue after January 1, 2016. We were required to assess what our revenue would have been for the period from January 1, 2016 to December 31, 2017 under Topic 606. As a result of this analysis, we determined that the cumulative revenue we would have recognized under Topic 606 decreased by $53.6 million. We recorded this amount as a cumulative adjustment to our accumulated deficit as of December 31, 2017. We have labeled our prior period financial statements "as revised" to indicate the change required under the accounting rules.

The following tables summarize the adjustments we were required to make to amounts we originally reported in 2017 to adopt Topic 606 (in thousands, except per share amounts):

Condensed Consolidated Balance Sheet

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred revenue	$ 72,708	$ 35,318	$ 108,026
Accumulated deficit	$ (1,187,398)	$ (53,636)	$ (1,241,034)
Noncontrolling interest in Akcea Therapeutics, Inc.	$ 87,847	$ (3,580)	$ 84,267
Total stockholders' equity	$ 418,719	$ (53,439)	$ 365,280

Condensed Consolidated Statement of Operations

	Three Months Ended September 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 32,890	$ —	$ 32,890
Licensing and other royalty revenue	879	848	1,727
Total commercial revenue	33,769	848	34,617
Research and development revenue under collaborative agreements	87,142	(3,445)	83,697
Total revenue	$ 120,911	$ (2,597)	$ 118,314
Income (loss) from operations	$ 13,909	$ (2,597)	$ 11,312
Net income (loss)	$ (4,896)	$ (2,597)	$ (7,493)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (976)	$ (1,635)	$ (2,611)
Net income (loss) per share, basic and diluted	$ 0.00	$ (0.02)	$ (0.02)

	Nine Months Ended September 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 60,467	$ —	$ 60,467
Licensing and other royalty revenue	4,983	656	5,639
Total commercial revenue	65,450	656	66,106
Research and development revenue under collaborative agreements	269,917	10,364	280,281
Total revenue	$ 335,367	$ 11,020	$ 346,387
Income from operations	$ 26,227	$ 11,020	$ 37,247
Net income (loss)	$ (12,636)	$ 11,020	$ (1,616)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (8,716)	$ 11,982	$ 3,266
Net income (loss) per share, basic	$ 0.02	$ 0.11	$ 0.13
Net income (loss) per share, diluted	$ 0.02	$ 0.11	$ 0.13

Condensed Consolidated Statement of Cash Flows

	Nine Months Ended September 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (12,636)	$ 11,020	$ (1,616)
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Deferred contract revenue	$ 42,091	$ (11,020)	$ 31,071
Cash and cash equivalents at beginning of period	$ 84,685	$ —	$ 84,685
Cash and cash equivalents at end of period	$ 159,184	$ —	$ 159,184

Under Topic 606, compared to Topic 605, our revenue decreased $2.6 million for the three months ended September 30, 2017, and increased $11.0 million for the nine months ended September 30, 2017. The change in our revenue was primarily due to:

- A change in how we recognize milestone payments: Topic 606 requires us to amortize more of the milestone payments we achieve, rather than recognizing the milestone payments in full in the period in which we achieved the milestone event as we did under Topic 605. This change resulted in an increase of $0.5 million and $27.9 million for the three and nine months ended September 30, 2017, respectively.

- A change in how we calculate revenue for payments we are recognizing into revenue over time: Under Topic 605, we amortized payments into revenue evenly over the period of our obligations. When we made a change to our estimated completion period, we recognized that change on a prospective basis. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. Each period, we review our "inputs" such as our level of effort expended, including the time we estimate it will take us to complete the activities, or costs incurred relative to the total expected inputs to satisfy the performance obligation. For certain collaborations, such as Bayer, Janssen and Novartis, the input method resulted in a change to the revenue we had previously recognized using a straight-line amortization method. This change resulted in a decrease of $4.0 million and $17.5 million for the three and nine months ended September 30, 2017, respectively.

Our updated revenue recognition policy reflecting Topic 606 is as follows:

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 condensed 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 expect to add product sales from TEGSEDI to our commercial revenue in the fourth quarter of 2018 as a result of TEGSEDI's approval in the U.S., EU and Canada. We will also recognize as commercial revenue future sales milestone payments and royalties we earn under our partnerships.

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.

Our collaboration agreements are detailed in Note 6, *Collaborative Arrangements and Licensing Agreements*. 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 when we enter into a collaboration agreement in which we provide our partner with an option to license a drug 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 drug 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 drug 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. 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.

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. Our accounting for SPINRAZA royalties did not change as a result of adopting Topic 606.

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 new SMA collaboration with Biogen, we received a $25 million upfront payment in December 2017. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $25 million upfront payment using an input method over the estimated period of time we are providing R&D services. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion. Under Topic 605, we amortized upfront payments evenly over the period of our obligation.

Milestone Payments

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 drug is approved by the applicable regulator. 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. Under Topic 606, we allocated this payment to our R&D services performance obligation. We are recognizing revenue from this milestone payment over our estimated period of performance. Under Topic 605, this milestone payment was recognized in full in the third quarter of 2017, which was the period in which we achieved the milestone event.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event. For example, in the third quarter of 2018, we earned a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of IONIS-AZ4-2.5-L$_{Rx}$. Our revenue recognition of milestone payments we earn based on our partners' activities did not change as a result of adopting Topic 606.

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 third quarter of 2018, we earned a $12 million license fee when our majority-owned affiliate, Akcea, entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Our recognition of license fees did not change as a result of adopting Topic 606.

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 standalone 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 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our accounting treatment for our Bayer collaboration. Our allocation of the consideration we received for the Bayer amendment did not change as a result of adopting Topic 606. However, the method in which we are recognizing revenue related to our R&D services performance obligation did change. We are amortizing revenue related to our R&D services performance obligation using the input method under Topic 606.

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. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the 2018 strategic neurology collaboration with Biogen.

Contracts Receivable

Our contracts receivable balance represents the amounts we have billed our partners for goods we have delivered or services we have performed that are due to us unconditionally. When we bill our partners 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. Our contracts receivable balance as of December 31, 2017 did not change when we adopted Topic 606.

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. Our unbilled SPINRAZA royalties as of December 31, 2017 did not change when we adopted Topic 606.

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 and nine months ended September 30, 2018, we recognized $37.2 million and $80.4 million of revenue from amounts that were in our beginning deferred revenue balances for those periods, respectively. During the three and nine months ended September 30, 2017, we recognized $31.6 million and $84.4 million of revenue from amounts that were in our beginning deferred revenue balances for those periods, respectively. Refer to our revenue recognition policy above detailing how we recognize revenue for further discussion.

The following table summarizes the adjustments we were required to make to our deferred revenue amounts to adopt Topic 606 (in thousands):

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred revenue	72,708	35,318	108,026
Total deferred revenue	$ 179,173	$ 54,189	$ 233,362

Our deferred revenue balance increased $54.2 million at December 31, 2017 under Topic 606, compared to Topic 605. The increase was primarily related to the change in the accounting for certain milestone payments and the way in which we amortize payments. Under Topic 605, we previously recognized the majority of the milestone payments we earned in the period we achieved the milestone event, which did not impact our deferred revenue balance. Under Topic 606 we are now amortizing more milestone payments over the period of our performance obligation, which adds to our deferred revenue balance. Additionally, under Topic 605 we amortized payments evenly over the period of our obligation. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. The increase in deferred revenue relates to agreements with the following partners:

- $24.2 million from Biogen;
- $15.9 million from AstraZeneca;
- $11.8 from Novartis; and
- $2.3 million from other partners.

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 and third 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. We reflected this increase in our ownership percentage in these financial statements as an adjustment to noncontrolling interest. In October 2018, we received an additional 1.7 million shares of Akcea's stock when TEGSEDI received marketing authorization in the U.S., increasing our ownership to approximately 76 percent. 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 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 September 30, 2018, we held an equity investment in one publicly held company, 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.

In January 2018, we adopted the amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires us to measure and record our equity investments at fair value. Additionally, the amended accounting guidance requires us to recognize the changes in fair value in our consolidated statement of operations, instead of through accumulated other comprehensive income. Prior to 2018, we accounted for our equity investments in privately held companies under the cost method of accounting. Under the amended guidance we account for our equity investments in privately held companies at their 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. Our adoption of this guidance did not have an impact on our results.

Inventory valuation

We reflect our inventory on our 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 drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs as R&D expenses when we begin to manufacture API for a particular drug if the drug has not been approved for marketing by a regulatory agency.

We obtained the first regulatory approval for TEGSEDI in July 2018. At September 30, 2018 and December 31, 2017, 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 drugs and historical write-offs. We did not record any inventory write-offs for the nine months ended September 30, 2018 and 2017.

Research, development and patent expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs and other expenses that are directly related to our research and development operations. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our condensed consolidated balance sheet and we expense them as the services are provided.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets.

Use of estimates

The preparation of condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States requires 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 and nine months ended September 30, 2018 and 2017 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 loss per share for the three months ended September 30, 2018, was calculated as follows (in thousands, except per share amounts):

Three months ended September 30, 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Income (Loss) Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	65,538	$ (0.73)	$ (47,843)
Akcea's net loss attributable to our ownership			$ (47,843)
Ionis' stand-alone net income			43,226
Net loss available to Ionis common stockholders			$ (4,616)
Weighted average shares outstanding			143,314
Basic net loss per share			$ (0.03)

Akcea's net loss per share calculation for the nine months ended September 30, 2018 included two components: (1) Akcea's net loss from its statement of operations and (2) deemed distributions related to the license of TEGSEDI in the second quarter of 2018. Because we own more than 50 percent of Akcea, we and Akcea are under common control. As such, Akcea accounted for the TEGSEDI transaction using common control guidance. Accordingly, Akcea recorded the license we granted to them at carrying value. In addition, Akcea recorded the consideration it paid to us in excess of the carrying value as a deemed distribution. Accounting rules required Akcea to include these deemed distributions in their net loss per share calculation as if Akcea had paid us a dividend.

Our basic net loss per share for the nine months ended September 30, 2018, was calculated as follows (in thousands, except per share amounts):

Nine months ended September 30, 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	57,347	$ (1.93)	$ (110,680)
Akcea's net loss attributable to our ownership			$ (110,680)
Ionis' stand-alone net income			67,517
Net income available to Ionis common stockholders			$ (43,162)
Weighted average shares outstanding			132,518
Basic net loss per share			$ (0.33)

Prior to Akcea's IPO in July 2017, we owned Akcea series A convertible preferred stock, which included a six percent cumulative dividend. Upon completion of Akcea's IPO in July 2017, our preferred stock was converted into common stock on a 1:1 basis. The preferred stock dividend was not paid at the IPO because the IPO was not a liquidation event or a change in control. During the three and nine months ended September 30, 2017, Akcea used a two-class method to compute its net income (loss) per share because it had both common and preferred shares outstanding during the periods. The two-class method required Akcea to calculate its net income (loss) per share for each class of stock by dividing total distributable losses applicable to preferred and common stock, including the six percent cumulative dividend contractually due to series A convertible preferred shareholders, by the weighted-average of preferred and common shares outstanding during the requisite period. Since Akcea used the two-class method, accounting rules required us to include our portion of Akcea's net income (loss) per share for both Akcea's common and preferred shares that we owned in our calculation of basic and diluted net income (loss) per share for three and nine months ended September 30, 2017.

Our basic net income per share for the three months ended September 30, 2017, was calculated as follows (in thousands, except per share amounts):

Three months ended September 30, 2017	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	36,556	$ (0.33)	$ (12,063)
Preferred shares	5,651	(0.01)	(57)
Akcea's net loss attributable to our ownership			$ (12,120)
Ionis' stand-alone net income			10,144
Net loss available to Ionis common stockholders			$ (1,976)
Weighted average shares outstanding			124,370
Basic net income per share			$ (0.02)

Our basic net income per share for the nine months ended September 30, 2017, was calculated as follows (in thousands, except per share amounts):

Nine months ended September 30, 2017	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	12,319	$ (3.12)	$ (38,435)
Preferred shares	21,055	(2.16)	(45,479)
Akcea's net loss attributable to our ownership			$ (83,914)
Ionis' stand-alone net income			100,235
Net income available to Ionis common stockholders			$ 16,321
Weighted average shares outstanding			123,746
Basic net income per share			$ 0.13

Dilutive net income (loss per share)

For the three and nine months ended September 30, 2018 and for the three months ended September 30, 2017, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

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

For the nine months ended September 30, 2017, 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 those periods. Diluted common equivalent shares for the nine months ended September 30, 2017 consisted of the following (in thousands except per share amounts):

Nine months ended September 30, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 16,321	123,746	$ 0.13
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,658	
Shares issuable upon restricted stock award issuance	—	430	
Shares issuable related to our ESPP	—	24	
Income available to Ionis common stockholders, plus assumed conversions	$ 16,321	125,858	$ 0.13

For the nine months ended September 30, 2017, the calculation excluded the 1 percent and 2¾ percent notes because the effect on diluted earnings per share was anti-dilutive.

Accumulated other comprehensive loss

We include unrealized gains and losses on investments, net of taxes, in accumulated other comprehensive income (loss) along with adjustments we make to reclassify realized gains and losses on investments from other accumulated comprehensive income (loss) to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income (loss) for the three and nine months ended September 30, 2018 and 2017 (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Beginning balance accumulated other comprehensive loss	$ (32,637)	$ (30,372)	$ (31,759)	$ (30,358)
Unrealized gains (losses) on securities (1)	133	215	(834)	610
Amounts reclassified from accumulated other comprehensive loss	—	—	—	(374)
Currency translation adjustment	(28)	(42)	61	(77)
Net current period other comprehensive income (loss)	105	173	(773)	159
Ending balance accumulated other comprehensive loss	$ (32,532)	$ (30,199)	$ (32,532)	$ (30,199)

(1) There was no income tax expense or benefit related to elements of other comprehensive income (loss) for the three and nine months ended September 30, 2018 and 2017.

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 drugs 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 nine months ended September 30, 2018 and 2017, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2018	2017
Risk-free interest rate	2.3%	1.8%
Dividend yield	0.0%	0.0%
Volatility	63.1%	66.1%
Expected life	4.6 years	4.5 years

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2018	2017
Risk-free interest rate	2.8 %	2.2 %
Dividend yield	0.0 %	0.0 %
Volatility	61.5 %	61.2 %
Expected life	6.6 years	6.6 years

ESPP:

	Nine Months Ended September 30,	
	2018	2017
Risk-free interest rate	1.8%	0.8%
Dividend yield	0.0%	0.0%
Volatility	47.3%	59.9%
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 and members of our board of directors for the nine months ended September 30, 2018 was $51.83 and $42.88 per share, respectively.

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2018 and 2017 (in thousands). Our consolidated non-cash stock-based compensation expense includes $12.7 million and $4.7 million of stock-based compensation expense for Akcea for the three months ended September 30, 2018 and 2017, respectively, and $31.2 million and $11.8 million for the nine months ended September 30, 2018 and 2017, respectively.

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Research, development and patent	$ 18,780	$ 16,181	$ 57,698	$ 48,443
Selling, general and administrative	16,103	5,291	39,512	15,199
Total non-cash stock-based compensation expense	$ 34,883	$ 21,472	$ 97,210	$ 63,642

As of September 30, 2018, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $139.5 million and $32.6 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 1.3 years and 1.6 years, respectively.

Impact of recently issued accounting standards

In February 2016, the FASB issued amended accounting guidance related to lease accounting, which will require us to record all leases with a term longer than one year on our balance sheet. When we record leases on our balance sheet under the new guidance, we will record a liability with a value equal to the present value of payments we will make over the life of the lease and an asset representing the underlying leased asset. The new accounting guidance requires us to determine if our leases are operating or financing leases. We will record expense for operating leases on a straight-line basis as an operating expense. If we determine a lease is a financing lease, we will record both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease. The new lease standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted. We will adopt this guidance on January 1, 2019. We can choose from two methods of adoption. The first method requires us to reflect our leases on our balance sheet in the earliest comparative period presented in our financial statements. The second method requires us to reflect the impact of adoption on the date we adopt the new guidance and recognize a cumulative-effect adjustment to the opening balance of our accumulated deficit in that period. We are currently determining the method we will use to adopt the new guidance and assessing the effects the new guidance will have on our consolidated financial statements and disclosures.

In June 2016, the FASB issued guidance that changes the measurement of credit losses for most financial assets and certain other instruments. If we have credit losses, this updated guidance requires us to record allowances for these instruments under a new expected credit loss model. This model requires us to estimate the expected credit loss of an instrument over its lifetime, which represents the portion of the amortized cost basis we do not expect to collect. 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 consolidated financial statements and disclosures.

In December 2017, the SEC staff issued guidance to address how companies should account for the Tax Act of 2017, or the Tax Act, when an entity does not have the necessary information to complete the accounting for the Tax Act and gives entities up to one year from the enactment of the Tax Act to finalize their amounts. We recognized provisional amounts in our 2017 financial statements and in these financial statements. The ultimate impact may differ materially from these provisional amounts due to, among other things, additional analysis, changes in our interpretations and assumptions, additional regulatory guidance that may be issued, and other actions we may take resulting from the Tax Act. We will assess and update our provisional amounts and disclosures, as necessary, at year end 2018.

In February 2018, the FASB issued updated guidance for reclassification of tax effects from accumulated other comprehensive income (loss). The updated guidance gives entities an option to reclassify amounts included in accumulated other comprehensive income (loss) that under the Tax Act do not have a way to be relieved, and allows a one-time reclassification to retained earnings. The updated guidance is effective for all entities for fiscal years beginning after December 31, 2018, and interim periods within those fiscal years. Early adoption is permitted, and adoption is optional. We are currently assessing the effects this updated guidance could have on our consolidated financial statements and timing of potential adoption.

In June 2018, the FASB issued updated guidance to simplify the accounting for stock-based compensation expense for nonemployees. Specifically, we are now expensing grants to nonemployees in a similar manner as grants to employees and our Board of Directors. Previously, we had to re-value these grants at each reporting period to reflect the current fair value. Under the amended guidance, we value grants to nonemployees when we grant them and we will not adjust their value for future changes. We adopted this guidance in the second quarter of 2018 on a prospective basis. The updated guidance did not have a material impact to our financial results.

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 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 anticipate we will adopt this updated guidance on January 1, 2019 and we do not expect it to have a significant impact on our disclosures.

3. Investments

As of September 30, 2018, 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 September 30, 2018:

One year or less	80%
After one year but within two years	15%
After two years but within three years	5%
Total	100%

As illustrated above, at September 30, 2018, 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 September 30, 2018, we had an ownership interest of less than 20 percent in four private companies and one public company with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd. The publicly-traded company is Antisense Therapeutics Limited.

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

September 30, 2018	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 841,397	$ 23	$ (1,264)	$ 840,156
Debt securities issued by U.S. government agencies	143,008	2	(169)	142,841
Debt securities issued by the U.S. Treasury (2)	154,280	—	(89)	154,191
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	49,873	—	(330)	49,543
Total securities with a maturity of one year or less	1,188,558	25	(1,852)	1,186,731
Corporate debt securities	240,208	16	(1,420)	238,804
Debt securities issued by U.S. government agencies	32,435	—	(109)	32,326
Debt securities issued by the U.S. Treasury	9,872	—	(10)	9,862
Debt securities issued by states of the U.S. and political subdivisions of the states	31,666	—	(551)	31,115
Total securities with a maturity of more than one year	314,181	16	(2,090)	312,107
Total available-for-sale securities	$ 1,502,739	$ 41	$ (3,942)	$ 1,498,838

December 31, 2017	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities	$ 500,599	$ 2	$ (752)	$ 499,849
Debt securities issued by U.S. government agencies	83,926	—	(212)	83,714
Debt securities issued by the U.S. Treasury	29,428	—	(17)	29,411
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	29,240	4	(122)	29,122
Total securities with a maturity of one year or less	643,193	6	(1,103)	642,096
Corporate debt securities	148,663	8	(1,059)	147,612
Debt securities issued by U.S. government agencies	52,779	—	(168)	52,611
Debt securities issued by the U.S. Treasury	1,409	—	(2)	1,407
Debt securities issued by states of the U.S. and political subdivisions of the states	65,550	—	(740)	64,810
Total securities with a maturity of more than one year	268,401	8	(1,969)	266,440
Total available-for-sale securities	$ 911,594	$ 14	$ (3,072)	$ 908,536

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

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

The following is a summary of our investments we consider to be temporarily impaired at September 30, 2018. 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.

(In thousands)	Number of Investments	Less than 12 Months of Temporary Impairment: Estimated Fair Value	Less than 12 Months of Temporary Impairment: Unrealized Losses	More than 12 Months of Temporary Impairment: Estimated Fair Value	More than 12 Months of Temporary Impairment: Unrealized Losses	Total Temporary Impairment: Estimated Fair Value	Total Temporary Impairment: Unrealized Losses
Corporate debt securities	495	$ 889,172	$ (1,687)	$ 83,706	$ (997)	$ 972,878	$ (2,684)
Debt securities issued by U.S. government agencies	51	132,231	(139)	26,862	(139)	159,093	(278)
Debt securities issued by the U.S. Treasury	32	164,053	(99)	—	—	164,053	(99)
Debt securities issued by states of the U.S. and political subdivisions of the states	48	25,687	(191)	51,747	(690)	77,434	(881)
Total temporarily impaired securities	626	$ 1,211,143	$ (2,116)	$ 162,315	$ (1,826)	$ 1,373,458	$ (3,942)

4. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We classify the majority of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the nine months ended September 30, 2018, there were no transfers between our Level 1 and Level 2 investments. When we recognize transfers between levels of the fair value hierarchy, we recognize the transfer on the date the event or change in circumstances that caused the transfer occurs.

The following tables present the major security types we held at September 30, 2018 and December 31, 2017 that are regularly measured and carried at fair value. At September 30, 2018 and December 31, 2017, we did not have any financial instruments that we valued using Level 3 inputs. 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 September 30, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 395,649	$ 395,649	$ —
Corporate debt securities (2)	1,078,960	—	1,078,960
Debt securities issued by U.S. government agencies (3)	175,167	—	175,167
Debt securities issued by the U.S. Treasury (3)	164,053	164,053	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	80,658	—	80,658
Total	$ 1,894,487	$ 559,702	$ 1,334,785

	At December 31, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 86,262	$ 86,262	$ —
Corporate debt securities (3)	647,461	—	647,461
Debt securities issued by U.S. government agencies (3)	136,325	—	136,325
Debt securities issued by the U.S. Treasury (3)	30,818	30,818	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	93,932	—	93,932
Total	$ 994,798	$ 117,080	$ 877,718

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

(2) At September 30, 2018, $19.7 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

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

(4) At December 31, 2017, $3.5 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

Other Fair Value Disclosures

Novartis Future Stock Purchase

In January 2017, we and Akcea entered into a SPA with Novartis. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or our common stock at a premium if an IPO did not occur by April 2018. Therefore, at the inception of the SPA, we recorded a $5.0 million asset representing the fair value of the potential future premium we could have received if Novartis purchased our common stock. We determined the fair value of the future premium by calculating the value based on the stated premium in the SPA and estimating the probability of an Akcea IPO. We also included a lack of marketability discount when we determined the fair value of the premium because we would have issued unregistered shares to Novartis if they had purchased our common stock. We measured this asset using Level 3 inputs and recorded it in other assets on our consolidated balance sheet. Because Akcea completed its IPO before April 2018, Novartis did not purchase additional shares of Ionis stock. Therefore, we wrote-off the remaining balance to other expenses in the third quarter of 2017 because this asset no longer had any value.

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

Beginning balance of Level 3 instruments at January 1, 2017	$ —
Value of the potential premium we would have received from Novartis at inception of the SPA (January 2017)	5,035
Recurring fair value adjustment during the nine months ended September 30, 2017	(5,035)
Ending balance of Level 3 instruments at September 30, 2017	$ —

Convertible Notes

Our 1 percent notes had a fair value of $725.7 million at September 30, 2018. 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. Other Obligations

Line of Credit Arrangement

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

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

Additionally, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of September 30, 2018 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 and the building that houses our manufacturing facility for $79.4 million and $14.0 million, respectively. We financed the purchase of our primary R&D facility and our 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 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.

6. Collaborative Arrangements and Licensing Agreements

Below, we have included all of our significant collaborations because we adopted Topic 606 on January 1, 2018. We have included new disclosures for each of our collaborations as required under Topic 606.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved drug to treat people with spinal muscular atrophy, or SMA. In December 2017, we entered into a collaboration with Biogen to identify new antisense drugs for the treatment of SMA. Additionally, we and Biogen are currently developing six other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$ for ALS, IONIS-MAPT$_{Rx}$ for Alzheimer's disease, IONIS-C9$_{Rx}$ for ALS, and IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. Most recently, in April 2018, we entered into a new strategic collaboration for the treatment of neurological diseases with Biogen. From inception through September 2018, we have received over $1.9 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 when we entered into the 2018 strategic neurology collaboration.

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. In December 2016, the FDA approved SPINRAZA for the treatment of SMA in pediatric and adult patients.

From inception through September 2018, we earned $717 million in total revenue under our SPINRAZA collaboration, including $281 million in revenue from SPINRAZA royalties and $436 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on any sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on sales of SPINRAZA. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

Over the course of our SPINRAZA collaboration, we identified two performance obligations, which were to perform R&D services and to deliver the SPINRAZA license to Biogen. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance through December 2016. We recognized the $75 million license fee for SPINRAZA as revenue when we delivered the license to Biogen in July 2016 because Biogen 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 Biogen.

We also earned additional milestone payments subsequent to delivering the license to Biogen that we recognized in full in the period each milestone payment became probable because we did not have a performance obligation related to each milestone payment. For example, we received $90 million of milestone payments for the approval of SPINRAZA in the EU and Japan in 2017 and recognized the full amounts into revenue in the period Biogen achieved the milestone events.

Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurodegenerative diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-MAPT$_{Rx}$ for Alzheimer's disease under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities and costs for that drug.

Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. The $210 million per program consists of up to $10 million in development milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales of any drugs resulting from each of the three programs. From inception through September 2018, we have received $58 million in milestone payments and upfront fees under this collaboration. We will achieve the next payment of $7.5 million if we continue to advance IONIS-MAPT$_{Rx}$.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $30 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in December 2020. From inception through September 2018, we have included $40 million in total payments in the transaction price for our R&D services performance obligation.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs Biogen is pursuing under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs after Phase 2 proof of concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities and costs for that drug. We are currently advancing five drugs, IONIS-SOD1$_{Rx}$, IONIS-C9$_{Rx}$, IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ under this collaboration. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and milestone payments per program. The $260 million per program consists of approximately $60 million in development milestones, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any antisense drugs developed under this collaboration. If Biogen chooses to advance drugs using other modalities, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in milestone payments per program. The $90 million per program consists of up to $35 million in development milestone payments and up to $55 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered single-digit royalties on sales from any drugs using non-antisense modalities developed under this collaboration. From inception through September 2018, we have received over $170 million in upfront fees, milestone payments and other payments under this collaboration, not including a $10 million milestone payment we earned in the third quarter of 2018 for Biogen's initiation of a Phase 1 study for IONIS-C9$_{Rx}$ which we received in the fourth quarter of 2018. We will achieve the next payment of up to $10 million if we advance a program under this collaboration.

At the commencement of our strategic neurology collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $100 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in September 2019. From inception through September 2018, we have included $145 million in total payments in the transaction price for our R&D services performance obligation. In the third quarter of 2018, we earned a $10 million milestone payment when Biogen initiated a Phase 1 study of IONIS-C9$_{Rx}$. We recognized this milestone payment in full in the third quarter because we do not have any performance obligations related to this milestone payment. Additionally, we concluded that the payment is not related to our R&D services performance obligation.

New antisense drugs for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense drugs for the treatment of SMA. Biogen will have the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for all further global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in December 2017. We will receive development and regulatory milestone payments from Biogen if new drugs advance towards marketing approval. In total over the term of our collaboration, we are eligible to receive up to $1.2 billion in license fees, milestone payments and other payments, including up to $80 million for the achievement of development milestones, up to $180 million for the achievement of commercialization milestones and up to $800 million for the achievement of sales milestones. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales. We will achieve the next payment of up to $60 millionfor the license of a drug under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined the transaction price to be the $25 million upfront payment we received when we entered into the collaboration. We allocated the transaction price to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in December 2020.

2018 Strategic Neurology Collaboration

In April 2018, we and Biogen entered into a new strategic collaboration to develop novel antisense drugs for a broad range of neurological diseases and entered into a SPA. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for these diseases for 10 years. We are responsible for the identification of antisense drug candidates based on selected targets, while Biogen will have the option to license therapies arising out of this collaboration and will be responsible for and pay for non-clinical studies, clinical development, manufacturing, and commercialization.

In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at a 25 percent cash premium and $375 million in an upfront payment. We are eligible to receive up to $270 million for each drug that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales. We will achieve the next payment of $7.5 million if Biogen designates a target under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined our transaction price to be $552 million, comprised of $375 million from the upfront payment and $177 million for the premium paid by Biogen for its purchase of our common stock. We determined the fair value of the premium we received by using the stated premium in the SPA and applying a lack of marketability discount. We included a lack of marketability discount in our valuation of the premium because Biogen received restricted shares. We allocated the transaction price to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in June 2028.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
SPINRAZA royalties (commercial revenue)	$ 70.0	$ 32.9	$ 167.7	$ 60.5
R&D revenue	34.8	54.9	66.9	137.1
Total revenue from our relationship with Biogen	104.8	87.8	234.6	197.6
Percentage of total revenue	72%	74%	58%	57%

Our condensed consolidated balance sheet at September 30, 2018 and December 31, 2017 included deferred revenue of $593.6 million and $93.6 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

AstraZeneca

Cardiac, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiac, renal and metabolic diseases. Under our collaboration AstraZeneca has licensed three drugs from us. As part of the agreement, we granted AstraZeneca an exclusive license to IONIS-AZ4-2.5-L_{Rx}, a drug we designed to treat cardiovascular disease and our first drug that combines our Generation 2.5 and LIgand-Conjugated Antisense, or LICA, technology. We also granted AstraZeneca the option to license a drug for each additional target advanced under this research collaboration. In February 2018, AstraZeneca licensed a second drug under our collaboration, IONIS-AZ5-2.5$_{Rx}$, a drug we designed to treat a genetically associated form of kidney disease. In March 2018, AstraZeneca licensed a third drug under our collaboration, IONIS-AZ6-2.5-L_{Rx}, a drug we designed to inhibit an undisclosed target to treat patients with nonalcoholic steatohepatitis, or NASH. AstraZeneca is responsible for all further global development, regulatory and commercialization activities and costs for IONIS-AZ4-2.5-L_{Rx}, IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L_{Rx} and any other future drugs AstraZeneca licenses.

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $4 billion as drugs under this collaboration advance, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through September 2018, we have received over $165 million in upfront fees, license fees, milestone payments, and other payments under this collaboration, including a $10 million milestone payment we earned in the third quarter of 2018 when AstraZeneca initiated a Phase 1 trial for IONIS-AZ4-2.5-L_{Rx}. We will achieve the next payment of $10 million under this collaboration if we advance a drug under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for AstraZeneca. We determined the transaction price to be the $65 million upfront payment we received and we allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy this performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy this performance obligation in August 2021. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. From inception through September 2018, we have included $90 million in payments in the transaction price for our R&D services performance obligation.

We identified separate performance obligations upon AstraZeneca's license of IONIS-AZ5-2.5 $_{Rx}$ and IONIS-AZ6-2.5-L_{Rx} in the first quarter of 2018 because the licenses are distinct from our other performance obligation and each other. We recognized each $30 million license fee in the first quarter of 2018 because AstraZeneca had full use of the licenses without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the licenses after we delivered them to AstraZeneca.

In the third quarter of 2018, we earned a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of IONIS-AZ4-2.5-L_{Rx}. We recognized this milestone payment in full in the third quarter because we do not have any performance obligations related to this milestone payment. Additionally, we concluded that the payment is not related to our R&D services performance obligation.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs to treat cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize danvatirsen (formerly IONIS-STAT3-2.5$_{Rx}$) for the treatment of cancer. AstraZeneca is now responsible for all global development, regulatory and commercialization activities for danvatirsen. We and AstraZeneca have evaluated danvatirsen in people with head and neck cancer, advanced lymphoma and advanced metastatic hepatocellular carcinoma. AstraZeneca is evaluating danvatirsen in combination with Imfinzi (durvalumab), AstraZeneca's programmed death ligand, or PD-L1, blocking drug, in people with head and neck cancer, metastatic bladder cancer and metastatic non-small cell lung cancer. In addition, we and AstraZeneca established an oncology research program. AstraZeneca has the option to license drugs resulting from the program, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities and costs for such drug.

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. If AstraZeneca successfully develops danvatirsen and another drug under the research program, we could receive license fees and milestone payments of up to more than $450 million, including up to $152 million for the achievement of development milestones and up to $275 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low to mid-teens on sales from any drugs resulting from these programs. From inception through September 2018, we have received $97.8 million in upfront fees, milestone payments, and other payments under this oncology collaboration, not including nearly $30 million in milestone payments we achieved when AstraZeneca advanced two programs in the fourth quarter of 2018. We will achieve the next payment of up to $25.0 million if we advance a drug under our cancer research program with AstraZeneca.

At the commencement of this collaboration, we identified four performance obligations. We determined the transaction price to be the $31 million in upfront payments we received. We allocated the transaction price based on the estimated stand-alone selling price of each of our performance obligations and recognized the associated revenue over the period of our performance. We recognized revenue for three of our obligations over our period of performance, concluding in March 2014. Our remaining performance obligation was to perform R&D services. We allocated $7.6 million to this performance obligation and recognized the associated revenue over the period of our performance, which ended in February 2018. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
R&D revenue	$ 14.2	$ 4.8	$ 86.5	$ 14.8
Percentage of total revenue	10%	4%	21%	4%

Our condensed consolidated balance sheet at September 30, 2018 and December 31, 2017 included deferred revenue of $44.9 million and $57.7 million, respectively, related to our relationship with AstraZeneca.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. We were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis. Under the terms of the agreement, we received a $100 million upfront payment in the second quarter of 2015. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. In conjunction with the decision to advance these programs, we received a $75 million payment from Bayer. We are conducting a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to develop IONIS-FXI-L$_{Rx}$ through Phase 1. Following these studies and Bayer's decision to further advance these programs, Bayer will be responsible for all global development, regulatory and commercialization activities and costs for both drugs.

We are eligible to receive additional milestone payments as each drug advances toward the market. In total over the term of this collaboration, we are eligible to receive up to $385 million in license fees, milestone payments and other payments, including up to $125 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both drugs combined. From inception through September 2018, we have received over $175 million from our Bayer collaboration. We will achieve the next payment of $10 million if a program advances under this collaboration.

At the commencement of this collaboration, we identified three performance obligations. We determined the transaction price to be the $100 million in upfront payment we received. We allocated the transaction price based on the relative stand-alone selling prices of each of our performance obligations and recognized the associated revenue as follows:

- We recognized $91.2 million for the exclusive license of IONIS-FXI$_{Rx}$ in May 2015 because Bayer had full use of the license without any continuing involvement from us.
- We recognized $4.3 million for the R&D services for IONIS-FXI$_{Rx}$ over the period of our performance, which ended in November 2016.
- We allocated $4.5 million for API, which we are recognizing into revenue as we deliver the API.

In February 2017, when we amended our collaboration with Bayer, we identified two new performance obligations, one for the license of IONIS-FXI-L$_{Rx}$ and one for R&D services. We determined the transaction price to be the $75 million payment. We allocated $64.9 million to the license of IONIS-FXI-L$_{Rx}$ based on its estimated stand-alone selling price and recognized the associated revenue upon our delivery of the license in the first quarter of 2017. We allocated $10.1 million to our R&D services performance obligation based on an estimated stand-alone selling price. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our R&D services performance obligation in May 2019.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with Bayer (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
R&D revenue	$ 1.9	$ 0.4	$ 3.3	$ 66.0
Percentage of total revenue	1%	0%	1%	19%

Our condensed consolidated balance sheet at September 30, 2018 and December 31, 2017 included deferred revenue of $6.0 million and $9.3 million, respectively, related to our relationship with Bayer.

Janssen Biotech, Inc.

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the gastrointestinal tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under the terms of the agreement, we received $35 million in upfront payments. We are eligible to receive up to more than $800 million in license fees and milestone payments for these programs, including up to $175 million for the achievement of development milestones, up to $440 million for the achievement of regulatory milestones and up to $180 million for the achievement of commercialization milestones. From inception through September 2018, we have received $75 million, including $15 million in license fees when Janssen licensed IONIS-JBI1-2.5$_{Rx}$ and IONIS-JBI2-2.5$_{Rx}$ from us in 2016 and 2017, respectively. We also received $5 million in January 2018 for the initiation of a Phase 1 study of IONIS-JBI1-2.5$_{Rx}$ in late 2017. In addition, we are eligible to receive tiered royalties up to the near teens on sales from any drugs resulting from this collaboration. We will achieve the next payment of $5 million if Janssen continues to advance a target under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Janssen. We determined the transaction price to be the $35 million upfront payments we received. We allocated the $35 million to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, through November 2017.

We identified separate performance obligations each time Janssen licensed one of our drugs under our collaboration because the licenses we granted to Janssen were distinct from our other performance obligations. We recognized the $10 million license fee for IONIS-JBI1-2.5$_{Rx}$ in July 2016 and $5 million for the license of IONIS-JBI2-2.5$_{Rx}$ in November 2017, because Janssen had full use of the licenses without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the licenses after we delivered them to Janssen.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with Janssen (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
R&D revenue	$ 0.9	$ 3.4	$ 6.6	$ 18.1
Percentage of total revenue	1%	3%	2%	5%

We did not have any deferred revenue from our relationship with Janssen at September 30, 2018 or December 31, 2017.

Roche

Huntington's Disease

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease, or HD, based on our antisense technology. Roche had the option to license the drugs from us through the completion of the first Phase 1 trial. Under the agreement, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We evaluated a drug targeting HTT, IONIS-HTT$_{Rx}$, in a Phase 1/2a clinical study in people with early stage HD.

In December 2017, upon completion of the Phase 1/2a study, Roche exercised its option to license IONIS-HTT$_{Rx}$ and is now responsible for the global development, regulatory and commercialization activities for IONIS-HTT$_{Rx}$. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013. In December 2016, we updated development activities for IONIS-HTT$_{Rx}$ and as a result we were eligible for an additional $3 million payment, which we achieved in 2017. We are eligible to receive up to $365 million in a license fee and milestone payments including up to $70 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on any sales of any product resulting from this alliance. From inception through September 2018, we have received over $110 million in upfront fees, milestone payments and license fees for advancing IONIS-HTT$_{Rx}$, including the $45 million license fee we received in January 2018 for IONIS-HTT$_{Rx}$. We will achieve the next payment of $35 million if Roche initiates a pivotal study for IONIS-HTT$_{Rx}$.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the $30 million upfront payment we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, through September 2017.

We identified a second performance obligation upon Roche's license of IONIS-HTT$_{Rx}$ in the fourth quarter of 2017 because the license we granted to Roche is distinct from our other performance obligation. We recognized the $45 million license fee for IONIS-HTT$_{Rx}$ as revenue at that time because Roche 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 Roche.

We do not have any remaining performance obligations related to IONIS-HTT$_{Rx}$ under this collaboration with Roche, however we can still earn additional payments and royalties as Roche advances IONIS-HTT$_{Rx}$.

IONIS-FB-L$_{Rx}$ for Complement-Mediated Diseases

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 are exploring the drug in 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.

Under this new collaboration agreement, we received a $75 million upfront payment in October 2018. We are eligible to receive up to $684 million in development, regulatory and sales milestone payments and license fees. In addition, we are also eligible to receive tiered royalties from the high teens to twenty percent on net sales. We will achieve the next payment of $20 million when we advance the Phase 2 study in patients with dry AMD.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
R&D revenue	$ 1.8	$ 4.5	$ 5.4	$ 5.9
Percentage of total revenue	1%	4%	1%	2%

We did not have any deferred revenue from our relationship with Roche at September 30, 2018 or December 31, 2017.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Under the terms of the agreement, we received upfront payments of $35 million.

GSK is advancing two drugs targeting hepatitis B virus, or HBV, under our collaboration: IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$. GSK is currently conducting Phase 2 studies for both of these drugs, which we designed to reduce the production of viral proteins associated with HBV infection. In March 2016, we and GSK amended the development plan for IONIS-HBV$_{Rx}$ to allow GSK to conduct all further development activities for this program. GSK has the exclusive option to license the drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee.

Under our agreement, if GSK successfully develops these drugs and achieves pre-agreed sales targets, we could receive license fees and milestone payments of $262 million, including up to $47.5 million for the achievement of development milestones, up to $120 million for the achievement of regulatory milestones and up to $70 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance. From inception through September 2018, we have received more than $162 million in payments under this alliance with GSK. We will achieve the next payment of up to $25 million if GSK licenses a drug under this program.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for GSK. We determined the transaction price to be the $35 million upfront payment we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, through March 2015. We do not have any remaining performance obligations under our collaboration with GSK, however we can still earn additional payments and royalties as GSK advances these drugs.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
R&D revenue	$ 0.1	$ 4.6	$ 1.5	$ 14.4
Percentage of total revenue	0%	4%	0%	4%

Our revenue for the nine months ended September 30, 2017, was from our work on the programs under our collaboration with GSK. We did not have any deferred revenue from our relationship with GSK at September 30, 2018 or December 31, 2017.

Akcea Collaborations

The following collaboration agreements relate to Akcea, our majority owned affiliate. Our consolidated results include all the revenue earned and cash received under these collaboration agreements. 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 drug. If Novartis exercises an option for one of these drugs, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such drug.

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it retained $60 million and paid us $15 million as a sublicense fee. If Novartis exercises its option for a drug, Novartis will pay Akcea a license fee equal to $150 million for each drug it licenses. In addition, for AKCEA-APO(a)-L_{Rx}, Akcea is eligible to receive up to $600 million in milestone payments, including $25 million for the achievement of a development milestone, up to $290 million for the achievement of regulatory milestones and up to $285 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx}, Akcea is eligible to receive up to $530 million in milestone payments, including $25 million for the achievement of a development milestone, up to $240 million for the achievement of regulatory milestones and up to $265 million for the achievement of commercialization milestones. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee. Akcea plans to co-commercialize any licensed drug commercialized by Novartis in selected markets under terms and conditions that we plan to negotiate with Novartis in the future, through its specialized sales force.

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

At the commencement of this collaboration, we identified four separate performance obligations:

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

We determined that the R&D services for each drug and the API for each drug were distinct from our other performance obligations.

We determined our transaction price to be $108.4 million, comprised of the following:

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

We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $64.0 million for the R&D services for AKCEA-APO(a)-L_{Rx};

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

We are recognizing revenue related to the R&D services for the AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$ performance obligations as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy the significant portion of our performance obligation for AKCEA-APO(a)-L$_{Rx}$ by December 2018 with the remainder by the end of March 2019. We currently estimate we will satisfy the significant portion of our performance obligation for AKCEA-APOCIII-L$_{Rx}$ by June 2019 with the remainder by the end of December 2019. We recognized the amount attributed to the API supply for AKCEA-APO(a)-L$_{Rx}$ when we delivered it to Novartis in 2017. We recognized the amount attributed to the API supply for AKCEA-APOCIII-L$_{Rx}$ when we delivered it to Novartis in May 2018.

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 consolidated balance sheet.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
R&D revenue	$ 7.2	$ 9.9	$ 42.7	$ 21.7
Percentage of total revenue	5%	8%	10%	6%

Our condensed consolidated balance sheet at September 30, 2018 and December 31, 2017 included deferred revenue of $34.8 million and $70.7 million, respectively, related to our relationship with Novartis.

PTC Therapeutics

In August 2018, Akcea entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Under the license agreement, Akcea will receive up to $26 million of payments, including $12 million which it received in the third quarter of 2018, $6 million upon the earlier of FDA or EMA approval of WAYLIVRA and up to $8 million of regulatory milestone payments. Akcea will receive royalties from PTC in the mid-20 percent range on net sales in Latin America for each drug. PTC's obligation to pay Akcea royalties begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC recognizes revenue of at least $10 million in Latin America. These royalties may be reduced upon expiration of certain patents or if a generic competitor negatively impacts PTC's market share. Consistent with the agreements between Ionis and Akcea, the companies will share all payments, including royalties.

At the commencement of this collaboration, we identified two performance obligations, which were the licenses Akcea granted to PTC to commercialize TEGSEDI and WAYLIVRA in Latin America in the third quarter of 2018. Akcea recognized $12 million in license fee revenue at that time because PTC had full use of both licenses without any continuing involvement from Akcea. Akcea does not have any remaining performance obligations under its collaboration with PTC. Akcea can still earn additional payments and royalties as PTC commercializes the drugs.

Akcea is responsible for the 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 SG&A expense. For example, during the third quarter of 2018, we recognized $7.2 million of sublicense revenue in our Ionis Core operating segment results related to our portion of the PTC license fee Akcea paid us. In our consolidated results, we eliminate this sublicense revenue and expense. Any cash Akcea receives is included in our consolidated balance sheet.

During the three and nine months ended September 30, 2018 and 2017, we earned the following revenue from our relationship with PTC (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
R&D revenue	$ 12.0	$ 0.0	$ 12.0	$ 0.0
Percentage of total revenue	8%	—	3%	—

Our condensed consolidated balance sheet at September 30, 2018 and December 31, 2017 did not include any deferred revenue related to our relationship with PTC.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics. At September 30, 2018 we owned approximately 75 percent of Akcea. In October 2018, we received an additional 1.7 million shares of Akcea's stock when TEGSEDI was approved by the FDA, increasing our ownership percentage to 76 percent. 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 drugs for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with rare and serious diseases.

The following tables show our segment revenue and income (loss) from operations for the three and nine months ended September 30, 2018 and 2017 (in thousands), respectively.

Three Months Ended September 30, 2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 70,010	$ —	$ —	$ 70,010
Licensing and other royalty revenue	7,946	12,000	(7,200)	12,746
Total commercial revenue	77,956	12,000	(7,200)	82,756
R&D revenue under collaborative agreements	100,105	7,241	(44,707)	62,639
Total segment revenue	$ 178,061	$ 19,241	$ (51,907)	$ 145,395
Total operating expenses	$ 87,664	$ 84,249	$ (7,946)	$ 163,967
Income (loss) from operations	$ 90,397	$ (65,008)	$ (43,961)	$ (18,572)

Three Months Ended September 30, 2017 (as revised)	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 32,890	$ —	$ —	$ 32,890
Licensing and other royalty revenue	1,727	—	—	1,727
Total commercial revenue	34,617	—	—	34,617
R&D revenue under collaborative agreements	73,791	9,906	—	83,697
Total segment revenue	$ 108,408	$ 9,906	$ —	$ 118,314
Total operating expenses	$ 81,019	$ 26,013	$ (30)	$ 107,002
Income (loss) from operations	$ 27,389	$ (16,107)	$ 30	$ 11,312

Nine Months Ended September 30, 2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 167,743	$ —	$ —	$ 167,743
Licensing and other royalty revenue	9,432	12,000	(7,200)	14,232
Total commercial revenue	177,175	12,000	(7,200)	181,975
R&D revenue under collaborative agreements	232,850	42,670	(49,936)	225,584
Total segment revenue	$ 410,025	$ 54,670	$ (57,136)	$ 407,559
Total operating expenses	$ 279,084	$ 213,428	$ (12,796)	$ 479,716
Income (loss) from operations	$ 130,941	$ (158,758)	$ (44,340)	$ (72,157)

Nine Months Ended September 30, 2017 (as revised)	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 60,467	$ —	$ —	$ 60,467
Licensing and other royalty revenue	5,639	—	—	5,639
Total commercial revenue	66,106	—	—	66,106
R&D revenue under collaborative agreements	312,976	21,712	(54,407)	280,281
Total segment revenue	$ 379,082	$ 21,712	$ (54,407)	$ 346,387
Total operating expenses	$ 242,753	$ 120,884	$ (54,497)	$ 309,140
Income (loss) from operations	$ 136,329	$ (99,172)	$ 90	$ 37,247

The following table shows our total assets by segment at September 30, 2018 and December 31, 2017 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
September 30, 2018	$ 2,446,425	$ 379,128	$ (577,641)	$ 2,247,913
December 31, 2017 (as revised)	$ 1,342,578	$ 268,804	$ (288,608)	$ 1,322,774

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as ten percent or more of our total revenue, was as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017 (as revised)	2018	2017 (as revised)
Partner A	72%	74%	58%	57%
Partner B	10%	4%	21%	4%
Partner C	5%	8%	10%	6%
Partner D	8%	0%	3%	0%
Partner E	1%	0%	1%	19%

Contracts receivables from two significant partners comprised approximately 84 percent of our contracts receivables at September 30, 2018 and December 31, 2017.

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, this Report includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA, TEGSEDI, WAYLIVRA 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. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our annual report on Form 10-K for the year ended December 31, 2017, 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.

Overview

We are leaders in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics. Using this platform, we have developed a large, diverse and advanced pipeline of potentially first-in-class and/or best-in-class drugs that we believe can provide high value for patients with significant unmet medical needs. In this way, we believe we are fundamentally changing medicine with the goal to transform the lives of those suffering from severe, often life-threatening, diseases.

We made significant progress toward this goal with the commercial launch of SPINRAZA for the treatment of SMA in pediatric and adult patients. SMA is a leading genetic cause of death in infants marked by progressive, debilitating muscle weakness. SPINRAZA became the first and only approved drug to treat people with SMA and is now the standard of care for this debilitating disease. Our partner, Biogen, is responsible for global commercial activities. Since regulatory approval in December 2016, we have earned more than $280 million in commercial revenue from SPINRAZA royalties.

TEGSEDI is now approved in the U.S., the EU and Canada and Akcea's launch activities for TEGSEDI are underway. We believe TEGSEDI has the potential to become the preferred treatment option for many people with hATTR. Our goal is to free these people from the burden of their disease. hATTR is a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body. We licensed TEGSEDI to Akcea, our majority owned affiliate, focused on developing and commercializing drugs to treat patients with rare and serious diseases. By licensing TEGSEDI to Akcea, we believe we will maximize the commercial potential of TEGSEDI, while optimizing our commercial participation. We estimate that there are approximately 50,000 patients globally with hATTR, the majority of which have symptoms of polyneuropathy. Additionally, we and Akcea are continuing to build our TTR franchise by moving AKCEA-TTR-L$_{Rx}$ forward rapidly to address the larger patient population, which includes hereditary and wild-type ATTR patients.

We and Akcea are developing WAYLIVRA to treat two severe and rare, genetically defined diseases, familial chylomicronemia syndrome, or FCS, and familial partial lipodystrophy, or FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. We estimate that FCS and FPL each affect 3,000 to 5,000 people globally. The clinical development program for WAYLIVRA consists of three Phase 3 studies called APPROACH, BROADEN and COMPASS. In the first quarter of 2017, we and Akcea reported positive Phase 3 data from the APPROACH study in patients with FCS. In December 2016, we and Akcea reported positive results from the Phase 3 COMPASS study in patients with triglycerides above 500 mg/dL. Based on the positive data from these Phase 3 studies, Akcea filed for marketing authorization for WAYLIVRA in the U.S., EU and Canada in the third quarter of 2017. We and Akcea are in active discussions with EMA and our review process is ongoing. In May 2018, an FDA advisory committee voted in favor of WAYLIVRA for the treatment of FCS. In August 2018, we received a complete response letter from the FDA regarding the New Drug Application, or NDA, for WAYLIVRA. In November 2018, we received a preliminary notification of a notice of noncompliance withdrawal letter from Health Canada for WAYLIVRA. We and Akcea are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA

In addition to commercializing TEGSEDI and preparing to commercialize WAYLIVRA, Akcea is focused on developing their other clinical-stage drugs: AKCEA-APO(a)-L$_{Rx}$, AKCEA-ANGPTL3-L$_{Rx}$, AKCEA-APOCIII-L$_{Rx}$ and AKCEA-TTR-L$_{Rx}$, each of which could potentially treat multiple patient populations. Moving these drugs into Akcea allows us to retain substantial value from them and ensures our core focus remains on innovation. As of October 2018, we owned approximately 76 percent of Akcea.

We are addressing a broad spectrum of diseases that affect millions of people, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease. We also are addressing rare diseases, such as acromegaly, familial amyotrophic lateral sclerosis, beta-thalassemia and Huntington's disease. We anticipate at least three of our drugs will enter pivotal studies before the end of 2019, representing our next wave of commercial opportunities. These drugs include IONIS-HTT$_{Rx}$, for patients with Huntington's disease, AKCEA-TTR-L$_{Rx}$, our LICA version of TEGSEDI for patients with all forms of TTR amyloidosis and AKCEA-APO(a)-L$_{Rx}$ for patients with high Lp(a) who are at risk for cardiovascular disease. We are also focusing on our Ionis-owned drugs that have the potential to move quickly toward the market, including IONIS-GHR-L$_{Rx}$ for patients with acromegaly.

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our products. Our partners bring substantial resources and expertise that augment and build upon our internal capabilities.

One of our partners is Biogen with which we have a strategic partnership. In April 2018, we and Biogen entered into a new strategic collaboration to develop novel antisense drug candidates for a broad range of neurological diseases. We received $1 billion from Biogen, comprised of $625 million to purchase our stock at a 25 percent cash premium and $375 million in an upfront payment. We also have partnerships with AstraZeneca, Bayer, GSK, Janssen, Novartis and Roche. Each of these companies brings significant expertise and global resources to develop and potentially commercialize the drugs under these partnerships. Lastly, we also work with a group of companies that can develop our drugs and utilize our technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Through our partnerships, we have created a broad and sustaining base of research and development, or R&D, revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Moreover, we have the potential to earn more than $20 billion in future milestone payments and licensing fees from our current partnerships. In late 2016, we began adding commercial revenue from SPINRAZA royalties to our existing R&D revenue base. Looking forward, we have the potential to increase our commercial revenue from SPINRAZA royalties from the continued growth we expect in the U.S., EU and in other markets globally. As a result of the FDA's, EMA's and Health Canada's approval of TEGSEDI, we expect to add product sales from TEGSEDI to our commercial revenue in the fourth quarter. We will further increase our commercial revenue if TEGSEDI is approved in additional markets and from WAYLIVRA, assuming it is approved. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through royalties, which can further increase our commercial revenue.

Financial Highlights

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	**2017**	**2018**	**2017**
Total revenue	$ 145,395	$ 118,314	$ 407,559	$ 346,387
Total operating expenses	$ 163,967	$ 107,002	$ 479,716	$ 309,140
Income (loss) from operations	$ (18,572)	$ 11,312	$ (72,157)	$ 37,247
Net loss	$ (20,365)	$ (7,493)	$ (87,747)	$ (1,616)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (4,559)	$ (2,611)	$ (46,335)	$ 3,266

Our revenue for the nine months ended September 30, 2018 was $408 million and increased compared to the same period in 2017, primarily from increased commercial revenue from SPINRAZA royalties. We expect to add product revenue from TEGSEDI this year.

Our operating expenses for the nine months ended September 30, 2018 were $480 million and increased compared to $309 million for the same period in 2017. The increase in operating expenses was primarily due to higher SG&A expenses as we prepared to commercialize TEGSEDI and WAYLIVRA. Our SG&A expenses also increased in the first nine months of 2018 compared to 2017 because of fees we owed under our in-licensing agreements related to SPINRAZA. As sales for SPINRAZA grow, our in-licensing expenses also increase but not at the same rate. We earn tiered royalties on annual SPINRAZA sales and pay nominal fixed third-party royalties that are not tiered. R&D expenses accounted for a smaller portion of the increase in operating expenses. In the fourth quarter of 2018, we expect our operating expenses to continue to increase primarily related to the commercialization of TEGSEDI.

During the first nine months of 2018, we received more than $1.3 billion in payments from our partners, primarily from Biogen for our 2018 strategic neurology collaboration to develop novel antisense drugs for a broad range of neurological diseases.

Recent Events *(Q3 2018 and subsequent activities)*

Business Highlights

- *SPINRAZA – the first and only approved treatment for people with spinal muscular atrophy*
  - SPINRAZA sales continued to grow in the third quarter, both in the U.S. and ex-U.S., with global sales of more than $1 billion for year-to-date 2018, as reported by Biogen
  - Nearly 6,000 SMA patients were on SPINRAZA as of the third quarter
  - In the U.S., the number of adult patients on therapy grew by over 20 percent compared to the second quarter. Adult SMA patients, which represent the largest and most undertreated patient segment, accounted for more than 50 percent of start forms in the third quarter
  - Access outside the U.S. expanded with formal reimbursement in 28 markets and continued revenue growth in the EU, Asia Pacific and Latin America

- *TEGSEDI (inotersen) – launched in multiple markets for the treatment of polyneuropathy of hATTR in adult patients*
  - TEGSEDI approved in the U.S., EU and Canada
  - Commercial patients in Germany on TEGSEDI
  - TEGSEDI prescriptions received in the U.S.

- *WAYLIVRA (volanesorsen) – under regulatory review for the treatment of people living with FCS*
  - Preparing for launch in the EU following approval
  - Planning to confirm a path forward in the U.S. and Canada

Pipeline and Business Progress

- We and Akcea reported positive top-line data from a Phase 2 study of AKCEA-APO(a)-L $_{Rx}$ in people with high levels of Lp(a) and established cardiovascular disease demonstrating robust target reductions and a favorable safety and tolerability profile
- We and Roche entered a new collaboration to develop IONIS-FB-L$_{Rx}$ for the treatment of people with complement-mediated diseases. We received a $75 million upfront payment and will be eligible for development, regulatory and sales milestone payments and license fees of up to $684 million plus royalties of up to 20 percent on commercial sales
- Positive Phase 1b/2 data for danvatirsen, in combination with durvalumab was presented at the European Society for Medical Oncology, or ESMO, 2018 Congress, demonstrating a response rate approximately double that of durvalumab alone, based on previous studies in patients with refractory head and neck cancer. We earned a $17.5 million milestone payment because AstraZeneca is advancing the program
- We completed enrollment in a Phase 2b study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on dialysis, with data planned for mid-2019
- We or our partners initiated clinical studies with IONIS-GHR-L$_{Rx}$ (Phase 2), IONIS-C9$_{Rx}$ (Phase 1/2), IONIS-FXI-L$_{Rx}$ and IONIS-AZ4-2.5-L$_{Rx}$ (Phase 1)
- We earned a $10 million milestone payment from AstraZeneca for advancing an undisclosed oncology program into development
- We appointed Dr. Michael Hayden and Mr. Peter N. Reikes 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 require us to make estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with our audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

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

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating the impact of the Tax Act and our net deferred income tax asset valuation allowance;
- Determining the fair value of convertible debt without the conversion feature; and
- Valuing premiums received under our collaborations

These critical accounting policies and estimates are included in our Annual Report on Form 10-K for the year ended December 31, 2017 in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations."

In the first quarter of 2018, we updated the following critical accounting policy:

- Assessing the propriety of revenue recognition and associated deferred revenue.

Our updated critical accounting policy is as follows:

Revenue Recognition

Adoption of New Revenue Recognition Accounting Standard (Topic 606)

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. This guidance supersedes the revenue recognition requirements we previously followed in Accounting Standards Codification, or ASC, Topic 605, *Revenue Recognition*, or Topic 605, and created a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. Under Topic 606, an entity will recognize revenue when it transfers control of promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. Further, an entity will recognize revenue upon satisfying the performance obligation(s) under the related contract. We adopted Topic 606 on January 1, 2018 under the full retrospective approach, which required us to revise our prior period revenue. Under Topic 606, we were required to review all of our ongoing collaboration agreements in which we recognized revenue after January 1, 2016. We were required to assess what our revenue would have been for the period from January 1, 2016 to December 31, 2017 under Topic 606. As a result of this analysis, we determined that the cumulative revenue we would have recognized under Topic 606 decreased by $53.6 million. We recorded this amount as a cumulative adjustment to our accumulated deficit as of December 31, 2017. We have labeled our prior period financial statements "as revised" to indicate the change required under the accounting rules.

The following tables summarize the adjustments we were required to make to amounts we originally reported in 2017 to adopt Topic 606 (in thousands, except per share amounts):

Condensed Consolidated Balance Sheet

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred revenue	$ 72,708	$ 35,318	$ 108,026
Accumulated deficit	$ (1,187,398)	$ (53,636)	$ (1,241,034)
Noncontrolling interest in Akcea Therapeutics, Inc.	$ 87,847	$ (3,580)	$ 84,267
Total stockholders' equity	$ 418,719	$ (53,439)	$ 365,280

Condensed Consolidated Statement of Operations

	Three Months Ended September 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 32,890	$ —	$ 32,890
Licensing and other royalty revenue	879	848	1,727
Total commercial revenue	33,769	848	34,617
Research and development revenue under collaborative agreements	87,142	(3,445)	83,697
Total revenue	$ 120,911	$ (2,597)	$ 118,314
Income (loss) from operations	$ 13,909	$ (2,597)	$ 11,312
Net income (loss)	$ (4,896)	$ (2,597)	$ (7,493)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (976)	$ (1,635)	$ (2,611)
Net income (loss) per share, basic and diluted	$ 0.00	$ (0.02)	$ (0.02)

	Nine Months Ended September 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 60,467	$ —	$ 60,467
Licensing and other royalty revenue	4,983	656	5,639
Total commercial revenue	65,450	656	66,106
Research and development revenue under collaborative agreements	269,917	10,364	280,281
Total revenue	$ 335,367	$ 11,020	$ 346,387
Income from operations	$ 26,227	$ 11,020	$ 37,247
Net income (loss)	$ (12,636)	$ 11,020	$ (1,616)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (8,716)	$ 11,982	$ 3,266
Net income (loss) per share, basic	$ 0.02	$ 0.11	$ 0.13
Net income (loss) per share, diluted	$ 0.02	$ 0.11	$ 0.13

Condensed Consolidated Statement of Cash Flows

	Nine Months Ended September 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (12,636)	$ 11,020	$ (1,616)
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Deferred contract revenue	$ 42,091	$ (11,020)	$ 31,071
Cash and cash equivalents at beginning of period	$ 84,685	$ —	$ 84,685
Cash and cash equivalents at end of period	$ 159,184	$ —	$ 159,184

Under Topic 606, compared to Topic 605, our revenue decreased $2.6 million for the three months ended September 30, 2017, and increased $11.0 million for the nine months ended September 30, 2017. The change in our revenue was primarily due to:

- A change in how we recognize milestone payments: Topic 606 requires us to amortize more of the milestone payments we achieve, rather than recognizing the milestone payments in full in the period in which we achieved the milestone event as we did under Topic 605. This change resulted in an increase of $0.5 million and $27.9 million for the three and nine months ended September 30, 2017, respectively.

- A change in how we calculate revenue for payments we are recognizing into revenue over time: Under Topic 605, we amortized payments into revenue evenly over the period of our obligations. When we made a change to our estimated completion period, we recognized that change on a prospective basis. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. Each period, we review our "inputs" such as our level of effort expended, including the time we estimate it will take us to complete the activities, or costs incurred relative to the total expected inputs to satisfy the performance obligation. For certain collaborations, such as Bayer, Janssen and Novartis, the input method resulted in a change to the revenue we had previously recognized using a straight-line amortization method. This change resulted in a decrease of $4.0 million and $17.5 million for the three and nine months ended September 30, 2017, respectively.

Our updated revenue recognition policy reflecting Topic 606 is as follows:

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 condensed 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 expect to add product sales from TEGSEDI to our commercial revenue in the fourth quarter of 2018 as a result of TEGSEDI's approval in the U.S., EU and Canada. We expect to further increase our commercial revenue if TEGSEDI is approved in additional markets and from WAYLIVRA, assuming it is approved. We will also recognize as commercial revenue future sales milestone payments and royalties we earn under our partnerships.

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, R&D, services, and manufacturing services.

Our collaboration agreements are detailed in Note 6, *Collaborative Arrangements and Licensing Agreements*. 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 when we enter into a collaboration agreement in which we provide our partner with an option to license a drug 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 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 drug 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 drug 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. 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.

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. Our accounting for SPINRAZA royalties did not change as a result of adopting Topic 606.

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 new SMA collaboration with Biogen, we received a $25 million upfront payment in December 2017. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $25 million upfront payment using an input method over the estimated period of time we are providing R&D services. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion. Under Topic 605, we amortized upfront payments evenly over the period of our obligation.

Milestone Payments

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 drug is approved by the applicable regulator. 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. Under Topic 606, we allocated this payment to our R&D services performance obligation. We are recognizing revenue from this milestone payment over our estimated period of performance. Under Topic 605, this milestone payment was recognized in full in the third quarter of 2017, which was the period in which we achieved the milestone event.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event. For example, in the third quarter of 2018, we earned a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of IONIS-AZ4-2.5-L$_{Rx}$. Our revenue recognition of milestone payments we earn based on our partners' activities did not change as a result of adopting Topic 606.

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 third quarter of 2018, we earned a $12 million license fee when our majority-owned affiliate, Akcea, entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Our recognition of license fees did not change as a result of adopting Topic 606.

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 standalone 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 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our accounting treatment for our Bayer collaboration. Our allocation of the consideration we received for the Bayer amendment did not change as a result of adopting Topic 606. However, the method in which we are recognizing revenue related to our R&D services performance obligation did change. We are amortizing revenue related to our R&D services performance obligation using the input method under Topic 606.

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 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. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the 2018 strategic neurology collaboration with Biogen.

Results of Operations

Revenue

Whenever we refer to prior period results, they reflect the impact of Topic 606, which we adopted in the first quarter of 2018.

Total revenue for the three and nine months ended September 30, 2018 was $145.4 million and $407.6 million, respectively, compared to $118.3 million and $346.4 million for the same periods in 2017 and was comprised of the following (amounts in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Revenue:		(as revised)		(as revised)
Commercial revenue:				
SPINRAZA royalties	$ 70,010	$ 32,890	$ 167,743	$ 60,467
Licensing and other royalty revenue	12,746	1,727	14,232	5,639
Total commercial revenue	82,756	34,617	181,975	66,106
R&D revenue:				
Amortization from upfront payments	31,066	22,892	92,185	70,145
Milestone payments	26,194	56,409	44,583	135,129
License fees	1,649	424	64,227	64,942
Other services	3,730	3,972	24,589	10,065
Total R&D revenue	62,639	83,697	225,584	280,281
Total revenue	$ 145,395	$ 118,314	$ 407,559	$ 346,387

The increase in revenue in the first nine months of 2018 compared to the same period in 2017 was primarily due to increasing commercial revenue from SPINRAZA royalties, which increased over 175 percent. Our R&D revenue for the first nine months of 2018 was significant and demonstrates our ability to generate sustainable revenue from our numerous partnerships.

R&D revenue from the amortization of upfront payments increased $22.0 million in the first nine months of 2018, compared to the same period in 2017, primarily due to our 2018 strategic neurology collaboration with Biogen which started in the second quarter of 2018. In the fourth quarter of 2018, we will add amortization revenue from our new collaboration with Roche to develop IONIS-FB-L_{Rx}.

Our 2018 R&D revenue from milestone payments was bolstered by two $10 million milestone payments in the third quarter, one from Biogen and one from AstraZeneca. In the same period of 2017, R&D revenue from milestone payments included $90 million of milestone payments from Biogen for SPINRAZA approval in the EU and Japan. Already in the fourth quarter of 2018, we have earned nearly $30 million in milestone payments from AstraZeneca.

Operating Expenses

Operating expenses for the three and nine months ended September 30, 2018 were $164.0 million and $479.7 million, respectively, and increased compared to $107.0 million and $309.1 million for the same periods in 2017. Our operating expenses increased year over year principally due to higher SG&A expenses as we prepared to commercialize TEGSEDI and WAYLIVRA. Our SG&A expenses also increased year over year because of fees we owed under our in-licensing agreements related to SPINRAZA. As sales for SPINRAZA grow, our in-licensing expenses also increase but not at the same rate. We earn tiered royalties on annual SPINRAZA sales and pay nominal fixed third-party royalties that are not tiered. R&D expenses accounted for a smaller portion of the increase in operating expenses. R&D expenses for the first nine months of 2018 increased, compared to the same period in 2017 primarily due to increases in drug development costs related to several drugs including AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, as we, with Akcea, advanced these programs in development. These increases reflect the investment we are making in advancing and expanding our pipeline. In the fourth quarter of 2018, we expect our operating expenses to continue to increase primarily related to the commercialization of TEGSEDI.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Ionis Core	$ 65,512	$ 64,239	$ 213,114	$ 190,924
Akcea Therapeutics	71,518	21,321	182,188	109,071
Elimination of intercompany activity	(7,946)	(30)	(12,796)	(54,497)
Subtotal	129,084	85,530	382,506	245,498
Non-cash compensation expense related to equity awards	34,883	21,472	97,210	63,642
Total operating expenses	$ 163,967	$ 107,002	$ 479,716	$ 309,140

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

Research, Development and Patent Expenses

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Research, development and patent expenses	$ 76,475	$ 64,033	$ 243,455	$ 197,915
Non-cash compensation expense related to equity awards	18,780	16,181	57,698	48,443
Total research, development and patent expenses	$ 95,255	$ 80,214	$ 301,153	$ 246,358

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Ionis Core	$ 49,452	$ 48,776	$ 158,860	$ 157,363
Akcea Therapeutics	27,068	15,287	89,940	95,049
Elimination of intercompany activity	(45)	(30)	(5,345)	(54,497)
Subtotal	76,475	64,033	243,455	197,915
Non-cash compensation expense related to equity awards	18,780	16,181	57,698	48,443
Total research, development and patent expenses	$ 95,255	$ 80,214	$ 301,153	$ 246,358

For the three and nine months ended September 30, 2018, our total research, development and patent expenses were $76.5 million and $243.5 million, respectively, and increased compared to $64.0 million and $197.9 million for the same periods in 2017. The increase in our R&D expenses for the first nine months of 2018, compared to the same period in 2017 was driven primarily by increases in drug development costs related to several drugs including AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$, as we, with Akcea, advanced these programs in development. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

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

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipelines. Our antisense drug discovery expenses are part of our Ionis Core business segment.

The following table sets forth information on antisense drug discovery expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 14,475	$ 14,071	$ 41,970	$ 39,831
Non-cash compensation expense related to equity awards	4,379	3,935	13,204	11,644
Total antisense drug discovery expenses	$ 18,854	$ 18,006	$ 55,174	$ 51,475

Antisense drug discovery expenses for the three and nine months ended September 30, 2018 were $14.5 million and $42.0 million, respectively, compared to $14.1 million and $39.8 million for the same periods in 2017. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
SPINRAZA	$ —	$ —	$ —	$ 10,561
WAYLIVRA	3,469	4,401	15,919	14,603
TEGSEDI	3,373	4,230	14,404	16,340
Other antisense development projects	21,413	11,183	62,580	32,852
Development overhead expenses	17,648	13,796	55,286	36,635
Total antisense drug development, excluding non-cash compensation expense related to equity awards	45,903	33,610	148,189	110,991
Non-cash compensation expense related to equity awards	8,434	6,968	25,922	20,980
Total antisense drug development expenses	$ 54,337	$ 40,578	$ 174,111	$ 131,971

Antisense drug development expenses were $45.9 million and $148.2 million for the three and nine months ended September 30, 2018, respectively, and increased compared to $33.6 million and $111.0 million for the same periods in 2017. During the first nine months of 2018, our development expenses for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} increased compared to the same period in 2017. We completed enrollment of the Phase 2 clinical study of AKCEA-APO(a)-L_{Rx} during the first quarter of 2018 and reported positive Phase 2 data in the third quarter of 2018. We also initiated a Phase 2 clinical study of AKCEA-APOCIII-L_{Rx} in patients with hypertriglyceridemia and established cardiovascular disease in the first quarter of 2018. Slightly offsetting these increases were decreased expenses for SPINRAZA and TEGSEDI. Specifically, we have transitioned all further development of SPINRAZA to Biogen and we completed our Phase 3 TEGSEDI trial in patients with hATTR with polyneuropathy in 2017. 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 September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Ionis Core	$ 20,821	$ 20,521	$ 71,767	$ 74,655
Akcea Therapeutics	25,082	13,089	76,422	84,730
Elimination of intercompany activity	—	—	—	(48,394)
Subtotal	45,903	33,610	148,189	110,991
Non-cash compensation expense related to equity awards	8,434	6,968	25,922	20,980
Total antisense drug development expenses	$ 54,337	$ 40,578	$ 174,111	$ 131,971

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

Manufacturing and Operations

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 8,085	$ 9,167	$ 30,083	$ 26,260
Non-cash compensation expense related to equity awards	2,236	1,693	7,024	5,143
Total manufacturing and operations expenses	$ 10,321	$ 10,860	$ 37,107	$ 31,403

Manufacturing and operations expenses were $8.1 million and $30.1 million for the three and nine months ended September 30, 2018, respectively, compared to $9.2 million and $26.3 million for the same periods in 2017. Manufacturing and operations expenses increased for the first nine months of 2018. Since accounting rules require us to expense launch supplies prior to obtaining approval, the increase in manufacturing expenses was primarily from the manufacturing of commercial supply of TEGSEDI, prior to its approval in the EU in July 2018. 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 September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Ionis Core	$ 6,931	$ 7,743	$ 24,659	$ 23,575
Akcea Therapeutics	1,154	1,424	10,653	8,698
Elimination of intercompany activity	—	—	(5,229)	(6,013)
Subtotal	8,085	9,167	30,083	26,260
Non-cash compensation expense related to equity awards	2,236	1,693	7,024	5,143
Total manufacturing and operations expenses	$ 10,321	$ 10,860	$ 37,107	$ 31,403

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 September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Personnel costs	$ 3,259	$ 2,608	$ 9,456	$ 8,174
Occupancy	2,379	2,132	6,281	6,086
Patent expenses	513	465	1,745	1,459
Depreciation and amortization	115	51	315	175
Insurance	364	480	1,991	1,153
Other	1,382	1,449	3,425	3,786
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	8,012	7,185	23,213	20,833
Non-cash compensation expense related to equity awards	3,731	3,585	11,548	10,676
Total R&D support expenses	$ 11,743	$ 10,770	$ 34,761	$ 31,509

R&D support expenses for the three and nine months ended September 30, 2018 were $8.0 million and $23.2 million, respectively, and were slightly higher compared to $7.2 million and $20.8 million for the same periods in 2017. R&D support expenses increased slightly primarily related to costs associated with the expansion of our business. 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 September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Ionis Core	$ 7,225	$ 6,441	$ 20,464	$ 19,303
Akcea Therapeutics	832	774	2,865	1,620
Elimination of intercompany activity	(45)	(30)	(116)	(90)
Subtotal	8,012	7,185	23,213	20,833
Non-cash compensation expense related to equity awards	3,731	3,585	11,548	10,676
Total R&D support expenses	$ 11,743	$ 10,770	$ 34,761	$ 31,509

Selling, General and Administrative Expenses

Selling, general and administrative expenses include costs associated with the pre-commercialization and commercialization activities for our drugs and costs to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of pre-commercialization, commercialization, legal, human resources, investor relations, and finance. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above. We also include 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 September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 52,609	$ 21,497	$ 139,051	$ 47,583
Non-cash compensation expense related to equity awards	16,103	5,291	39,512	15,199
Total selling, general and administrative expenses	$ 68,712	$ 26,788	$ 178,563	$ 62,782

Selling, general and administrative expenses were $52.6 million and $139.1 million for the three and nine months ended September 30, 2018, respectively, and increased compared to $21.5 million and $47.6 million for the same periods in 2017. The increase in SG&A expenses was principally due to the cost of preparing to commercialize TEGSEDI and WAYLIVRA, and an increase in the fees we owed under our in-licensing agreements related to SPINRAZA. We project our expenses will increase as we launch TEGSEDI and continue to prepare to launch WAYLIVRA. 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 September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Ionis Core	$ 16,060	$ 15,463	$ 54,254	$ 33,561
Akcea Therapeutics	44,450	6,034	92,248	14,022
Elimination of intercompany activity	(7,901)	—	(7,451)	—
Subtotal	52,609	21,497	139,051	—
Non-cash compensation expense related to equity awards	16,103	5,291	39,512	15,199
Total selling, general and administrative expenses	$ 68,712	$ 26,788	$ 178,563	$ 62,782

Akcea Therapeutics, Inc.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Development and patent expenses	$ 27,068	$ 15,287	$ 89,940	$ 95,049
Selling, general and administrative expenses	44,450	6,034	92,248	14,022
Total operating expenses, excluding non-cash compensation expense related to equity awards	71,518	21,321	182,188	109,071
Non-cash compensation expense related to equity awards	12,731	4,692	31,240	11,814
Total Akcea Therapeutics operating expenses	$ 84,249	$ 26,013	$ 213,428	$ 120,885

Operating expenses for Akcea were $71.5 million and $182.2 million for the three and nine months ended September 30, 2018, respectively, and increased compared to $21.3 million and $109.1 million for the same periods in 2017.

In the first nine months of 2017, $48.4 million of development and patent expenses was for one-time sublicensing expenses related to the Novartis collaboration recorded in the first quarter of 2017. $33.4 million of these expenses were non-cash and the remaining $15 million was paid to us. Excluding the $48.4 million of one-time expenses, Akcea's development and patent expenses increased $43.3 million in the nine months of 2018 compared to the same period in 2017 as Akcea made investments in advancing its pipeline, including AKCEA-APO(a)-LRx, and AKCEA-APOCIII-LRx.

For each period presented, we allocated a portion of Ionis' R&D support expenses, which are included in development and patent expenses in the table above, to Akcea for work we performed on behalf of Akcea.

Akcea's SG&A expenses increased in the first nine months of 2018 compared to the same period in 2017, primarily due to Akcea continuing to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch TEGSEDI and WAYLIVRA. For each period presented, we allocated a portion of Ionis' G&A expenses, which were included in Akcea's G&A expenses in the table above, to Akcea for work we performed on Akcea's behalf.

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

Investment Income

Investment income for the three and nine months ended September 30, 2018 was $10.0 million and $18.7 million, respectively, compared to $2.8 million and $7.5 million for the same periods in 2017. The increase in investment income was primarily due to our significantly higher average cash balance and an improvement in the market conditions during the first nine months of 2018 compared to the same period in 2017.

Interest Expense

Interest expense for the three and nine months ended September 30, 2018 was $11.3 million and $33.3 million, respectively, compared to $10.8 million and $34.0 million for the same periods in 2017.

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent notes, non-cash interest expense related to the long-term financing liability, which was replaced by mortgage debt for our primarily R&D and manufacturing facilities beginning in July 2017 and other miscellaneous debt.

In July 2017, we purchased the building that houses our primary R&D facility and the building that houses our manufacturing facility for $79.4 million and $14.0 million, respectively. As a result of the purchase of our primary R&D facility, we extinguished the financing liability we had previously recorded on our balance sheet. We financed the purchase of the buildings with mortgage debt of $51.3 million with an interest rate of 3.88 percent for our primary R&D facility and mortgage debt of $9.1 million with an interest rate of 4.2 percent for our manufacturing facility. Both mortgages mature in August 2027. The non-cash interest expense for our long-term financing liability was replaced with lower mortgage interest expense.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Convertible notes:				
Non-cash amortization of the debt discount and debt issuance costs	$ 8,856	$ 8,208	$ 26,072	$ 24,165
Interest expense payable in cash	1,714	1,714	5,141	5,373
Non-cash interest expense for long-term financing liability	—	308	—	3,660
Interest on mortgage for primary R&D and manufacturing facilities	607	505	1,802	505
Other	105	90	317	263
Total interest expense	$ 11,282	$ 10,825	$ 33,332	$ 33,966

Net Loss

We had a net loss of $20.4 million and $87.7 million for the three and nine months ended September 30, 2018, respectively, compared to $7.5 million and $1.6 million for the same periods in 2017. In 2018, the increase in our net loss was primarily due to increased operating expenses as we prepared to commercialize TEGSEDI and WAYLIVRA.

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

Prior to Akcea's initial public offering, or 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 and third 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. We reflected the increase in our ownership in these financial statements. Our noncontrolling interest in Akcea for the three and nine months ended September 30, 2018 was $15.8 million and $41.4 million, respectively, compared to $4.9 million for each of the same periods in 2017. We also have a corresponding account on our consolidated balance sheet called "Noncontrolling interest in Akcea Therapeutics, Inc." The net loss attributable to noncontrolling interest in Akcea increased during the first nine months of 2018 because we owned between approximately 68 percent and 75 percent during the entire period, compared to the first nine months of 2017 when we owned 100 percent of Akcea until its IPO in July 2017. Akcea's increased net loss also contributed to the year-over-year increase in net loss attributable to noncontrolling interest.

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

We had a net loss attributable to our common stockholders' of $4.6 million for the three months ended September 30, 2018, compared to $2.6 million for the same period in 2017. For the nine months ended September 30, 2018 we reported a net loss attributable to our common stockholders of $46.3 million, compared to net income attributable to our common stockholders of $3.3 million for the same period in 2017.

For the three months ended September 30, 2018, basic and diluted net loss per share were $0.03, compared to $0.02 for the same period in 2017. For the nine months ended September 30, 2018, basic and diluted net loss per share were $0.33, compared to basic and diluted net income per share of $0.51 and $0.13 for the same periods in 2017, respectively.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Beginning in December 2016 we added commercial revenue from SPINRAZA royalties. From our inception through September 30, 2018, we have earned approximately $3.0 billion in revenue. We have 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 September 30, 2018, we have raised net proceeds of approximately $1.7 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 September 30, 2018, we had cash, cash equivalents and short-term investments of $2.0 billion and stockholders' equity of $840.1 million. In comparison, we had cash, cash equivalents and short-term investments of $1.0 billion and stockholders' equity of $365.3 million at December 31, 2017. Our cash, cash equivalents and short-term investments increased in the first nine months of 2018 primarily from the $1 billion payment we received from Biogen for our 2018 strategic neurology collaboration.

At September 30, 2018, we had consolidated working capital of $1.8 billion compared to $925.1 million at December 31, 2017. As of September 30, 2018, our debt and other obligations totaled $764.9 million compared to $759.7 million at December 31, 2017.

The following table summarizes our contractual obligations as of September 30, 2018. 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)	$ 709.4	$ 6.9	$ 13.7	$ 688.8	$ —
Building mortgage payments	$ 81.4	$ 2.4	$ 4.8	$ 5.9	$ 68.3
Financing arrangements (principal and interest payable)	$ 12.8	$ 12.8	$ —	$ —	$ —
Other obligations (principal and interest payable)	$ 1.1	$ 0.1	$ 0.1	$ 0.1	$ 0.8
Operating leases	$ 26.6	$ 3.1	$ 5.9	$ 5.2	$ 12.4
Total	$ 831.3	$ 25.3	$ 24.5	$ 700.0	$ 81.5

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 September 30, 2018, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At September 30, 2018, we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

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

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

Financing Arrangements

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

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

Additionally, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of September 30, 2018 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 and the building that houses our manufacturing facility for $79.4 million and $14.0 million, respectively. 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 September 30, 2018 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 September 30, 2018. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2018.

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 implemented internal controls to ensure we adequately evaluated our contracts and properly assessed the impact of the new revenue recognition accounting guidance we adopted on January 1, 2018 reflected in our financial statements. 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 significant 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

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, which are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead asked the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents infringes those patents, and requesting monetary damages to compensate for such infringement. In the trial for this case held in March 2016, the jury upheld all ten of the asserted claims of the patents-in-suit. The jury then decided that we and Merck are entitled to four percent of $5 billion in past sales of sofosbuvir. Gilead stated it would appeal the jury's finding of validity. In the meantime, Gilead asserted two additional non-jury defenses: waiver and unclean hands. Although the judge rejected the waiver defense, she granted Gilead's motion claiming that the patents are unenforceable against it under the doctrine of unclean hands. We believe this ruling is contrary to the relevant law and the facts of the case. Accordingly, in July 2016, together with Merck we appealed the decision to the Court of Appeals for the Federal Circuit. Gilead cross-appealed on the issue of validity. In April 2018, the Court of Appeals issued its ruling affirming the District Court's finding of unenforceability based on unclean hands. Having upheld the ruling that the patents are unenforceable against Gilead, the court did not reach the question of validity. In September 2018, we requested a hearing before the Supreme Court. In that request, we asserted that it was improper for the trial court to overturn the jury verdict on a matter of law on the basis of the equitable defense of unclean hands. Gilead will file its reply brief in the fourth quarter of 2018 and we expect to be notified in 2019 whether the Court will hear our case. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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, 2017.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

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

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

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

The degree of market acceptance for our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, depends upon a number of factors, including the:

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

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

For example, the product label for TEGSEDI in the United States 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. Therefore, we expect the product label for WAYLIVRA will require periodic blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these drugs. 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 and Akcea plan to have greater involvement with physicians and patients, if we and Akcea 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 drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, will not contribute significant revenues.

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

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

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

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

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 drugs, 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, AVXS-101, RG7916, and LMI070 could compete with SPINRAZA and metreleptin and Gemcabene could compete with WAYLIVRA; patisiran, tafamadis, diflunisal, tolcapone, PRX004 and ALN-TTRsc02 could compete with TEGSEDI. For example, patisiran is approved in the United States and Europe for a similar indication as TEGSEDI.

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

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

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 United States, TEGSEDI’s label contains a boxed warning for thrombocytopenia and glomerulonephritis,
- TEGSEDI requires periodic blood and urine monitoring, and
- in the United States 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. 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, WAYLIVRA and TEGSEDI.

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, we may not generate product revenue from TEGSEDI.

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 in the initial indications Akcea plans to pursue, Akcea will need to optimize and maintain a specialty sales force in each global region it expects to market TEGSEDI, 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 delay or preclude TEGSEDI's launch. 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 has incurred expenses prior to the launch of TEGSEDI to integrate and manage the marketing and sales infrastructure. If regulatory requirements or other factors cause the commercial launch of TEGSEDI to be less successful than expected, Akcea would incur expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI. Akcea's sales force and marketing teams may not successfully commercialize TEGSEDI.

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

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 drugs, 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 United States who would fit within our target patient populations for our drugs have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our drugs affordable.

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

If Biogen cannot manufacture finished drug product for SPINRAZA or the post-launch supply of the active drug substance for SPINRAZA, SPINRAZA may not 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 drugs, including WAYLIVRA, and additional approvals for SPINRAZA and TEGSEDI, we or our partners cannot sell them in the applicable markets.*

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

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our drugs. It is possible that regulatory agencies will not approve our drugs including, WAYLIVRA for marketing or additional marketing authorizations for SPINRAZA or TEGSEDI. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, Akcea received a complete response letter, or CRL, from the FDA and a preliminary notification of a 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. The regulatory authorities in Europe could have a similar response to the marketing authorization application pending in Europe.

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

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

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

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

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

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

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;

- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- 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 drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

In addition, our current drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, are chemically similar to each other. As a result, a safety observation we encounter with one of our drugs could have, or be perceived by a regulatory authority to have, an impact on a different drug we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our drugs or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our drugs: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. Similarly, we have an ongoing Phase 3 study of 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 drug. 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, could reduce the commercial potential or viability of our drugs.

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

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

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

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

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

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 September 30, 2018, we had an accumulated deficit of approximately $1.3 billion and stockholders' equity of approximately $840.1 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our 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. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

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

As described above, we have incurred net losses. 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.

As of December 31, 2017, we had federal and California net operating loss carryforwards of approximately $561.1 million and $887.1 million, respectively. The federal net operating loss carryforwards will begin to expire, if not utilized, beginning in 2024. These net operating loss carryforwards could expire unused and be unavailable to offset future income tax liabilities. 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. It is possible that we have experienced an ownership change limitation. 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 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 drugs. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

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

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. 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 drugs.

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

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

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

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

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for, 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, WAYLIVRA and TEGSEDI, the price of our securities could decrease.

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

Our success depends to a significant degree upon whether we can continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other 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 United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business. For example, in November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court for the Northern District of California. Intellectual property lawsuits may be costly and may not be resolved in our favor.

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

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of September 30, 2018, we had cash, cash equivalents and short-term investments equal to approximately $2.0 billion. If we do not meet our goals to successfully commercialize our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- successful commercialization for SPINRAZA and TEGSEDI;
- marketing approvals for WAYLIVRA;
- the profile and launch timing of our drugs, including WAYLIVRA and TEGSEDI;
- 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 drugs.

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding September 30, 2018, the market price of our common stock ranged from $39.07 to $65.51 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, marketing authorization, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to SPINRAZA, WAYLIVRA and TEGSEDI. 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. We manufacture the finished drug product for WAYLIVRA and TEGSEDI at third-party contract manufacturers.

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

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we and our contract manufacturers use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities 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.

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

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

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

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

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

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

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

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

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

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

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

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

The comprehensive tax reform bill could adversely affect our business and financial condition.

The Tax Act significantly revises the Internal Revenue Code of 1986, as amended. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35 percent to a flat rate of 21 percent, limitation of the tax deduction for interest expense to 30 percent of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80 percent of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

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.

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	Second Amendment to Research Collaboration, Option and License Agreement of December 22, 2014, by and between Ionis Pharmaceuticals, Inc. and Janssen Biotech Inc. Portions of this exhibit have been omitted and separately filed with the SEC.
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 September 30, 2018, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

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

SIGNATURES

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 6, 2018
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	November 6, 2018

Exhibit 10.1

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

August 7th, 2018

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

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

Re: *Second Amendment to Research Collaboration, Option and License Agreement of December 22, 2014*

Dear Madame or Sir:

Reference is made to the Research Collaboration, Option and License Agreement of December 22, 2014 (the "***Agreement***"), by and between Janssen Biotech Inc. ("***JBI***"), and Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.; hereinafter "***Ionis***"), or individually as "***Party***" or collectively as "***Parties***." Reference is also made to the First Amendment of December 21, 2016 ("***First Amendment***") between JBI and Ionis. This document is a "***Second Amendment***" to the Agreement and the "***Second Amendment Effective Date***" shall be the date of the last signature below.

In general, the Parties agreed to modify the Agreement to reflect alignment on the terms and conditions which will enable JBI to expand the JBI [***] Field to include the [***] delivery of the JBI [***] Development Candidate.

To effectuate the agreed upon changes, the Parties agree to the provisions described herein. Defined terms used but not defined herein have the meaning ascribed to such terms in the Agreement.

Agreement Provisions

Confirmation – Section 3.1 – JBI has exercised its Option for the [***] Development Candidate (IONIS-[***]) and has paid the License Fee under Section 6.4.

Amendment of Section 4.1.6 – The Parties agree that Section 4.1.6 of the Agreement which was added in the First Amendment is hereby deleted in its entirety and replaced with the following:

> **[***] Administration of JBI [***] Development Candidate**. The Parties acknowledge that JBI has elected to expand the JBI [***] Field to include the [***] delivery of the JBI [***] Development Candidate for the treatment of diseases of the gastrointestinal tract ("***Expanded GI Field***") by providing the JRC written notice of such [***] election.
>
> In order for JBI to retain its right to develop the JBI [***] Development Candidate in the Expanded GI Field, JBI shall pay an expansion fee of $[***] ("***Expansion Fee***") to Ionis upon JBI's decision to progress the JBI [***] Development Candidate to a [***] [***] with [***] delivery. In the event that Janssen makes the decision to discontinue the development of any and all [***] formulations of the JBI [***] Development Candidate prior to a [***] with [***] delivery, JBI shall pay the expansion fee to Ionis upon the later of (1) [***] and (2) [***]. If JBI has not paid Ionis the Expansion Fee in accordance with this section 4.1.6 by the start of the [***], then JBI's right to develop the JBI [***] Development Candidate in the Expanded GI Field will expire. JBI and Ionis will negotiate commercially reasonable terms for managing the continued Development and Commercialization of IONIS-[***] in the Expanded GI Field in accordance with Section 5.7.
>
> If JBI progresses a JBI [***] Development Candidate in the Expanded GI Field, all other provisions of the Agreement shall apply to the Expanded GI Field and, if applicable, Net Sales from [***] delivered and a [***] delivered JBI [***] Development Candidate will be aggregated when calculating payments due under the Agreement royalty tiers.

Amendment of Section 5.7 - The Parties agree that Section 5.7 which was added in the First Amendment is hereby deleted in its entirety and replaced with the following:

> **Development and Commercialization Cooperation.** The Parties will convene to negotiate commercially reasonable terms for managing the continued Development and Commercialization of IONIS-[***] by both Parties, including procedures for the mutual exchange of [***] and [***] information associated with IONIS-[***] no later than [***] days following the later of (1) [***] or (2) [***].

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

Very truly yours,

/s/ Catherine Owen
Catherine Owen

President, JBI Biotech, Inc.

AGREED & ACCEPTED:

/s/ Brett Monia
Name: Brett Monia
Title: Chief Operating Officer
Date: August 13, 2018

Ionis Pharmaceuticals, Inc.

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: November 6, 2018

/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: November 6, 2018

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

Exhibit 32.1

CERTIFICATION

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

1. The Company's Quarterly Report on Form 10-Q for the period ended September 30, 2018, 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: November 6, 2018

/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.