UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 2020

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 000-19125

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

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.

Large Accelerated Filer ☒	Accelerated Filer ☐
Non-accelerated Filer ☐	Smaller Reporting Company ☐ Emerging Growth Company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange 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 July 29, 2020 was 139,697,030.

IONIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

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)

	June 30, 2020 (Unaudited)	December 31, 2019
ASSETS		
Current assets:		
Cash and cash equivalents	$ 530,181	$ 683,287
Short-term investments	1,818,435	1,816,257
Contracts receivable	27,834	63,034
Inventories	23,722	18,180
Other current assets	131,015	139,839
Total current assets	2,531,187	2,720,597
Property, plant and equipment, net	172,618	153,651
Patents, net	27,700	25,674
Long-term deferred tax assets	305,980	305,557
Deposits and other assets	41,465	27,633
Total assets	$ 3,078,950	$ 3,233,112
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 7,407	$ 16,067
Accrued compensation	22,822	37,357
Accrued liabilities	67,802	66,769
Income taxes payable	27,943	32,514
Current portion of long-term obligations and other current liabilities	4,966	2,026
Current portion of deferred contract revenue	100,401	118,272
Total current liabilities	231,341	273,005
Long-term deferred contract revenue	448,576	490,060
0.125 percent convertible senior notes	445,150	434,711
1 percent convertible senior notes	284,083	275,333
Long-term obligations, less current portion	15,057	15,543
Long-term mortgage debt	59,948	59,913
Total liabilities	1,484,155	1,548,565
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 139,489,405 and 140,339,615 shares issued and outstanding at June 30, 2020 (unaudited) and December 31, 2019, respectively	139	140
Additional paid-in capital	2,271,630	2,203,778
Accumulated other comprehensive loss	(16,440)	(25,290)
Accumulated deficit	(878,154)	(707,534)
Total Ionis stockholders' equity	1,377,175	1,471,094
Noncontrolling interest in Akcea Therapeutics, Inc.	217,620	213,453
Total stockholders' equity	1,594,795	1,684,547
Total liabilities and stockholders' equity	$ 3,078,950	$ 3,233,112

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	**2019**	**2020**	**2019**
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 71,746	$ 70,502	$ 137,754	$ 130,212
Product sales, net	16,364	9,865	31,523	16,619
Licensing and other royalty revenue	1,624	7,932	4,419	9,555
Total commercial revenue	89,734	88,299	173,696	156,386
Research and development revenue under collaborative agreements	55,803	75,514	105,209	304,640
Total revenue	145,537	163,813	278,905	461,026
Expenses:				
Cost of products sold	3,012	1,364	5,561	2,406
Research, development and patent	122,264	106,165	239,214	212,582
Selling, general and administrative	72,015	75,111	147,009	143,332
Total operating expenses	197,291	182,640	391,784	358,320
Income (loss) from operations	(51,754)	(18,827)	(112,879)	102,706
Other income (expense):				
Investment income	9,243	13,735	19,459	25,880
Interest expense	(11,173)	(11,802)	(22,163)	(23,402)
Gain on investments	9,625	—	9,887	—
Other income (expenses)	(149)	(45)	(249)	(192)
Income (loss) before income tax (expense) benefit	(44,208)	(16,939)	(105,945)	104,992
Income tax (expense) benefit	439	6,927	3,696	(24,119)
Net income (loss)	(43,769)	(10,012)	(102,249)	80,873
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	11,924	9,136	22,178	2,694
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (31,845)	$ (876)	$ (80,071)	$ 83,567
Basic net income (loss) per share	$ (0.23)	$ (0.01)	$ (0.58)	$ 0.62
Shares used in computing basic net income (loss) per share	139,352	140,247	139,391	139,419
Diluted net income (loss) per share	$ (0.23)	$ (0.01)	$ (0.58)	$ 0.61
Shares used in computing diluted net income (loss) per share	139,352	140,247	139,391	142,499

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	**2019**	**2020**	**2019**
Net income (loss)	$ (43,769)	$ (10,012)	$ (102,249)	$ 80,873
Unrealized gains on debt securities, net of tax	11,204	3,452	9,251	7,775
Currency translation adjustment	74	(96)	82	(11)
Comprehensive income (loss)	(32,491)	(6,656)	(92,916)	88,637
Comprehensive loss attributable to noncontrolling interests	(11,441)	(9,136)	(21,695)	(2,696)
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. stockholders	$ (21,050)	$ 2,480	$ (71,221)	$ 91,333

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Three Months Ended June 30, 2019 and 2020
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at March 31, 2019	139,624	$ 140	$ 2,117,969	$ (27,608)	$ (882,850)	$ 1,207,651	$ 179,769	$ 1,387,420
Net loss	—	—	—	—	(876)	(876)	—	(876)
Change in unrealized gains, net of tax	—	—	—	3,452	—	3,452	—	3,452
Foreign currency translation	—	—	—	(96)	—	(96)	—	(96)
Issuance of common stock in connection with employee stock plans	774	—	34,943	—	—	34,943	—	34,943
Stock-based compensation expense	—	—	41,933	—	—	41,933	—	41,933
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(5)	—	(438)	—	—	(438)	—	(438)
Noncontrolling interest in Akcea Therapeutics, Inc	—	—	(17,185)	—	—	(17,185)	8,049	(9,136)
Balance at June 30, 2019	140,393	$ 140	$ 2,177,222	$ (24,252)	$ (883,726)	$ 1,269,384	$ 187,818	$ 1,457,202
Balance at March 31, 2020	139,282	$ 139	$ 2,233,644	$ (27,235)	$ (846,309)	$ 1,360,239	$ 210,172	$ 1,570,411
Net loss	—	—	—	—	(31,845)	(31,845)	—	(31,845)
Change in unrealized gains, net of tax	—	—	—	11,204	—	11,204	—	11,204
Foreign currency translation	—	—	—	74	—	74	—	74
Issuance of common stock in connection with employee stock plans	214	—	8,800	—	—	8,800	—	8,800
Stock-based compensation expense	—	—	48,442	—	—	48,442	—	48,442
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(7)	—	(367)	—	—	(367)	—	(367)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(18,889)	(483)	—	(19,372)	7,448	(11,924)
Balance at June 30, 2020	139,489	$ 139	$ 2,271,630	$ (16,440)	$ (878,154)	$ 1,377,175	$ 217,620	$ 1,594,795

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Six Months Ended June 30, 2019 and 2020
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2018	137,929	$ 138	$ 2,047,250	$ (32,016)	$ (967,293)	$ 1,048,079	$ 139,081	$ 1,187,160
Net income	—	—	—	—	83,567	83,567	—	83,567
Change in unrealized gains, net of tax	—	—	—	7,775	—	7,775	—	7,775
Foreign currency translation	—	—	—	(11)	—	(11)	—	(11)
Issuance of common stock in connection with employee stock plans	2,600	2	102,002	—	—	102,004	—	102,004
Stock-based compensation expense	—	—	87,437	—	—	87,437	—	87,437
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(136)	—	(8,034)	—	—	(8,034)	—	(8,034)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(51,433)	—	—	(51,433)	48,737	(2,696)
Balance at June 30, 2019	140,393	$ 140	$ 2,177,222	$ (24,252)	$ (883,726)	$ 1,269,384	$ 187,818	$ 1,457,202
Balance at December 31, 2019	140,340	$ 140	$ 2,203,778	$ (25,290)	$ (707,534)	$ 1,471,094	$ 213,453	$ 1,684,547
Net loss	—	—	—	—	(80,071)	(80,071)	—	(80,071)
Change in unrealized gains, net of tax	—	—	—	9,251	—	9,251	—	9,251
Foreign currency translation	—	—	—	82	—	82	—	82
Issuance of common stock in connection with employee stock plans	821	—	16,451	—	—	16,451	—	16,451
Repurchases and retirements of common stock	(1,478)	(1)	—	—	(90,549)	(90,550)	—	(90,550)
Stock-based compensation expense	—	—	89,233	—	—	89,233	—	89,233
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(194)	—	(11,970)	—	—	(11,970)	—	(11,970)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(25,862)	(483)	—	(26,345)	4,167	(22,178)
Balance at June 30, 2020	139,489	$ 139	$ 2,271,630	$ (16,440)	$ (878,154)	$ 1,377,175	$ 217,620	$ 1,594,795

See accompanying notes.

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

	Six Months Ended June 30,	
	2020	**2019**
Operating activities:		
Net income (loss)	$ (102,249)	$ 80,873
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:		
Depreciation	6,360	6,253
Amortization of right-of-use operating lease assets	784	1,035
Amortization of patents	999	948
Amortization of premium (discount) on investments, net	3,842	(5,163)
Amortization of debt issuance costs	1,236	957
Amortization of convertible senior notes discount	17,807	17,661
Stock-based compensation expense	89,233	87,437
Gain on investments	(9,887)	—
Non-cash losses related to patents, licensing and property, plant and equipment and investments	211	203
Provision for deferred income taxes	(2,513)	14,436
Changes in operating assets and liabilities:		
Contracts receivable	35,200	(16,255)
Inventories	(3,018)	(5,736)
Other current and long-term assets	1,064	(6,372)
Accounts payable	(14,939)	(16,104)
Accrued compensation	(14,535)	(9,219)
Other current liabilities	(1,968)	3,283
Deferred contract revenue	(59,355)	(73,643)
Net cash provided by (used in) operating activities	(51,728)	80,594
Investing activities:		
Purchases of short-term investments	(976,284)	(1,049,274)
Proceeds from sale of short-term investments	982,173	877,966
Purchases of property, plant and equipment	(18,178)	(7,243)
Acquisition of licenses and other assets, net	(3,023)	(2,310)
Net cash used in investing activities	(15,312)	(180,861)
Financing activities:		
Proceeds from issuance of equity, net	16,453	102,004
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(11,971)	(8,034)
Repurchases and retirements of common stock	(90,548)	—
Net cash provided by (used in) financing activities	(86,066)	93,970
Net increase in cash and cash equivalents	(153,106)	(6,297)
Cash and cash equivalents at beginning of period	683,287	278,820
Cash and cash equivalents at end of period	$ 530,181	$ 272,523
Supplemental disclosures of cash flow information:		
Interest paid	$ 3,093	$ 4,776
Income taxes paid	$ 49	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Right-of-use assets obtained in exchange for lease liabilities	$ —	$ 13,920
Amounts accrued for capital and patent expenditures	$ 6,461	$ 3,073

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and six months ended June 30, 2020 and 2019 on the same basis as the audited financial statements for the year ended December 31, 2019. 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. Our operating results for the interim periods may not be indicative of what our operating results will be 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, 2019 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In the condensed consolidated financial statements, we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our majority-owned affiliate, Akcea Therapeutics, Inc. and its wholly owned subsidiaries. We formed Akcea in December 2014. In July 2017, Akcea completed an initial public offering, or IPO. Since Akcea's IPO, our ownership has ranged from 68 percent to 77 percent. At June 30, 2020, our ownership of Akcea was approximately 76 percent. We reflect changes in our ownership of Akcea in our financial statements in the period the change occurs. For example, we reflected an increase in our ownership when we received 6.9 million shares of Akcea common stock as payment for the sublicense fee Akcea owed us for Pfizer's license of vupanorsen (formerly AKCEA-ANGPTL3-L_{Rx}) in the fourth quarter of 2019.

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

2. Significant Accounting Policies

Revenue Recognition

Our Revenue Sources

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our 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 will also recognize as commercial revenue sales milestone payments and royalties we earn in the future under our partnerships.

Commercial Revenue: Product sales, net

We added product sales from TEGSEDI to our commercial revenue in the fourth quarter of 2018 and we added product sales from WAYLIVRA to our commercial revenue in the third quarter of 2019. In the U.S., we distribute TEGSEDI through an exclusive distribution agreement with a third-party logistics company, or 3PL, that takes title to TEGSEDI. The 3PL is our sole customer in the U.S. The 3PL then distributes TEGSEDI to a specialty pharmacy and a specialty distributor, which we collectively refer to as wholesalers, who then distribute TEGSEDI to health care providers and patients. In Europe, prior to the third quarter of 2019 we distributed TEGSEDI through a non-exclusive distribution model with a 3PL that took title to TEGSEDI. The 3PL was our sole customer in Europe. The 3PL in Europe then distributed TEGSEDI to hospitals and pharmacies. In the third quarter of 2019, we began using distributors to sell both TEGSEDI and WAYLIVRA directly to hospitals and pharmacies in Europe.

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.

In Note 6, *Collaborative Arrangements and Licensing Agreements*, we have included our collaborations with substantive changes during the first half of 2020 from those included in Note 6 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019.

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

First we 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 of the consideration is probable.

2. Identify the performance obligations

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

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

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

3. Determine the transaction price

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

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and are usually based on scientific progress. For example, in the first quarter of 2020, we earned a $10 million milestone payment from AstraZeneca when AstraZeneca advanced ION532 targeting APOL1 for the treatment of kidney disease under our cardiovascular, renal and metabolic diseases collaboration. We did not consider the milestone payment probable until AstraZeneca achieved the milestone event because advancing ION532 was a contingent event that was not within our control. We recognized the milestone payment in full in the period the milestone event was achieved because we did not have any remaining performance obligations related to the milestone payment.

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

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 we may receive from future product sales;
- Estimated contractual milestone payments we may receive;
- 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.

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. For example, in the third quarter of 2019, we updated our estimate of the total effort we expected to expend to satisfy our performance obligation under our 2013 Strategic Neurology collaboration with Biogen. As of September 30, 2019, we had completed a significant portion of the research and development services. In this example, we expected to complete the remainder of our services in 2020. As a result of our change in estimate, in the third quarter of 2019, we recorded a cumulative catch up adjustment of $16.5 million to decrease revenue. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019 for further discussion of the cumulative catch up adjustment we made in 2019.

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, including royalties from SPINRAZA sales, in the period in which the counterparty sells the related product and recognizes the related revenue, which in certain cases may require us to estimate our royalty revenue.

Commercial Revenue: Product sales, net

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

Reserves for Product sales

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

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

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

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

Managed care rebates: We are subject to rebates in connection with value-based agreements with certain of our commercial payers. We record these rebates as an accrual on our condensed consolidated balance sheet in the same period we recognize the related revenue. We estimate our managed care rebates based on our estimated payer mix and the applicable contractual rebate rate.

Trade discounts: We provide customary invoice discounts on product sales to our U.S. customer for prompt payment. We record this discount as a reduction of product sales in the period in which we recognize the related product revenue.

Distribution services: We receive and pay for various distribution services from our U.S. and EU customers and wholesalers in the U.S.. We classify the costs for services we receive that are either not distinct from the sale of the product or for which we cannot reasonably estimate the fair value as a reduction of product sales. To the extent that the services we receive are distinct from the sale of the product, we classify the costs for such services as SG&A expenses.

Product returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the product's expiration date. We estimate the amount of product sales that our customer may return. We record our return estimate as an accrued refund liability on our condensed consolidated balance sheet with a corresponding offset reducing our product sales in the same period we recognize the related sale. Based on our distribution model for product sales, contractual inventory limits with our customer and wholesalers and the price of the product, we have had minimal returns to date and we believe we will continue to have minimal returns. Our EU customers generally only take title to the product after they receive an order from a hospital or pharmacy and therefore they do not maintain excess inventory levels of our products. Accordingly, we have limited return risk in the EU and we do not estimate returns in the EU.

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

Research and development revenue under collaboration agreements:

Upfront payments

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

Milestone payments

We are required to include additional consideration in the transaction price when it is probable. We typically include milestone payments for R&D services in the transaction price when they are achieved. We include these milestone payments when they are achieved because there is considerable uncertainty in the research and development processes that trigger these payments. Similarly, we include approval milestone payments in the transaction price once the medicine is approved by the applicable regulatory agency. We will recognize sales-based milestone payments in the period in which 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 first quarter of 2020, we achieved a $7.5 million milestone payment from Biogen when we advanced IONIS-$MAPT_{Rx}$ under our 2012 neurology collaboration. We added this payment to the transaction price and allocated it to our R&D services performance obligation for IONIS-$MAPT_{Rx}$. We are recognizing revenue related to this milestone payment over our estimated period of performance.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation. For example, in the first quarter of 2020, we recognized a $10 million milestone payment when AstraZeneca advanced ION532 targeting APOL1 for the treatment of kidney disease under our cardiovascular, renal and metabolic diseases collaboration agreement. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized the milestone payment in full in the first quarter of 2020.

License fees

We generally recognize as revenue the total amount we determine to be the relative 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 second quarter of 2020, we earned a $13 million license fee from AstraZeneca when AstraZeneca licensed ION736, a medicine targeting FOXP3 to treat cancer.

Sublicense fees

We recognize sublicense fee revenue in the period in which a party, who has already licensed our technology, further licenses the technology to another party because we do not have any performance obligations related to the sublicense. For example, in the second quarter of 2019, we earned a $20 million sublicense fee when Alnylam Pharmaceuticals sublicensed our technology to Regeneron Pharmaceuticals.

Amendments to Agreements

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

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

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

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. As part of the 2017 amendment, Bayer paid us $75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, to provide R&D services and to deliver API. We allocated the $75 million transaction price to these performance obligations. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019 for further discussion of the Bayer collaboration.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same partner. We evaluate such agreements to determine whether we should account for them individually as distinct arrangements or whether the separate agreements should be combined and accounted for together. We evaluate the following to determine the accounting for the agreements:

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

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

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

Contracts Receivable

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

Unbilled SPINRAZA Royalties

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

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our condensed consolidated balance sheet. During the three months ended June 30, 2020 and 2019, we recognized $39.6 million and $46.9 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. During the six months ended June 30, 2020 and 2019, we recognized $61.9 million and $87.2 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Products Sold

Our cost of products sold includes manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of our products. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of products sold. Prior to obtaining regulatory approval of TEGSEDI in July 2018 and WAYLIVRA in May 2019, we expensed as research and development expenses a significant portion of the costs we incurred to produce the initial commercial launch supply for each medicine.

Noncontrolling Interest in Akcea Therapeutics, Inc.

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. Since Akcea's IPO, our ownership has ranged from 68 percent to 77 percent. At June 30, 2020, our ownership of Akcea was approximately 76 percent. We reflect changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the change occurs. During 2019, we received the following additional shares of Akcea common stock:

- 2.8 million shares in the first quarter of 2019 as payment for the sublicense fee Akcea owed us for Novartis's license of AKCEA-APO(a)-L_{Rx}, and
- 6.9 million shares in the fourth quarter of 2019 as payment for the sublicense fee Akcea owed us for Pfizer's license of vupanorsen.

The shares third parties own represent an interest in Akcea's equity that we do control. However, as we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our condensed consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our condensed consolidated balance sheet. In addition, we record a noncontrolling interest adjustment to account for the stock options Akcea grants, which if exercised, will dilute our ownership in Akcea. This adjustment is a reclassification within stockholders' equity from additional paid-in capital to noncontrolling interest in Akcea equal to the amount of stock-based compensation expense Akcea had recognized.

Cash, Cash Equivalents and Investments

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

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At June 30, 2020, we held equity investments in two publicly held companies, ProQR Therapeutics N.V., or ProQR, and Antisense Therapeutics Limited, or ATL. We also held equity investments in five privately-held companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd.

We are required to measure and record our equity investments at fair value and to recognize the changes in fair value in our condensed consolidated statement of operations. 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. For example, during the second quarter of 2020, we revalued our investments in two privately-held companies, Dynacure and Ribo because the companies sold additional equity securities that were similar to those we own. These observable price changes resulted in us recognizing a $6.3 million gain on our investment in Dynacure and a $3 million gain on our investment in Ribo in our condensed consolidated statement of operations during the three months ended June 30, 2020.

Inventory Valuation

We reflect our inventory on our condensed consolidated balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We capitalize the costs of raw materials that we purchase for use in producing our medicines because until we use these raw materials, they have alternative future uses, which we refer to as clinical raw materials. We include in inventory raw material costs for medicines that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single medicine. For example, if one of our medicines failed, we could use the raw materials for that medicine to manufacture our other medicines. We expense these costs as R&D expenses when we begin to manufacture API for a particular medicine if the medicine has not been approved for marketing by a regulatory agency.

We obtained the first regulatory approval for TEGSEDI in July 2018 and for WAYLIVRA in May 2019. At June 30, 2020, our physical inventory for TEGSEDI and WAYLIVRA included API that we produced prior to when we obtained regulatory approval. As such, this API has no cost basis as we had previously expensed the costs as R&D expenses.

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. We did not record any material inventory write-offs for the six months ended June 30, 2020. Total inventory was $23.7 million and $18.2 million as of June 30, 2020 and December 31, 2019, respectively, and consisted of the following (in thousands):

	June 30, 2020	December 31, 2019
Raw materials:		
Raw materials- clinical	$ 9,967	$ 9,363
Raw materials- commercial	9,543	6,520
Total raw materials	19,510	15,883
Work in process	3,471	2,039
Finished goods	741	258
Total inventory	$ 23,722	$ 18,180

Leases

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

As our current leases do not provide an interest rate implicit in the lease, we used our incremental borrowing rate, based on the information available on the date we adopted Topic 842 (January 2019) or as of the lease inception date in determining the present value of future payments. We recognize rent expense for our minimum lease payments on a straight-line basis over the expected term of our lease. We recognize period expenses, such as common area maintenance expenses, in the period we incur the expense.

Research, Development and Patent Expenses

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

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the U.S. 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. When we identify patents and patent applications that we are not actively pursuing, we write off any associated costs.

Income Taxes

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

Long-lived Assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs, 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 U.S. requires management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Basic and Diluted Net 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 six months ended June 30, 2020 and 2019 considered our net income (loss) for Ionis on a stand-alone basis plus our share of Akcea's net income (loss) for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's net income (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 June 30, 2020, was calculated as follows (in thousands, except per share amounts):

Three months ended June 30, 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation
Ionis' portion of Akcea's net loss	77,095	$ (0.49)	$ (37,665)
Akcea's net loss attributable to our ownership			$ (37,665)
Ionis' stand-alone net income			5,807
Net loss available to Ionis common stockholders			$ (31,858)
Weighted average shares outstanding			139,352
Basic net loss per share			$ (0.23)

Our basic net loss per share for the six months ended June 30, 2020, was calculated as follows (in thousands, except per share amounts):

Six months ended June 30, 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation
Ionis' portion of Akcea's net loss	77,095	$ (0.91)	$ (70,348)
Akcea's net loss attributable to our ownership			$ (70,348)
Ionis' stand-alone net loss			(9,822)
Net loss available to Ionis common stockholders			$ (80,170)
Weighted average shares outstanding			139,391
Basic net loss per share			$ (0.58)

Our basic net loss per share for the three months ended June 30, 2019, was calculated as follows (in thousands, except per share amounts):

Three months ended June 30, 2019	Weighted Average Shares Owned in Akcea	Akcea's Net Income Per Share	Basic Net Loss Per Share Calculation
Ionis' portion of Akcea's net loss	70,221	$ (0.40)	$ (28,244)
Akcea's net loss attributable to our ownership			$ (28,244)
Ionis' stand-alone net income			27,311
Net loss available to Ionis common stockholders			$ (933)
Weighted average shares outstanding			140,247
Basic net loss per share			$ (0.01)

Our basic net income per share for the six months ended June 30, 2019, was calculated as follows (in thousands, except per share amounts):

Six months ended June 30, 2019	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Income Per Share Calculation
Ionis' portion of Akcea's net loss	69,406	$ (0.06)	$ (4,380)
Akcea's net loss attributable to our ownership			$ (4,380)
Ionis' stand-alone net income			91,008
Net income available to Ionis common stockholders			$ 86,628
Weighted average shares outstanding			139,419
Basic net income per share			$ 0.62

Diluted net income (loss) per share

For the three and six months ended June 30, 2020 and the three months ended June 30, 2019, 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:

- 0.125 percent convertible senior notes (for the three and six months ended June 30, 2020);
- 1 percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

For the six months ended June 30, 2019, we had net income available to Ionis common stockholders. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period.

We calculated our diluted net income per share for the six months ended June 30, 2019 as follows (in thousands except per share amounts):

Six months ended June 30, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 86,628	139,419	$ 0.62
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	2,327	
Shares issuable upon restricted stock award issuance	—	745	
Shares issuable related to our Employee Stock Purchase Plan	—	8	
Income available to Ionis common stockholders	$ 86,628	142,499	$ 0.61

For the six months ended June 30, 2019, the calculation excluded our 1 percent convertible senior notes, or 1% Notes, because the effect on diluted earnings per share was anti-dilutive. For the six months ended June 30, 2019, we did not have our 0.125 percent convertible senior notes.

Convertible Debt

At issuance, we accounted for our convertible debt instruments, including our 0.125 percent senior convertible notes, or 0.125% Notes, and 1% Notes that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate on the date the notes were issued. In reviewing debt issuances, we were not able to identify any comparable companies that issued non-convertible debt instruments at the time of the issuance of the convertible notes. Therefore, we estimated the fair value of the liability component of our notes by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities.

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

Segment Information

We have two operating segments, our Ionis Core segment and Akcea Therapeutics, our majority-owned affiliate. Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with serious and rare 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 and we bill Akcea for these expenses.

Stock-based Compensation Expense

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

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. For the six months ended June 30, 2020 and 2019, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	Six Months Ended June 30,	
	2020	**2019**
Risk-free interest rate	1.6%	2.4%
Dividend yield	0.0%	0.0%
Volatility	58.9%	60.3%
Expected life	4.7 years	4.6 years

Ionis ESPP:

	Six Months Ended June 30,	
	2020	**2019**
Risk-free interest rate	1.1%	2.5%
Dividend yield	0.0%	0.0%
Volatility	47.2%	45.5%
Expected life	6 months	6 months

Ionis RSU's:

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four-year period. The weighted-average grant date fair value of RSUs granted to employees for the six months ended June 30, 2020 was $64.31 per share.

In addition to our stock plans, Akcea has its own stock plan under which it grants stock options and RSUs and under which it derives its stock-based compensation expense. The following are the weighted-average Black-Scholes assumptions Akcea used under its plan for the six months ended June 30, 2020 and 2019:

Akcea Employee Stock Options:

	Six Months Ended June 30,	
	2020	**2019**
Risk-free interest rate	1.3%	2.5%
Dividend yield	0.0%	0.0%
Volatility	74.5%	76.3%
Expected life	6.1 years	6.1 years

Akcea Board of Directors Stock Options:

	Six Months Ended June 30,	
	2020	2019
Risk-free interest rate	0.8%	1.9%
Dividend yield	0.0%	0.0%
Volatility	75.3%	74.3%
Expected life	5.7 years	6.3 years

Akcea ESPP:

	Six Months Ended June 30,	
	2020	2019
Risk-free interest rate	1.0%	2.5%
Dividend yield	0.0%	0.0%
Volatility	71.9%	64.1%
Expected life	6 months	6 months

Akcea RSU's:

The fair value of RSUs is based on the market price of Akcea's common stock on the date of grant. Akcea has granted RSUs with various vesting terms between six months and four years. The weighted-average grant date fair value of RSUs granted to employees for the six months ended June 30, 2020 was $15.76 per share.

The following table summarizes stock-based compensation expense for the three and six months ended June 30, 2020 and 2019 (in thousands). Our non-cash stock-based compensation expense included $16.1 million and $23.4 million of stock-based compensation expense for Akcea employees for the three and six months ended June 30, 2020, respectively, compared to $14.4 million and $32.9 million for the same periods in 2019.

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Cost of products sold	$ 350	$ 137	$ 587	$ 255
Research, development and patent	26,016	23,756	51,573	48,191
Selling, general and administrative	22,076	18,040	37,073	38,991
Total non-cash stock-based compensation expense	$ 48,442	$ 41,933	$ 89,233	$ 87,437

As of June 30, 2020, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $137.8 million and $103.7 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized non-cash stock-based compensation expense 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 1.7 years, respectively.

Amendments to Equity Plan

In June 2020, after receiving approval from our stockholders, we amended our 2002 Non-Employee Directors' Stock Option Plan. The amendments included:

- An increase to the total number of shares reserved for issuance under the plan from 2 million to 2.8 million shares;
- A reduction to the amount of the automatic awards under the plan;
- A revision to the vesting schedule of awards; and
- An extension of the term of the plan.

Share Repurchase Program

In September 2019, our board of directors approved an initial share repurchase program of up to $125 million of our common stock. In 2019, we repurchased 535,000 shares for $34.4 million. In the first quarter of 2020, we repurchased an additional 1.5 million shares for $90.6 million.

Impact of Recently Issued Accounting Standards

In June 2016, the FASB issued guidance that changes the measurement of credit losses for most financial assets and certain other instruments. If we have credit losses, this updated guidance requires us to record allowances for these instruments under a new expected credit loss model. This model requires us to estimate the expected credit loss of an instrument over its lifetime, which represents the portion of the amortized cost basis we do not expect to collect. The new guidance requires us to remeasure our allowance in each reporting period we have credit losses. We adopted this new guidance on January 1, 2020. This guidance did not have an impact on our condensed consolidated financial statements.

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. We adopted this guidance on January 1, 2020 on a prospective basis. This guidance did not have an impact on our condensed consolidated financial statements.

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

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

We adopted this new guidance on January 1, 2020. This guidance did not have a significant impact on our condensed consolidated financial statements.

3. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of June 30, 2020:

One year or less	69%
After one year but within two years	23%
After two years but within three years	8%
Total	100%

As illustrated above, at June 30, 2020, 92 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.

We invest in available-for-sale securities with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Standard & Poor’s, or S&P, Moody’s or Fitch, respectively.

At June 30, 2020, we had an ownership interest of less than 20 percent in five private companies and two public companies with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd. The publicly-traded companies are ATL and ProQR.

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

June 30, 2020	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 652,555	$ 4,275	$ (17)	$ 656,813
Debt securities issued by U.S. government agencies	139,810	673	(9)	140,474
Debt securities issued by the U.S. Treasury (2)	325,925	815	(7)	326,733
Debt securities issued by states of the U.S. and political subdivisions of the states	68,651	214	(3)	68,862
Other municipal debt securities	902	7	—	909
Total securities with a maturity of one year or less	1,187,843	5,984	(36)	1,193,791
Corporate debt securities	485,487	8,780	(121)	494,146
Debt securities issued by U.S. government agencies	118,538	521	(28)	119,031
Debt securities issued by the U.S. Treasury	58,334	588	(4)	58,918
Debt securities issued by states of the U.S. and political subdivisions of the states	50,514	371	(3)	50,882
Total securities with a maturity of more than one year	712,873	10,260	(156)	722,977
Total available-for-sale securities	$ 1,900,716	$ 16,244	$ (192)	$ 1,916,768
Equity securities:				
Total equity securities included in other current assets (3)	$ 4,712	$ —	$ (2,322)	$ 2,390
Total equity securities included in deposits and other assets (4)	15,019	9,318	—	24,337
Total equity securities	19,731	9,318	(2,322)	26,727
Total available-for-sale and equity securities	$ 1,920,447	$ 25,562	$ (2,514)	$ 1,943,495

December 31, 2019	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 669,665	$ 1,451	$ (43)	$ 671,073
Debt securities issued by U.S. government agencies	188,216	303	(43)	188,476
Debt securities issued by the U.S. Treasury (2)	327,670	232	(27)	327,875
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	21,065	26	(5)	21,086
Total securities with a maturity of one year or less	1,206,616	2,012	(118)	1,208,510
Corporate debt securities	428,627	2,911	(43)	431,495
Debt securities issued by U.S. government agencies	140,988	57	(117)	140,928
Debt securities issued by the U.S. Treasury	35,822	9	(12)	35,819
Debt securities issued by states of the U.S. and political subdivisions of the states	19,309	18	(6)	19,321
Total securities with a maturity of more than one year	624,746	2,995	(178)	627,563
Total available-for-sale securities	$ 1,831,362	$ 5,007	$ (296)	$ 1,836,073
Equity securities:				
Total equity securities included in other current assets (3)	4,712	—	(870)	3,842
Total equity securities included in deposits and other assets (4)	10,000	—	—	10,000
Total equity securities	14,712	—	(870)	13,842
Total available-for-sale and equity securities	$ 1,846,074	$ 5,007	$ (1,166)	$ 1,849,915

(1) We hold our available-for-sale securities at amortized cost.

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

(3) Our equity securities included in other current assets consisted of our investments in publicly-traded companies. We recognize publicly-traded equity securities at fair value.

(4) Our equity securities included in deposits and other assets consisted of our investments in privately-held companies. We recognize our private company equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer on our condensed consolidated balance sheet.

The following is a summary of our investments we consider to be temporarily impaired at June 30, 2020 (in thousands). We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	37	$ 87,460	$ (138)	$ —	$ —	$ 87,460	$ (138)
Debt securities issued by U.S. government agencies	10	44,389	(33)	26,997	(4)	71,386	(37)
Debt securities issued by the U.S. Treasury	9	110,067	(11)	—	—	110,067	(11)
Debt securities issued by states of the U.S. and political subdivisions of the states	22	7,763	(6)	—	—	7,763	(6)
Total temporarily impaired securities	78	$ 249,679	$ (188)	$ 26,997	$ (4)	$ 276,676	$ (192)

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 most of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

The following tables present the major security types we held at June 30, 2020 and December 31, 2019 that we regularly measure and carry at fair value. At June 30, 2020 and December 31, 2019, a portion of our ProQR investment was subject to trading restrictions that extend to the fourth quarter of 2020; as a result, we included a lack of marketability discount in valuing this investment, which is a Level 3 input. The amount we owned in ProQR did not change from December 31, 2019 to June 30, 2020. The tables below segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At June 30, 2020	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 363,019	$ 363,019	$ —	$ —
Corporate debt securities (2)	1,150,959	—	1,150,959	—
Debt securities issued by U.S. government agencies (3)	259,505	—	259,505	—
Debt securities issued by the U.S. Treasury (4)	385,651	385,651	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (5)	119,744	—	119,744	—
Other municipal debt securities (3)	909	—	909	—
Investment in ProQR Therapeutics N.V. (6)	2,390	684	—	1,706
Total	$ 2,282,177	$ 749,354	$ 1,531,117	$ 1,706

	At December 31, 2019	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 418,406	$ 418,406	$ —	$ —
Corporate debt securities (7)	1,102,568	—	1,102,568	—
Debt securities issued by U.S. government agencies (8)	329,404	—	329,404	—
Debt securities issued by the U.S. Treasury (3)	363,694	363,694	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	40,407	—	40,407	—
Investment in ProQR Therapeutics N.V. (6)	4,506	—	—	4,506
Total	$ 2,258,985	$ 782,100	$ 1,472,379	$ 4,506

The following footnotes reference lines on our condensed consolidated balance sheet:

(1) Included in cash and cash equivalents.

(2) $32.4 million was included in cash and cash equivalents, with the difference included in short-term investments.

(3) Included in short-term investments.

(4) $59.7 million was included in cash and cash equivalents, with the difference included in short-term investments.

(5) $6.2 million was included in cash and cash equivalents, with the difference included in short-term investments.

(6) Included in other current assets.

(7) $19.0 million was included in cash and cash equivalents, with the difference included in short-term investments.

(8) $0.8 million was included in cash and cash equivalents, with the difference included in short-term investments.

Convertible Notes

Our 1% Notes and 0.125% Notes had a fair value of $340.5 million and $536.5 million at June 30, 2020, respectively. 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. Income Taxes

The Coronavirus Aid, Relief, and Economic Security, or CARES, Act was enacted in March 2020. We considered our ability to estimate annual effective tax rates based on our pre-tax income projections, the income tax effects of the CARES Act, the realizability of our net deferred tax assets and the appropriateness of our valuation allowances.

Under the Tax Cut and Jobs Act of 2017, the utilization of federal net operating losses was limited to 80 percent of taxable income. The CARES Act temporarily removed this limitation and provides for the utilization of net operating loss carryforwards to offset 100 percent of taxable income. The 80 percent limitation enacted by the Tax Act is reinstated for tax years beginning in 2021.

In 2019, we recorded income tax expense related to Akcea due to the 80 percent limitation on the utilization of net operating losses in effect at the time. As a result of the temporary change in tax law provided by the CARES Act, we recorded a $1.7 million tax benefit in the first quarter of 2020 as we will now utilize federal net operating loss carryforwards to offset 100 percent of Akcea's taxable income for 2019. We recorded the tax benefit as a discrete item in the first quarter of 2020 because that was when the CARES Act was enacted.

We recorded an income tax benefit of $0.4 million and $3.7 million for the three and six months ended June 30, 2020, respectively, compared to an income tax benefit of $6.9 million and income tax expense of $24.1 million for the same periods in 2019. We recorded an income tax benefit for the first half of 2020 primarily due to Ionis' pre-tax loss for the period and the $1.7 million tax benefit related to Akcea. We did not record a tax benefit as a result of Akcea's pre-tax loss in the first half of 2020 because Akcea maintains a full valuation allowance against its deferred tax assets.

Our effective tax rate may vary from the U.S. federal statutory rate due to the change in the mix of earnings in tax jurisdictions with different statutory rates, benefits related to tax credits, the tax impact of non-deductible expenses and other permanent differences between income before taxes and taxable income, and changes to tax laws or rates. Our effective income tax rate of 3.5 percent for the six months ended June 30, 2020 differed from the U.S. federal statutory rate of 21 percent primarily due to Ionis' pre-tax loss for the period and the $1.7 million tax benefit related to Akcea.

6. Collaborative Arrangements and Licensing Agreements

Below, we have included our collaborations with substantive changes during the first six months of 2020 from those included in Note 6 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. In December 2017, we entered into a collaboration with Biogen to identify new antisense medicines for the treatment of SMA. We and Biogen are currently developing eight medicines to treat neurodegenerative diseases under these collaborations, including medicines to treat people with ALS, Alzheimer's disease and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through June 2020, we have received more than $2.6 billion from our Biogen collaborations.

During the three and six months ended June 30, 2020 and 2019, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	**2019**	**2020**	**2019**
SPINRAZA royalties (commercial revenue)	$ 71.7	$ 70.5	$ 137.8	$ 130.2
R&D revenue	26.0	31.9	47.4	56.4
Total revenue from our relationship with Biogen	$ 97.7	$ 102.4	$ 185.2	$ 186.6
Percentage of total revenue	67%	63%	66%	41%

During the first six months of 2020, we did not have any changes to our performance obligations or the timing in which we expect to recognize revenue under our Biogen collaborations, except as noted below.

Our condensed consolidated balance sheet at June 30, 2020 and December 31, 2019 included deferred revenue of $486.6 million and $525.8 million, respectively, related to our relationship with Biogen.

2012 Neurology

In the first quarter of 2020, we achieved a $7.5 million milestone payment from Biogen when we advanced IONIS-MAPT$_{Rx}$ in development. This milestone payment did not create a new performance obligation because it is part of our performance obligation to conduct development of IONIS-MAPT$_{Rx}$. Therefore, we included the $7.5 million milestone payment in our transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation. We are recognizing revenue for our IONIS-MAPT$_{Rx}$ development performance obligation based on the percentage of completion. From inception through June 2020, we have included $45.0 million in the transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation. We currently estimate we will satisfy our performance obligation in 2022. In August 2020, we achieved a $12 million milestone payment from Biogen when we advanced IONIS-MAPT$_{Rx}$. We will achieve the next payment of up to $25 million if we continue to advance IONIS-MAPT$_{Rx}$.

2013 Strategic Neurology

In July 2020, we achieved $18 million in milestone payments from Biogen when Biogen initiated a Phase 1/2 trial for ION464, a medicine targeting alpha-synuclein to treat patients with multiple system atrophy. We will achieve the next payment of up to $10 million if Biogen advances one of the medicines under this collaboration.

Research, Development and Commercialization Partners

AstraZeneca

We have two collaborations with AstraZeneca, one focused on the treatment of cardiovascular, renal and metabolic diseases and a second focused on the treatment of oncology diseases. We and AstraZeneca are currently developing several medicines under these collaborations, including medicines to treat people with cardiovascular disease, a genetically associated form of kidney disease, nonalcoholic steatohepatitis, or NASH and cancer. From inception through June 2020, we have received more than $300 million from our AstraZeneca collaborations.

During the three and six months ended June 30, 2020 and 2019, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
R&D revenue	$ 16.8	$ 3.8	$ 30.5	$ 7.8
Percentage of total revenue	12%	2%	11%	2%

Our condensed consolidated balance sheet at June 30, 2020 and December 31, 2019 included deferred revenue of $17.5 million and $25.0 million, respectively, related to our relationship with AstraZeneca.

During the first six months of 2020, we did not have any changes to our performance obligations or the timing in which we expect to recognize revenue under our AstraZeneca collaborations, except as noted below.

Cardiovascular, Renal and Metabolic Diseases Collaboration

In the first quarter of 2020, we achieved a $10 million milestone payment from AstraZeneca when AstraZeneca advanced ION532, a medicine targeting APOL1 for the treatment of kidney disease, in development. We concluded that this milestone payment was not related to our R&D services performance obligation. Therefore, we recognized the $10 million milestone payment in full in the first quarter of 2020 because we did not have any performance obligations related to this payment. We will achieve the next payment of up to $30 millionif AstraZeneca advances a medicine under this collaboration.

Oncology Collaboration

In the second quarter of 2020, we earned a $13 million license fee when AstraZeneca licensed ION736, a medicine targeting FOXP3 to treat cancer. We determined that the license was distinct from our other performance obligations. We recognized the license fee for ION736 as revenue in the second quarter of 2020 because AstraZeneca 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 AstraZeneca in the second quarter of 2020. We will achieve the next payment of $12 millionwhen AstraZeneca advances ION736 in development.

Janssen Biotech, Inc.

We have a collaboration with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat immune-mediated diseases of the gastrointestinal tract, or GI. Janssen is currently advancing ION253, a medicine for the treatment of immune-mediated GI disease, under this collaboration.

In July 2020, we achieved a $5 million milestone payment from Janssen when Janssen initiated a Phase 1 trial for ION253. We will achieve the next payment of $5 million if Janssen advances ION253 in development.

7. Segment Information

We have two reportable segments, Ionis Core and Akcea Therapeutics. At June 30, 2020 we owned approximately 76 percent of Akcea. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting our antisense technology to generate a broad pipeline of first-in-class and/or best-in-class medicines for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with serious and rare diseases. Akcea generates revenue from TEGSEDI and WAYLIVRA product sales and from its collaborations.

The following tables show our segment revenue and income (loss) from operations for the three and six months ended June 30, 2020 and 2019 (in thousands), respectively.

Three Months Ended June 30, 2020	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 71,746	$ —	$ —	$ 71,746
Product sales, net	—	16,364	—	16,364
Licensing and other royalty revenue	2,237	—	(613)	1,624
Total commercial revenue	73,983	16,364	(613)	89,734
R&D revenue under collaborative agreements	55,070	6,013	(5,280)	55,803
Total segment revenue	$ 129,053	$ 22,377	$ (5,893)	$ 145,537
Total operating expenses	$ 131,177	$ 73,468	$ (7,354)	$ 197,291
Loss from operations	$ (2,124)	$ (51,091)	$ 1,461	$ (51,754)

Three Months Ended June 30, 2019	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 70,502	$ —	$ —	$ 70,502
Product sales, net	—	9,865	—	9,865
Licensing and other royalty revenue	4,896	6,036	(3,000)	7,932
Total commercial revenue	75,398	15,901	(3,000)	88,299
R&D revenue under collaborative agreements	64,791	10,723	—	75,514
Total segment revenue	$ 140,189	$ 26,624	$ (3,000)	$ 163,813
Total operating expenses	$ 121,774	$ 65,328	$ (4,462)	$ 182,640
Income (loss) from operations	$ 18,415	$ (38,704)	$ 1,462	$ (18,827)

Six Months Ended June 30, 2020	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 137,754	$ —	$ —	$ 137,754
Product sales, net	—	31,523	—	31,523
Licensing and other royalty revenue	5,835	—	(1,416)	4,419
Total commercial revenue	143,589	31,523	(1,416)	173,696
R&D revenue under collaborative agreements	103,561	6,928	(5,280)	105,209
Total segment revenue	$ 247,150	$ 38,451	$ (6,696)	$ 278,905
Total operating expenses	$ 266,602	$ 134,800	$ (9,618)	$ 391,784
Loss from operations	$ (19,452)	$ (96,349)	$ 2,922	$ (112,879)

Six Months Ended June 30, 2019	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 130,212	$ —	$ —	$ 130,212
Product sales, net	—	16,619	—	16,619
Licensing and other royalty revenue	6,519	6,036	(3,000)	9,555
Total commercial revenue	136,731	22,655	(3,000)	156,386
R&D revenue under collaborative agreements	225,347	167,785	(88,492)	304,640
Total segment revenue	$ 362,078	$ 190,440	$ (91,492)	$ 461,026
Total operating expenses	$ 236,290	$ 202,938	$ (80,908)	$ 358,320
Income (loss) from operations	$ 125,788	$ (12,498)	$ (10,584)	$ 102,706

The following table shows our total assets by segment at June 30, 2020 and December 31, 2019 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
June 30, 2020	$ 3,397,604	$ 527,937	$ (846,591)	$ 3,078,950
December 31, 2019	$ 3,478,081	$ 599,250	$ (844,219)	$ 3,233,112

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

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

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, the Report includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority-owned affiliate. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report and described in additional detail in our annual report on Form 10-K for the year ended December 31, 2019, which is on file with the U.S. Securities and Exchange Commission and is available from us, and those identified within Part II Item 1A. Risk Factors of this Report. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

Overview

We are a leader in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics that we believe has fundamentally changed medicine and transformed the lives of people with devastating diseases. Our large, diverse and advancing pipeline has over 40 potential first-in-class and/or best-in-class medicines designed to address a broad range of diseases, including neurological, cardio-renal, metabolic, infectious and pulmonary diseases. The medicines in our pipeline address patients with diseases ranging from rare to common. We have three commercial medicines approved in major markets around the world, SPINRAZA, TEGSEDI and WAYLIVRA. We have four medicines in pivotal studies, tominersen for Huntington's disease, tofersen for SOD1-ALS, AKCEA-APO(a)-L_{Rx} for cardiovascular disease, or CVD, and AKCEA-TTR-L_{Rx} for TTR amyloidosis.

With our strong financial position, we have the resources to continue to execute on our plan to invest in areas of our business that we believe have the potential to create value for patients and shareholders. By the end of this year, we plan to have six pivotal studies underway and report clinical proof-of-concept data for six medicines. We also plan to expand the reach of our antisense technology by optimizing additional routes of administration, such as oral and pulmonary for which we expect clinical data this year. Additionally, this year, we are continuing to prioritize the growth and advancement of our Ionis-owned pipeline. Building on our achievements to date, we believe that continued advances in our pipeline and technology will enable us to achieve our goal of 10 or more new drug applications through the end of 2025.

Our goal is to determine the optimal development and commercialization strategy for each medicine in our pipeline, while ensuring we remain focused on innovation and delivering substantial value for patients in need and shareholders. With this goal firmly in mind, this year we plan to further develop our commercial strategy and capabilities to ensure we maximize the value of each of our medicines.

By building on our strong foundation and continuing to focus on our strategic priorities, we believe we are achieving our vision of becoming one of the most successful and innovative companies in the healthcare industry. We intend to continue to pursue our vision by executing on our strategic priorities: advancing our Ionis-owned pipeline, further developing our commercial strategies and capabilities, and expanding the reach of our antisense technology.

Commercial Medicines

SPINRAZA is a global foundation-of-care for the treatment of patients of all ages with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Biogen, our partner responsible for commercializing SPINRAZA worldwide, reported that as of June 30, 2020, over 11,000 patients were on SPINRAZA therapy in markets around the world. Additionally, as of June 30, 2020, SPINRAZA was approved in over 50 countries with formal reimbursement in over 40 countries. From inception through June 30, 2020, we have earned more than $1.2 billion in revenues from our SPINRAZA collaboration, including more than $780 million in royalties on sales of SPINRAZA.

TEGSEDI, a once weekly, self-administered subcutaneous medicine, was approved in 2018 in the U.S., EU and Canada for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis, or hATTR, a debilitating, progressive, and fatal disease. Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat patients with serious and rare diseases, launched TEGSEDI in the U.S. and EU in late 2018. As of the end of July 2020, TEGSEDI was commercially available in 15 countries. Akcea plans to expand the global launch of TEGSEDI by launching in additional countries. In Latin America, PTC Therapeutics, or PTC, through its exclusive license from Akcea, is launching TEGSEDI in Brazil and is working towards access in additional Latin American countries.

WAYLIVRA, a once weekly, self-administered, subcutaneous medicine, received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. Akcea launched WAYLIVRA in the EU in the third quarter of 2019 and is leveraging its existing commercial infrastructure in Europe to market WAYLIVRA. PTC, through its exclusive license agreement with Akcea, is working to expand access to WAYLIVRA across Latin America, beginning in Brazil. In the second quarter of 2020, PTC submitted the WAYLIVRA marketing application for approval in Brazil to ANVISA.

Medicines in Pivotal Phase 3 Studies

Our medicines in pivotal studies include tominersen for Huntington's disease, tofersen for SOD1-ALS, AKCEA-APO(a)-L_{Rx} for cardiovascular disease, or CVD, and AKCEA-TTR-L_{Rx} for TTR amyloidosis. In April 2020, Roche completed enrollment of the Phase 3 study for tominersen. Tominersen has been granted orphan drug designation in the U.S. and EU and PRIME designation in the EU. Additionally, the Phase 3 study for tofersen continues to progress in patients with SOD1-ALS. Tofersen has been granted orphan drug designation in the U.S. and EU. In January 2020, Novartis began enrollment in the HORIZON Phase 3 cardiovascular outcome study of AKCEA-APO(a)-L_{Rx} in patients with established cardiovascular disease and elevated Lp(a). AKCEA-APO(a)-L_{Rx} was recently granted Fast Track Designation by the FDA as a potential treatment for people at significant risk for cardiovascular disease due to elevated levels of lipoprotein(a), or Lp(a). Our broad Phase 3 program for AKCEA-TTR-L_{Rx} is also progressing.

COVID-19

As a company focused on improving the health of people around the world, our priority during the COVID-19 pandemic is the safety of our employees, their families, the healthcare workers who work with us and the patients who rely on our medicines. We are also focused on maintaining the quality of our studies and meeting timelines. While we have experienced some impacts on our business as a result of the COVID-19 pandemic, we believe our mitigation efforts and financial strength will allow us to manage through this crisis and continue to execute on our strategic initiatives. Because the situation is extremely fluid we are continuing to evaluate the impact COVID-19 could have on our business, including but not limited to the impact on our commercial products and the medicines in our pipeline.

Financial Highlights

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	**2019**	**2020**	**2019**
Total revenue	$ 145,537	$ 163,813	$ 278,905	$ 461,026
Total operating expenses	$ 197,291	$ 182,640	$ 391,784	$ 358,320
Income (loss) from operations	$ (51,754)	$ (18,827)	$ (112,879)	$ 102,706
Net income (loss)	$ (43,769)	$ (10,012)	$ (102,249)	$ 80,873
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (31,845)	$ (876)	$ (80,071)	$ 83,567

Commercial revenue from SPINRAZA royalties increased to $72 million and $138 million for the three and six months ended June 30, 2020, respectively, compared to the same periods in 2019. Product sales from TEGSEDI and WAYLIVRA increased to $16 million and $32 million for the three and six months ended June 30, 2020, respectively, compared to the same periods in 2019. R&D revenue was $56 million and $105 million for the three and six months ended June 30, 2020, respectively. Our R&D revenue in the six months ended June 30, 2019 included $185 million from two large items, including a $150 million license fee we earned from Novartis when it licensed AKCEA-APO(a)-L_{Rx}. We anticipate our R&D revenue will be higher in the second half of 2020, compared to the first half of 2020.

Our operating expenses for the three and six months ended June 30, 2020 were $197.3 million and $391.8 million, respectively, and increased over the same periods in 2019, principally due to our investments in our strategic priorities, including the Phase 3 program for AKCEA-TTR-L_{Rx} and our Ionis-owned pipeline. We expect our operating expenses to continue to increase during the second half of 2020 as we continue to advance our strategic priorities.

We ended the second quarter of 2020, with $2.3 billion in cash and short-term investments. We believe our strong financial position should enable us to continue to execute on our corporate goals throughout 2020 and beyond.

Recent Business Highlights *(Q2 2020 and subsequent activities)*

Commercial Medicine Highlights

- SPINRAZA: a global foundation-of-care for the treatment of SMA patients of all ages
  - $495 million in worldwide sales in the second quarter of this year
  - More than 11,000 patients were on SPINRAZA treatment worldwide at the end of the second quarter, including patients across commercial, expanded access and clinical trial settings
  - The Phase 4 RESPOND study to evaluate SPINRAZA benefit in patients with a suboptimal clinical response to Zolgensma® (onasemnogene abeparvovec) is expected to begin early next year
  - The DEVOTE study evaluating a higher dose of SPINRAZA with the potential to deliver even greater efficacy in SMA patients of all ages is progressing
  - New clinical data from the NURTURE and SHINE studies, as well as new real-world data, further support SPINRAZA's durable efficacy and established safety profile across SMA patients of all ages

- TEGSEDI: the only approved at-home subcutaneous therapy for the treatment of hereditary transthyretin amyloidosis (hATTR) with polyneuropathy in adult patients
  - Commercially available in 15 countries
  - Reimbursement approved in Portugal, Spain, Italy and Austria
  - Expanding commercial availability in additional EU countries and in Latin America this year

- WAYLIVRA: the only approved treatment in the EU for adults with genetically confirmed familial chylomicronemia syndrome (FCS) at high risk for pancreatitis
  - Launch progressing in Germany, Austria, Greece and through the ATU in France; launching in additional EU countries this year
  - Filed for marketing approval in Brazil; refiling new drug application for U.S. marketing authorization

Second Quarter 2020 and Recent Pipeline Highlights

- Completed enrollment in the global GENERATION HD1 Phase 3 study of tominersen in patients with Huntington's disease
- Progressed multiple neurological disease medicines under our broad Biogen collaboration
  - Published data from the Phase 1/2 study of tofersen in the *New England Journal of Medicine*
  - Progressed the IONIS-MAPT$_{Rx}$ long-term extension study in patients with Alzheimer's disease and achieved a $12 million milestone payment
  - Advanced ION464 into a Phase 1/2 study in patients with multiple system atrophy and achieved an $18 million milestone payment
- Advanced medicines for the treatment of cancer and immune-mediated GI disease
  - Licensed ION736 to AstraZeneca for the treatment of cancer and achieved a $13 million license fee
  - Initiated a Phase 1 study of ION253 for the treatment of immune-mediated GI disease and achieved a $5 million milestone payment from Janssen
- Expanded the Ionis-owned pipeline with the addition of ION363 for the treatment of FUS-ALS

Critical Accounting Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with the audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting estimates and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

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

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Estimating our income taxes

There have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our Annual Report on Form 10-K for the year ended December 31, 2019.

Results of Operations

Revenue

Our revenue was as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 71,746	$ 70,502	$ 137,754	$ 130,212
Product sales, net	16,364	9,865	31,523	16,619
Licensing and other royalty revenue	1,624	7,932	4,419	9,555
Total commercial revenue	89,734	88,299	173,696	156,386
R&D revenue:				
Amortization from upfront payments	27,925	40,556	49,071	75,345
Milestone payments	6,737	12,016	29,856	52,032
License fees	14,669	21,626	14,669	172,689
Other services	6,472	1,316	11,613	4,574
Total R&D revenue	55,803	75,514	105,209	304,640
Total revenue	$ 145,537	$ 163,813	$ 278,905	$ 461,026

In the first half of 2020, our commercial revenue increased over 10 percent, compared to the same period in 2019. Commercial revenue from SPINRAZA royalties increased six percent and product sales from TEGSEDI and WAYLIVRA nearly doubled, compared to the same period in 2019.

We earn our R&D revenue from multiple sources. Our R&D revenue can fluctuate depending on the timing of events. Our R&D revenue in the six months ended June 30, 2020 included more than $50 million from our neurology disease franchise and more than $25 million from our cardio-renal franchise. Additionally, in the second quarter of 2020, we earned $13 million from AstraZeneca under our oncology collaboration. We anticipate our R&D revenue will be higher in the second half of 2020, compared to the first half of 2020.

Our R&D revenue in the six months ended June 30, 2019 included $185 million from two large items, including a $150 million license fee we earned from Novartis when it licensed AKCEA-APO(a)-L_{Rx}. Additionally, our amortization from upfront payments for the six months ended June 30, 2019, was higher compared to the same period in 2020 because it included amortization from collaborations for which we have completed our R&D services performance obligations.

Already in the third quarter of 2020, we have generated several milestone payments, including $18 million from Biogen when Biogen advanced ION464, a medicine targeting alpha-synuclein to treat patients with multiple system atrophy, into a Phase 1/2 study, $12 million from Biogen for continuing to advance IONIS-$MAPT_{Rx}$ in development and a $5 million milestone payment from Janssen when Janssen initiated a Phase 1 trial for ION253.

Operating Expenses

Operating expenses for the three and six months ended June 30, 2020 were $197.3 million and $391.8 million, respectively, and increased compared to $182.6 million and $358.3 million for the same periods in 2019. The increase was principally due to our investments in our strategic priorities, including the Phase 3 program for AKCEA-TTR-L_{Rx} and our Ionis-owned pipeline. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the second half of 2020 as we continue to advance our strategic priorities.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Ionis Core	$ 95,671	$ 82,739	$ 190,689	$ 161,254
Akcea Therapeutics	60,795	62,430	121,897	190,536
Elimination of intercompany activity	(7,353)	(4,462)	(9,618)	(80,908)
Subtotal	149,113	140,707	302,968	270,882
Non-cash compensation expense related to equity awards	48,442	41,933	89,233	87,438
Total operating expenses	$ 197,555	$ 182,640	$ 392,201	$ 358,320

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

Cost of Products Sold

Our cost of products sold consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA and certain associated period costs. Prior to the regulatory approval of TEGSEDI and WAYLIVRA, we expensed as R&D expense a significant portion of the cost of producing TEGSEDI and WAYLIVRA that Akcea is using in the commercial launches. We expect cost of products sold to increase as we deplete these inventories.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	**2019**	**2020**	**2019**
Ionis Core	$ —	$ —	$ —	$ —
Akcea Therapeutics	4,693	5,645	9,239	7,972
Elimination of intercompany activity	(2,031)	(4,419)	(4,253)	(5,822)
Subtotal	2,662	1,227	4,986	2,151
Non-cash compensation expense related to equity awards	350	137	587	255
Total operating expenses	$ 3,012	$ 1,364	$ 5,573	$ 2,406

We began recognizing cost of products sold for TEGSEDI in the third quarter of 2018 when TEGSEDI was approved and for WAYLIVRA in the second quarter of 2019 when WAYLIVRA was approved. Our cost of products sold increased in six months ended June 30, 2020, compared to the same period in 2019, primarily due to the increase in commercial product sales. In its cost of products sold Akcea includes the amortization for milestone payments it made to us related to the U.S. and European approvals of TEGSEDI. Akcea is recognizing this amortization over TEGSEDI's remaining estimated patent life. We eliminate this amortization in our consolidated results. All amounts exclude non-cash compensation expense related to equity awards.

Research, Development and Patent Expenses

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	**2019**	**2020**	**2019**
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 96,248	$ 82,409	$ 187,642	$ 164,391
Non-cash compensation expense related to equity awards	26,016	23,756	51,572	48,191
Total research, development and patent expenses	$ 122,264	$ 106,165	$ 239,214	$ 212,582

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	**2019**	**2020**	**2019**
Ionis Core	$ 75,323	$ 64,745	$ 150,754	$ 126,072
Akcea Therapeutics	26,247	17,707	42,253	113,405
Elimination of intercompany activity	(5,322)	(43)	(5,365)	(75,086)
Subtotal	96,248	82,409	187,644	164,391
Non-cash compensation expense related to equity awards	26,016	23,756	51,572	48,191
Total research, development and patent expenses	$ 122,264	$ 106,165	$ 239,214	$ 212,582

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. This function is also responsible for making investments in complementary technologies to expand the reach of antisense 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 and were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 18,751	$ 15,693	$ 37,117	$ 30,325
Non-cash compensation expense related to equity awards	6,090	5,297	12,396	10,790
Total antisense drug discovery expenses	$ 24,841	$ 20,990	$ 49,513	$ 41,115

Antisense drug discovery expenses increased for the three and six months ended June 30, 2020, compared to the same periods in 2019, due to expenses we incurred related to advancing and expanding our research programs, including investments we made in complementary technologies to expand the reach of antisense technology. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
AKCEA TTR-L_{Rx}	$ 5,847	$ 1,599	$ 11,426	$ 2,540
WAYLIVRA	2,272	3,134	3,277	5,105
TEGSEDI	3,483	3,426	7,796	8,117
Other antisense development projects	24,491	23,979	46,608	45,348
Development overhead expenses	17,828	16,850	35,761	35,794
Total antisense drug development, excluding non-cash compensation expense related to equity awards	53,921	48,988	104,868	96,904
Non-cash compensation expense related to equity awards	14,019	11,118	25,806	23,352
Total antisense drug development expenses	$ 67,940	$ 60,106	$ 130,674	$ 120,256

Our development expenses increased for the three and six months ended June 30, 2020 compared to the same periods in 2019. The increase in development expenses primarily related to our broad Phase 3 program for AKCEA-TTR-L_{Rx}, which we initiated in late 2019 and other medicines in our Ionis-owned pipeline. These increases were slightly offset by decreases in expenses for WAYLIVRA and vupanorsen, for which Akcea completed the Phase 2 studies in early 2020. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Ionis Core	$ 40,847	$ 34,952	$ 79,949	$ 64,022
Akcea Therapeutics	13,074	14,036	24,919	107,882
Elimination of intercompany activity	—	—	—	(75,000)
Subtotal	53,921	48,988	104,868	96,904
Non-cash compensation expense related to equity awards	14,019	11,118	25,806	23,352
Total antisense drug development expenses	$ 67,940	$ 60,106	$ 130,674	$ 120,256

Akcea's development expenses in the first six months of 2019 included a $75 million sublicense fee it paid us related to Novartis' license of AKCEA-APO(a)-L_{Rx}. We eliminated this expense in our consolidated results. Excluding this fee, Akcea's development expenses decreased primarily because Akcea completed the Phase 2 study of vupanorsen in early 2020.

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 medicines 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 medicine. Although we may characterize a medicine 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 medicines based on each medicine's particular needs at that time. This means we are constantly shifting resources among medicines. Therefore, what we spend on each medicine during a particular period is usually a function of what is required to keep the medicines progressing in clinical development, not what medicines 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 medicine to another and cannot be used to accurately predict future costs for each medicine. And, because we always have numerous medicines in preclinical and early stage clinical research, the fluctuations in expenses from medicine to medicine, in large part, offset one another. If we partner a medicine, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Manufacturing and Development Chemistry

Expenditures in our manufacturing and development chemistry function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. Our manufacturing and development chemistry 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 development chemistry expenses were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 13,880	$ 9,328	$ 25,863	$ 19,482
Non-cash compensation expense related to equity awards	2,832	2,524	5,664	4,581
Total manufacturing and development chemistry expenses	$ 16,712	$ 11,852	$ 31,527	$ 24,063

Manufacturing and development chemistry expenses increased for the three and six months ended June 30, 2020, compared to the same periods in 2019. The increase in manufacturing and development chemistry expenses was primarily related to investments in AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx} API. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Ionis Core	$ 10,458	$ 8,062	$ 20,768	$ 16,860
Akcea Therapeutics	8,702	1,266	10,374	2,621
Elimination of intercompany activity	(5,280)	—	(5,280)	—
Subtotal	13,880	9,328	25,862	19,482
Non-cash compensation expense related to equity awards	2,832	2,524	5,664	4,581
Total manufacturing and development chemistry expenses	$ 16,712	$ 11,852	$ 31,527	$ 24,063

R&D Support

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Personnel costs	$ 3,505	$ 3,414	$ 7,343	$ 7,324
Occupancy	2,439	2,254	4,881	4,431
Patent expenses	559	673	1,231	1,196
Depreciation and amortization	163	138	325	259
Insurance	619	412	1,229	823
Other	2,411	1,509	4,787	3,647
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	9,696	8,400	19,796	17,680
Non-cash compensation expense related to equity awards	3,075	4,816	7,706	9,467
Total R&D support expenses	$ 12,771	$ 13,216	$ 27,502	$ 27,147

R&D support expenses for the three and six months ended June 30, 2020 increased slightly compared to the same periods in 2019. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Ionis Core	$ 5,267	$ 6,038	$ 12,920	$ 14,864
Akcea Therapeutics	4,471	2,405	6,960	2,902
Elimination of intercompany activity	(42)	(43)	(85)	(86)
Subtotal	9,696	8,400	19,795	17,680
Non-cash compensation expense related to equity awards	3,075	4,816	7,706	9,467
Total R&D support expenses	$ 12,771	$ 13,216	$ 27,502	$ 27,147

Selling, General and Administrative Expenses

Selling, general and administrative, or SG&A, expenses include personnel and outside costs associated with the pre-commercialization and commercialization activities for our medicines and costs to support our company, our employees and our stockholders including, legal, human resources, investor relations, and finance. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above. We also include fees we owe under our in-licensing agreements related to SPINRAZA.

The following table sets forth information on SG&A expenses (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 50,203	$ 57,071	$ 110,341	$ 104,341
Non-cash compensation expense related to equity awards	22,076	18,040	37,073	38,991
Total selling, general and administrative expenses	$ 72,279	$ 75,111	$ 147,414	$ 143,332

SG&A expenses were lower for the three months ended June 30, 2020, compared to the same period in 2019, principally due to reductions in travel and marketing events for Akcea as a result of the COVID-19 pandemic. SG&A expenses were higher for the six months ended June 30, 2020, compared to the same period in 2019, principally due to our investments in the global launches of TEGSEDI and WAYLIVRA to support expansion into new countries. All amounts exclude non-cash compensation expense related to equity awards.

Our SG&A expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Ionis Core	$ 20,348	$ 17,994	$ 39,935	$ 35,181
Akcea Therapeutics	29,855	39,077	70,406	69,159
Subtotal	50,203	57,071	110,341	104,340
Non-cash compensation expense related to equity awards	22,076	18,040	37,073	38,992
Total selling, general and administrative expenses	$ 72,279	$ 75,111	$ 147,414	$ 143,332

Akcea Therapeutics, Inc.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Cost of products sold	$ 4,693	$ 5,645	$ 9,238	$ 7,971
Development and patent expenses	26,247	17,707	42,253	38,406
Sublicense fee to Ionis	—	—	—	75,000
Selling, general and administrative expenses	29,855	39,077	70,406	69,159
Profit (loss) share for TEGSEDI commercialization activities	(3,447)	(11,465)	(10,498)	(20,521)
Total operating expenses, excluding non-cash compensation expense related to equity awards	57,348	50,965	111,399	170,015
Non-cash compensation expense related to equity awards	16,120	14,363	23,402	32,923
Total Akcea Therapeutics operating expenses	$ 73,468	$ 65,328	$ 134,801	$ 202,938

See discussion of fluctuations in Akcea operating expenses in the operating expense sections above.

For each period presented, we allocated a portion of Ionis' SG&A expenses to Akcea for work we performed on Akcea's behalf and we bill Akcea for these expenses. We included these allocated expenses in Akcea's SG&A expenses in the table above. All amounts exclude non-cash compensation expense related to equity awards.

In the first quarter of 2019, we began sharing profits and losses for TEGSEDI with Akcea under our TTR licensing agreement. As Akcea is the principal for all commercial activities related to the TTR License Agreement, Akcea records all activities related to TEGSEDI on a gross basis in its statement of operations based on the nature of the activity, including revenues, cost of products sold and sales and marketing expenses. Ionis' share of the net profit/loss from commercializing TEGSEDI is separately presented on Akcea's statement of operations on the line titled "Profit (loss) share for TEGSEDI commercialization activities". Since TEGSEDI is currently generating a loss, this represents the amount Ionis owes Akcea under the licensing agreement for Ionis' share of the net loss of TEGSEDI commercialization activities during the period. With the launch of WAYLIVRA in the third quarter of 2019, Akcea began paying Ionis royalties on WAYLIVRA product sales. We eliminate these amounts in our consolidated results.

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

Investment Income

Investment income for the three and six months ended June 30, 2020 was $9.2 million and $19.5 million, respectively, compared to $13.7 million and $25.9 million for the same periods in 2019. The decrease in investment income was primarily due to a decline in interest rates during the six months ended June 30, 2020 compared to the same periods in 2019.

Interest Expense

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Convertible notes:				
Non-cash amortization of the debt discount and debt issuance costs	$ 9,594	$ 9,382	$ 19,006	$ 18,582
Interest expense payable in cash	946	1,714	1,892	3,428
Interest on mortgage for primary R&D and manufacturing facilities	601	601	1,201	1,183
Other	32	105	64	209
Total interest expense	$ 11,173	$ 11,802	$ 22,163	$ 23,402

Our interest expense payable in cash decreased in the three and six months ended June 30, 2020, compared to the same periods in 2019 because we exchanged a significant portion of our 1% Notes for 0.125% Notes in December 2019.

Gain on Investments

We recorded a gain on investments of $9.9 million for the six months ended June 30, 2020. During the second quarter of 2020, we revalued our investments in two privately-held companies, Dynacure and Ribo because the companies sold additional equity securities that were similar to those we own. These observable price changes resulted in us recognizing a $6.3 million gain on our investment in Dynacure and a $3 million gain on our investment in Ribo in our condensed consolidated statement of operations during the three months ended June 30, 2020.

Income Tax Benefit (Expense)

We recorded an income tax benefit of $0.4 million and $3.7 million for the three and six months ended June 30, 2020, respectively. We recorded an income tax benefit of $6.9 million for the three months ended June 30, 2019 and income tax expense of $24.1 million for the six months ended June 30, 2019. We recorded an income tax benefit in the first half of 2020 primarily due to Ionis' pre-tax loss for the period and a $1.7 million tax benefit related to Akcea. We did not record a tax benefit as a result of Akcea's pre-tax loss in the first half of 2020 because Akcea maintains a full valuation allowance against its deferred tax assets.

Net Income (Loss)

We generated a net loss of $43.8 million and $102.2 million for the three and six months ended June 30, 2020, respectively, compared to a net loss of $10.0 million and net income of $80.9 million for the same periods in 2019. Our net loss for the six months ended June 30, 2020 was primarily due to decreased revenue year-over-year, as discussed above in the revenue section.

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

At June 30, 2020, we owned approximately 76 percent of Akcea. The shares of Akcea third parties own represent an interest in Akcea's equity that we do not control. However, because we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our condensed consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line called "Net loss attributable to noncontrolling interest in Akcea" on our statement of operations. Our noncontrolling interest in Akcea on our statement of operations for the three and six months ended June 30, 2020, was a loss of $11.9 million and $22.2 million, respectively, compared to $9.1 million and $2.7 million for the same periods in 2019.

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 $31.8 million for the three months ended June 30, 2020 compared to $0.9 million for the same period in 2019. For the six months ended June 30, 2020 we reported a net loss attributable to our common stockholders of $80.1 million compared to net income attributable to our common stockholders of $83.6 million for the same period in 2019.

Basic and diluted net loss per share for the three months ended June 30, 2020 were $0.23 compared to $0.01 for the same period in 2019. For the six months ended June 30, 2020, basic and diluted net loss per share were $0.58. Basic and diluted net income per share for the six months ended June 30, 2019 were $0.62 and $0.61, respectively.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and product sales. From our inception through June 30, 2020, we have earned approximately $4.4 billion in revenue. We also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through June 30, 2020, we have raised net proceeds of approximately $2.0 billion from the sale of our equity securities. Additionally, we have borrowed approximately $1.5 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

Our key liquidity metrics and capital resources, including our cash, cash equivalents and short-term investments, working capital and debt obligations did not change significantly at June 30, 2020 compared to December 31, 2019.

The following table summarizes our contractual obligations as of June 30, 2020. 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:

Contractual Obligations	**Payments Due by Period (in millions)**				
(selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
0.125% Notes (principal and interest payable)	$ 551.9	$ 0.7	$ 1.3	$ 549.9	$ —
1% Notes (principal and interest payable)	$ 314.5	$ 3.1	$ 311.4	$ —	$ —
Building mortgage payments	$ 77.1	$ 2.4	$ 5.7	$ 6.9	$ 62.1
Operating leases	$ 21.8	$ 3.2	$ 5.5	$ 4.8	$ 8.3
Other obligations (principal and interest payable)	$ 1.0	$ 0.1	$ 0.1	$ 0.1	$ 0.7
Total	$ 966.3	$ 9.5	$ 324.0	$ 561.7	$ 71.1

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.

0.125 Percent Convertible Senior Notes and Call Spread

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. We completed this exchange to reduce our cash interest payments, increase our conversion price and extend our maturity for a large portion of our debt. Additionally, in conjunction with the December 2019 exchange, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the conversion price on our 0.125% even further.

The call spread cost us $52.6 million, of which $108.7 million was for the note hedge purchase, offset by $56.1 million we received for selling the warrants. We increased our effective conversion price to $123.38 with the same number of underlying shares as our 0.125% Notes.

Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants in additional paid-in capital in our condensed consolidated balance sheet. We exclude any shares of our common stock receivable by us under the note hedges from our calculation of diluted earnings per share as they are antidilutive. We will include the shares issuable under the warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

At June 30, 2020, we had the following 0.125% Notes outstanding (amounts in millions except price per share data):

	0.125% Notes
Outstanding principal balance	$ 548.8
Maturity date	December 2024
Interest rate	0.125 percent
Conversion price per share	$ 83.28
Total shares of common stock subject to conversion	6.6

Interest is payable semi-annually for the 0.125% Notes. The 0.125% Notes are convertible under certain conditions, at the option of the note holders. We can settle conversions of the 0.125% Notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 0.125% Notes prior to maturity, and no sinking fund is provided for them. Holders of the 0.125% 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 0.125% Notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

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% Notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes, or 2¾% Notes. In December 2016, we issued an additional $185.5 million of 1% Notes in exchange for the redemption of $61.1 million of our 2¾% Notes. In December 2019, we exchanged a portion of our 1% Notes for new 0.125% Notes. As a result, the principal balance of the 1% Notes following the exchange was $309.9 million.

At June 30, 2020, we had the following 1% Notes outstanding (amounts in millions except price per share data):

	1% Notes
Outstanding principal balance	$ 309.9
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	4.6

Interest is payable semi-annually for the 1% Notes. The 1% Notes are convertible under certain conditions, at the option of the note holders. We settle conversions of the 1% Notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 1% Notes prior to maturity, and no sinking fund is provided for them. Holders of the 1% 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% Notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million and our manufacturing facility for $14.0 million. We financed the purchase of these two facilities with mortgage debt of $60.4 million in total. 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 June 30, 2020 for the purchase of services, capital equipment and materials as part of our normal course of business.

We may enter into additional collaborations with partners which could 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 investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

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 condensed 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 June 30, 2020. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2020.

We also performed an evaluation of any changes in our internal controls over financial reporting that occurred during our last fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting. We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. That evaluation did not identify any changes in our internal controls over financial reporting that occurred during our latest fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding and may revise our estimates.

On July 16, 2020, a purported stockholder of Akcea filed an action in the Delaware Court of Chancery captioned John Makris, et al. v. Stanley T. Crooke, et al., C.A. No. 2020-0587, or the "Delaware Action." The plaintiff in the Delaware Action asserts claims against (i) current and former members of Akcea's board of directors; and (ii) Ionis, or collectively, the Defendants. The plaintiff asserts derivative claims on behalf of Akcea, which is a nominal defendant in the Delaware Action, as well as putatively direct claims on behalf of a purported class of Akcea's stockholders. The plaintiff in the Delaware action asserts that the Defendants breached their fiduciary duties in connection with the licensing transaction that we and Akcea entered into regarding TEGSEDI and AKCEA-TTR-L_{Rx}. The plaintiff also asserts an unjust enrichment claim against Ionis. The plaintiff's claims are similar to those asserted in a prior action in the Delaware Court of Chancery captioned City of Cambridge Retirement System v. Crooke, et al., C.A. No. 2019-0905, which was dismissed with prejudice to the named plaintiff only on April 8, 2020. We believe that the claims asserted in the Delaware Action are without merit and anticipate filing a motion to dismiss the claims.

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, 2019.

Risks Related to the COVID-19 Pandemic

Our business could be materially adversely affected by the effects of health epidemics. To date, we believe the impacts of the recent COVID-19 pandemic on our business are limited and manageable.*

Our business could be materially adversely affected by health epidemics in regions where we or our partners are commercializing our medicines, have concentrations of clinical trial sites or other business operations, and could cause significant disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, since December 2019, a novel strain of coronavirus, SARS-CoV-2, causing a disease referred to as COVID-19, has spread worldwide. In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic, or the COVID-19 Pandemic, and the U.S. government-imposed travel restrictions on travel between the U.S., Europe and certain other countries. In addition, the Governor of the State of California and the Governor of the Commonwealth of Massachusetts, the states in which our and Akcea's headquarters are located, respectively, each declared a state of emergency related to the spread of COVID-19 and issued executive orders that directed residents to stay at home.

In response to these public health directives and orders, we implemented work-from-home policies for most of our employees and generally suspended business-related travel. Akcea has also implemented work-from-home policies for its employees globally and generally suspended business-related travel. During the second quarter of 2020, some states began lifting restrictions and permitting certain offices to reopen, including the State of California and Commonwealth of Massachusetts. However, out of an abundance of caution and to protect the health and welfare of our employees, we continue to maintain work-from-home policies for most of our employees. The effects of these work-from-home and travel policies have thus far had a limited impact on our business.

These public health directives and orders have also impacted Akcea's sales efforts. For example, some physician and hospital policies that have been put in place as a result of the COVID-19 Pandemic restrict in-person access by third parties, which has in some cases impacted Akcea's commercialization efforts for TEGSEDI and WAYLIVRA. These and similar, and perhaps more severe, disruptions in our commercial operations could materially impact our business, operating results and financial condition in the future.

Quarantines, shelter-in-place, executive and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, could impact personnel at third-party manufacturing facilities in the U.S. and other countries, or the availability or cost of materials, which would disrupt our supply chain.

We have experienced impacts to our clinical trial operations due to the COVID-19 Pandemic; however, we believe such impacts are limited and manageable. Some examples of these impacts include:

- we have experienced some impact on clinical site initiation and patient enrollment due to restrictions imposed as a result of the COVID-19 Pandemic;
  - For example, in March 2020, Akcea instituted a temporary suspension of enrollment for new subjects in its Phase 3 studies of AKCEA-TTR-L_{Rx} based on advice from Akcea's trial advisory committee; however, enrollment has resumed as sites have come back online as local and regional restrictions have eased.
- some patients have not been able to comply with clinical trial protocols as quarantines have impeded patient movement and interrupted healthcare services;
- we have experienced some impact on our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19; and
- we have experienced some delays in necessary interactions with regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government or contractor personnel.

The spread of COVID-19 has caused a broad impact globally. While the potential economic impact brought by, and the duration of, the COVID-19 Pandemic may be difficult to assess or predict, it could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and has and could continue to affect the value of our securities.

The global COVID-19 Pandemic continues to rapidly evolve. While we have not yet experienced material adverse effects to our business as a result of the COVID-19 Pandemic, the ultimate impact of the COVID-19 Pandemic or a similar health epidemic is highly uncertain and subject to change. As such, we do not yet know the full extent of delays or impacts on our business, our clinical trials, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID-19 Pandemic closely.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

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

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

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

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

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

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

For example, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI is only available through 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, the product label for WAYLIVRA in the E.U. requires regular blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these medicines. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we and Akcea can better maintain patients on TEGSEDI and WAYLIVRA through our patient-centric commercial approach where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on our ability to conduct periodic blood and urine monitoring of our patients as a result of the current COVID-19 Pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If we or our partners fail to compete effectively, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, will not contribute significant revenues.

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

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

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

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

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

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization in certain geographic markets of products against targets that are also targets of products in our development pipeline. For example:

- ZOLGENSMA and risdiplam could compete with SPINRAZA;
- ONPATTRO, VYNDAQEL and VYNDAMAX, AG10 and vutrisiran could compete with TEGSEDI and AKCEA-TTR-L_{Rx};
- ARO-APOC3, metreleptin and gemcabene could compete with WAYLIVRA;
- WVE-120101/WVE-120102, Selistat and VX15 could compete with tominersen; and
- Arimoclomol could compete with tofersen.

Certain of our medicines may compete with our other medicines, which could reduce our expected revenues.

Certain of our medicines inhibit the production of the same protein. For example, WAYLIVRA inhibits the production of the same protein as AKCEA-APOCIII-L_{Rx} and TEGSEDI inhibits the production of the same protein as AKCEA-TTR-L_{Rx}. We believe the enhancements we incorporated into AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx} can provide greater patient convenience by allowing for significantly lower doses and less frequent administration compared to WAYLIVRA and TEGSEDI, respectively. As such, to the extent physicians and patients elect to use AKCEA-APOCIII-L_{Rx} or AKCEA-TTR-L_{Rx} instead of WAYLIVRA or TEGSEDI, respectively, it will reduce the revenue we derive from those medicines. In addition, while vupanorsen, AKCEA-APOCIII-L_{Rx} and WAYLIVRA use different mechanisms of action, if vupanorsen can effectively lower triglyceride levels in patients with familial chylomicronemia syndrome, or FCS, it may likewise reduce the revenue we derive from WAYLIVRA and AKCEA-APOCIII-L_{Rx}.

Our medicines could be subject to regulatory limitations following approval.

Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of medicines. Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development.

The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine through the product label and on advertising, promotional and distribution activities. For example:

- in the U.S., TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis;
- TEGSEDI requires periodic blood and urine monitoring;
- in the U.S., TEGSEDI is available only through a REMS program; and
- we expect WAYLIVRA will require periodic blood monitoring if approved in the U.S.

Prescription medicines may be promoted only for the approved indications in accordance with the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label may be subject to significant liability.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the E.U., we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA, EC or other foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and time consuming to fulfill.

If we or others identify side effects after any of our medicines are on the market, or if manufacturing problems occur subsequent to regulatory approval, or if we, our manufacturers or our partners fail to comply with regulatory requirements, we or our partners may, among other things, lose regulatory approval and be forced to withdraw products from the market, need to conduct additional clinical studies, incur restrictions on the marketing, distribution or manufacturing of the product, and/or change the labeling of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

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

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

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

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

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

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

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

To successfully commercialize TEGSEDI and WAYLIVRA, Akcea must effectively 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 WAYLIVRA in the initial indications Akcea is pursuing and to continue the commercialization of TEGSEDI, Akcea will need to optimize and maintain specialty sales forces in the global regions where it currently markets or expects to market TEGSEDI and WAYLIVRA, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine blood and urine monitoring and a medical affairs team.

Even though certain members of Akcea's management team and other employees have experience commercializing medicines, as a company Akcea has limited experience marketing, selling and distributing medicines, and there are significant risks involved in building, tailoring, optimizing and managing a commercial infrastructure. Since September 2019, Akcea has announced several changes to its senior leadership team, including the departure of its Chief Executive Officer, its President, its Chief Operating Officer, its Chief Financial Officer and the retirement of its Chief Medical Officer. Akcea has also appointed a new Chief Executive Officer, a new Chief Commercial Officer, a new Chief Operating Officer, a new General Counsel, a new Chief Financial Officer and a new Chief Medical Officer. The effectiveness of the senior leadership team following these transitions, new leaders as they fill in these roles, and any further transition as a result of these changes could impair Akcea's ability to manage its business.

It is expensive and time consuming for Akcea to maintain its own sales forces and related compliance protocols to market TEGSEDI and WAYLIVRA, and it will be increasingly expensive and time consuming when Akcea commercially launches additional medicines, if approved. Akcea may never successfully optimize or manage this capability and any failure could harm the commercial launch of WAYLIVRA or adversely affect TEGSEDI sales. Additionally, Akcea and its partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel. As a result of Akcea's receipt of a complete response letter, or CRL, from the FDA regarding the new drug application for WAYLIVRA, on September 6, 2018, Akcea enacted a plan to reorganize its workforce to better align with the immediate needs of the business. In connection with this reorganization plan, Akcea reduced its workforce by approximately 12% and will need to increase its operations and expand its use of third -party contractors if WAYLIVRA is approved in the U.S.

Akcea has incurred expenses launching, optimizing and managing the marketing and sales infrastructure for TEGSEDI in the E.U., Canada and the U.S., and WAYLIVRA in the E.U. If regulatory requirements or other factors cause the commercialization of TEGSEDI or WAYLIVRA to be less successful than expected in important markets, Akcea would incur additional expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI or WAYLIVRA. Akcea's sales force and marketing teams may not successfully commercialize TEGSEDI or WAYLIVRA.

To the extent we and Akcea decide to rely on third parties to commercialize TEGSEDI or WAYLIVRA in a particular geographic market, we may receive less revenue than if Akcea commercialized TEGSEDI or WAYLIVRA by itself. For example, in August 2018, Akcea granted PTC Therapeutics International Limited, or PTC Therapeutics, the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries, and Akcea will continue to rely on PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in those geographic markets. If PTC Therapeutics does not successfully commercialize TEGSEDI or WAYLIVRA, including as a result of delays or disruption caused by the current COVID-19 Pandemic, that may affect PTC Therapeutics' ability to commercialize TEGSEDI or WAYLIVRA, and Akcea may receive limited revenue for TEGSEDI or no revenue for WAYLIVRA in Latin America or certain Caribbean countries. In addition, in August 2018 Akcea entered into an agreement with Accredo Health Group, Inc., or Accredo, a subsidiary of Express Scripts, to be Akcea's specialty pharmacy partner for distribution of TEGSEDI in the U.S. Further, Akcea has less control over the sales efforts of other third parties, including PTC Therapeutics and Accredo, involved in commercializing TEGSEDI or WAYLIVRA.

If Akcea cannot effectively build and manage its distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable third party to perform such functions, the sales of TEGSEDI and WAYLIVRA may be adversely affected. Any 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.

In addition, in response to the public health directives and orders related to the COVID-19 Pandemic, Akcea implemented work-from-home policies for its employees globally and suspended business-related travel. The effects of the government orders and Akcea's work-from-home and travel policies in response to the COVID-19 Pandemic have thus far had a limited impact on Akcea's productivity, business and commercialization efforts for TEGSEDI and WAYLIVRA, but the effects of these orders and policies may become more significant in the future.

If government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, 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 payers. The majority of patients in the U.S. who would fit within our target patient populations for our medicines have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new medicines when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our medicines affordable. Accordingly, SPINRAZA, TEGSEDI and WAYLIVRA for FCS in the E.U. and, if approved, WAYLIVRA in the U.S. or Canada and for additional indications, and our medicines in development, will face competition from other therapies and medicines for limited financial resources. We or our partners may need to conduct post-marketing studies to demonstrate the cost-effectiveness of any future products to satisfy third-party payers. These studies might require us to commit a significant amount of management time and financial and other resources. Third-party payers may never consider our future products as cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U.S., no uniform policy of coverage and reimbursement for medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act, was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers, and continues to significantly impact the U.S. pharmaceutical industry. There remain judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as efforts by the Trump administration to repeal or replace certain aspects of the Affordable Care Act. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the Affordable Care Act are invalid as well. However, in March 2020, before the District Court could rule on the remaining provisions of the Affordable Care Act, the U.S. Supreme Court agreed to review the case. The Supreme Court is expected to rule on the case in its next session, which begins in October 2020. It is unclear how such litigation and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act and our business.

Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the U.S. and in international markets. For example, in the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries and legislation designed to, among other things, reform government program reimbursement methodologies for medicines and bring more transparency to drug pricing. At the federal level, the Trump administration's budget for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses and place limits on pharmaceutical price increases. On July 24, 2020, President Trump announced four executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals, including a policy that would tie Medicare Part B drug prices to international drug prices; one that directs the U.S. Department of Health and Human Services, or HHS, to finalize the Canadian drug importation proposed rule previously issued by HHS and makes other changes allowing for personal importation of drugs from Canada; one that directs HHS to finalize the rulemaking process on modifying the anti-kickback law safe harbors for plans, pharmacies, and pharmaceutical benefit managers; and one that reduces costs of insulin and epipens to patients of federally qualified health centers. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, and third-party payers, whether foreign or domestic, or governmental or commercial, may allocate their resources to address the current COVID-19 Pandemic or experience delays or disruptions in their ability to devote resources to coverage and reimbursement matters related to our products or medicines as a result of the COVID-19 Pandemic, which would negatively affect the potential commercial success of our products, our revenue and our profits.

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

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

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

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

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our medicines. It is possible that regulatory agencies will not approve our medicines for marketing or SPINRAZA, TEGSEDI or WAYLIVRA in additional markets or for additional indications. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or our medicines in development, the agency will not approve the specific medicine or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the medicine. For example, in August 2018 Akcea received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in Akcea's clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. Akcea also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Akcea are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA.

The FDA or other comparable foreign regulatory authorities can delay, limit or deny approval of a medicine for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical studies;
- we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a medicine is safe and effective for any indication;
- such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the U.S.;
- we or our partners may be unable to demonstrate that our medicine's clinical and other benefits outweigh its safety risks to support approval;
- such authorities may disagree with the interpretation of data from preclinical or clinical studies;
- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers who manufacture clinical and commercial supplies for our medicines; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

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

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

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

In the past, we have invested in clinical studies of medicines that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our medicines, including the studies of tominersen, tofersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}. If any of our medicines in clinical studies, including tominersen, tofersen, AKCEA-APO(a)-$L_{Rx,}$ and AKCEA-TTR-L_{Rx}, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

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

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies, including the studies of tominersen, tofersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a medicine on subjects in the trial;
- we, or our partners, 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;
- we or our partners, including our independent clinical investigators, contract research organizations and other third-party service providers on which we rely, may not identify, recruit and train suitable clinical investigators at a sufficient number of study sites or timely enroll a sufficient number of study subjects in the clinical study;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- 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;
- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our medicines; and
- the supply or quality of our medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

The current COVID-19 Pandemic could make some of these factors more likely to occur.

In addition, our current medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our medicines or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our medicines: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. This happened in connection with the conditional marketing approval for WAYLIVRA in the E.U., as the EC is requiring Akcea to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. Akcea has an ongoing OLE extension study of WAYLIVRA in patients with FCS and an OLE study of TEGSEDI in patients with hATTR, and an early access program, or EAP, for both WAYLIVRA and TEGSEDI. Adverse events or results from these studies or the EAPs could negatively impact Akcea's pending or future marketing approval applications for WAYLIVRA and TEGSEDI in patients with FCS or hATTR amyloidosis or the commercial opportunity for WAYLIVRA or TEGSEDI.

Any failure or delay in the clinical studies, including the studies of tominersen, tofersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}, could reduce the commercial potential or viability of our medicines.

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

To successfully commercialize any of our medicines, we or our partner would need to optimize and manage large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. We and Akcea rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities, including any interruption to our supply chain as a result of the current COVID-19 Pandemic, could limit the commercial success of our medicines.

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

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We, our partners 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 authorizations for our medicines, including authorizations for SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, or result in enforcement action after authorization that could limit the commercial success of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development.

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

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Pharmaceutical Research Associates, Inc., Icon Clinical Research Limited, Syneos Health, Inc., PPD and Medpace for the clinical studies for our medicines, including tominersen, tofersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations, including as a result of delays or disruption caused by the current COVID-19 Pandemic that may affect the third party's ability to conduct the clinical studies for our medicines, or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our medicines or additional marketing authorizations for TEGSEDI and WAYLIVRA.

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of June 30, 2020, we had an accumulated deficit of approximately $0.9 billion and stockholders' equity of approximately $1.4 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. If we do not continue to earn substantial revenue, we may incur additional operating losses in the future. We may not successfully develop any additional products or achieve or sustain future profitability.

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

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

Under the Tax Cut and Jobs Act of 2017, or the Tax Act, as modified by the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such U.S. federal net operating losses is limited to 80 percent of taxable income beginning in 2021. It is uncertain if and to what extent various states will conform to the federal Tax Act or the CARES Act. The CARES Act also reinstated the net operating loss carryback provisions whereby net operating losses incurred in calendar tax years 2018, 2019 and 2020 may be carried back to offset taxable income of the five tax years preceding the year of the loss.

In June 2020, California enacted Assembly Bill 85 (AB 85), which suspends NOLs and limits credit utilization to $5 million per year for the 2020, 2021 and 2022 tax years. We do not believe AB 85 will have an impact on our 2020 tax provision, but it is possible that it may in future years.

In addition, under Sections 382 and 383 of the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percent change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. A change in tax laws, treaties or regulations, or their interpretation, of any other country in which we operate could also affect us.

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

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

Our corporate partners are developing and/or funding many of the medicines in our development pipeline. For example, we are relying on:

- Roche for development and funding of tominersen;
- Novartis for development and funding of AKCEA-APO(a)-L_{Rx}; and
- Biogen for development and funding of tofersen.

If any of these pharmaceutical companies stops developing and/or funding these medicines, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these medicines on our own. Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, as part of a reprioritization of its pipeline and strategic review of its rare disease business, GSK declined its option to license TEGSEDI and IONIS-FB-L_{Rx}.

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

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

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

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

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

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

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our medicines, including SPINRAZA, tominersen, AKCEA-APO(a)-L_{Rx} and tofersen.

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain medicine will enter clinical trials, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization, or when our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions, many of which are outside of our control, including the current COVID-19 Pandemic. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to SPINRAZA, TEGSEDI, WAYLIVRA, tominersen, tofersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}, the price of our securities could decrease.

If we cannot protect our patent rights 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, secure and maintain intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the U.S. or in other countries and we may not be able to obtain, maintain or enforce our patents and other intellectual property rights which could impact our ability to compete effectively. 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.

We cannot be certain that the U.S. Patent and Trademark Office, or U.S. PTO, and courts in the U.S. or the patent offices and courts in foreign countries will consider the claims in our patents and applications covering SPINRAZA, TEGSEDI, WAYLIVRA, or any of our medicines in development as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, including through legal action.

If we or any licensor partner loses or cannot obtain patent protection for SPINRAZA, TEGSEDI, WAYLIVRA, or any of our other medicines in development, it could have a material adverse impact on our business.

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 may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

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

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

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorization, preclinical activities and commitment of significant additional resources prior to their successful commercialization. These activities will require significant cash. As of June 30, 2020, we had cash, cash equivalents and short-term investments equal to $2.3 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

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

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

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

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding June 30, 2020, the market price of our common stock ranged from $73.09 to $39.32 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, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

The current COVID-19 Pandemic has caused a significant disruption of global financial markets and has resulted in increased volatility in the trading price of our common stock. Additionally, broad market and industry factors may also materially harm the market price of our common stock irrespective of our operating performance. The stock market in general, and NASDAQ and the market for biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies which investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

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

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development. 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 medicines, 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.

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

We are dependent upon our own and third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, with third-party phishing and social engineering attacks in particular increasing in connection with the COVID-19 Pandemic. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, our efforts may not prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

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 adversely affected.

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

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

Provisions in our certificate of incorporation, convertible notes documents, call spread hedge transaction documents 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.

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 11.2 million shares of our common stock upon conversion of our convertible senior notes and up to 6.6 million shares may be issued in connection with the warrant transactions we entered into in connection with the issuance of our 0.125% Notes, in each case subject to customary anti-dilution adjustments. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

In addition, pursuant to the call spread transactions we entered into in connection with the pricing of our 0.125% Notes, the counterparties are likely to modify their hedge positions from time to time at or prior to the conversion or maturity of the notes by purchasing and selling shares of our common stock, other of our securities, or other instruments, including over-the-counter derivative instruments, that they may wish to use in connection with such hedging, which may have a negative effect on the conversion value of those notes and an adverse impact on the trading price of our common stock. The call spread transactions are expected generally to reduce potential dilution to holders of our common stock upon any conversion of our 0.125% Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0.125% Notes, as the case may be. However, the warrant transactions could separately have a dilutive effect to the extent that the market value per share of our common stock exceeds the applicable strike price of the warrants.

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

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

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

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

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us.

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 are currently experiencing substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government in response to the COVID-19 Pandemic. In the past, the failure, bankruptcy, or sale of various financial and other institutions created similar turmoil and uncertainty in such markets and industries. 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.

The impact on us of the vote by the United Kingdom to leave the European Union cannot be predicted.*

On June 23, 2016, the United Kingdom, or the U.K., voted to leave the E.U. in an advisory referendum, which is generally referred to as Brexit. In January 2020, the U.K. and the E.U. entered into a withdrawal agreement pursuant to which the U.K. formally withdrew from the E.U. on January 31, 2020. Following such withdrawal, the U.K. entered into a transition period scheduled to end on December 31, 2020, or the Transition Period. During the Transition Period, negotiations are expected to continue in relation to the customs and trading relationship between the U.K. and the E.U. following the expiry of the Transition Period. Due to the COVID-19 Pandemic, negotiations between the U.K. and the E.U. that have been scheduled since March have either been postponed or are occurring in a reduced forum via video conference. There is, therefore, an increased likelihood that the Transition Period may need to be extended beyond December 31, 2020 (although it remains the position of the U.K. government that it will not be extended).

In addition, as a result of Brexit, the European Medicines Agency, or EMA, formerly situated in London, relocated to Amsterdam. Following the Transition Period, there is a risk that the relocation will interrupt current administrative routines and occupy resources, which may generally adversely affect our dealings with the EMA. Further, there is considerable uncertainty resulting from a lack of precedent and the complexity of the U.K. and E.U.'s intertwined legal regimes as to how Brexit (following the Transition Period) will impact the life sciences industry in Europe, including our company, including with respect to ongoing or future clinical trials. The impact will largely depend on the model and means by which the U.K.'s relationship with the E.U. is governed post-Brexit. For example, following the Transition Period, the U.K. will no longer be covered by the centralized procedures for obtaining E.U.-wide marketing authorization from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products, including our product candidates, will be required in the UK, the potential process for which is currently unclear. Brexit may adversely affect and delay our ability to commercialize, market and sell our product candidates in the U.K.

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	Side Letter dated June 11, 2020 to the Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated October 17, 2018 (portions of the exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed).
10.2	Amendment No. 2 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015 (portions of the exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed).
10.3	Amended and Restated 2002 Non-Employee Directors' Stock Option Plan. Filed as an exhibit to the Registrant's Form DEF 14A filed with the SEC on April 24, 2020 and incorporated herein by reference.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended June 30, 2020, formatted in Inline Extensible Business Reporting Language (iXBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of stockholders' equity, (v) condensed consolidated statements of cash flows and (vi) notes to condensed consolidated financial statements (detail tagged).
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101).

* 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/ BRETT P. MONIA Brett P. Monia, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	August 5, 2020
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	August 5, 2020

Exhibit 10.1

CERTAIN IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THE EXHIBIT BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED. SUCH EXCLUDED INFORMATION HAS BEEN MARKED WITH "[***]".

June 11, 2020

Ionis Pharmaceuticals, Inc. 2855 Gazelle Court
Carlsbad, CA 92010 Attention: Brett Monia

Re: [***]

Dear Dr. Monia:

Reference is hereby made to that certain Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis Pharmaceuticals, Inc. ("Ionis") and Biogen MA Inc. ("Biogen") dated October 17, 2018 (the "Neurology II Agreement"), as supplemented and/or amended to date. Biogen and Ionis each may be referred to herein as a "Party" or collectively as the "Parties". Any capitalized terms not defined herein will have the meaning set forth in the Neurology II Agreement, as applicable.

The Parties acknowledge and agree that, notwithstanding anything to the contrary in the Neurology II Agreement:

(i) Milestones for [***]. For purposes of the [***] Collaboration Program only, the ALS Pre-Licensing Milestone Event set forth in the last row of Table 2 of Section 6.5 of the Neurology II Agreement shall be deleted in its entirety and replaced with the following:

[***]

(ii) Except as expressly amended herein, all other provisions of the Neurology II Agreement will remain in full force and effect.

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

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

Sincerely,

/s/Dale Morris
Dale Morris, Head Preclinical Safety
11-Jun-2020

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

By: /s/Brett Monia

Name: Brett Monia

Title: CEO

Date: June 17, 2020

Exhibit 10.2

CERTAIN IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THE EXHIBIT BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED. SUCH EXCLUDED INFORMATION HAS BEEN MARKED WITH "[***]".

AMENDMENT NO. 2

This Amendment No. 2 (the "**Amendment**") to the Strategic Collaboration Agreement dated July 31st, 2015, as previously amended by Amendment No. 1 dated October 18, 2018 (the "**Agreement**"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden ("**AstraZeneca**") and

(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 U.S.A. ("**Ionis**"),

and is made effective as of April 30, 2020 (the "**Amendment Effective Date**").

Recitals

WHEREAS, in accordance with the Agreement, AstraZeneca is Developing from the [***] Program both (i) [***] Products including [***] (each, a "[***] **Product**") and (ii) [***] Products (each, a "[***] **Product**"); and

WHEREAS, the Parties desire to amend and restate certain terms and conditions of the Agreement with respect to [***] Products under the [***] Program.

Agreement

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

1. Definitions

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

2. Modifications

a. With respect to the [***] Program, AstraZeneca will use Commercially Reasonable Efforts to [***] of the [***] Product known as [***] by [***].
b. Notwithstanding the provisions of Section 6.4 of the Agreement, upon the earlier of:

(i) [***] by AstraZeneca, its Affiliates or Sublicensees with respect to [***]; and

(ii) [***],

in accordance with Section 6.5.5 of the Agreement, AstraZeneca will pay to Ionis US$ [***], which shall satisfy AstraZeneca's obligations under Section 6.4 of the Agreement for the separate Product Milestone Event Payments of US$[***] for each of [***] and [***] for the Licensed Program that is the [***] Program.

If AstraZeneca, its Affiliates or Sublicensees are unable to achieve [***] by [***] for [***] due to [***] or any action or failure to act by a Third Party that is beyond the reasonable control of AstraZeneca, its Affiliates or Sublicensees, *provided* that AstraZeneca has taken all reasonable actions that would, in the normal course, be expected to have allowed such [***] by [***], then AstraZeneca will provide prompt written notice to Ionis containing sufficient detail and supporting documentation of the inability to achieve such [***], such notice to be provided no later than [***] (unless AstraZeneca becomes aware *after* [***] of the inability to achieve such [***], in which case AstraZeneca shall provide such notice as soon as practicable). Within [***] after such notice, the Parties will meet to discuss in good faith and agree upon an alternative timeframe applicable to such Product Milestone Event Payment. If the Parties cannot in good faith agree on such an alternative timeframe, then either Party may refer the matter to the Senior Vice President for Early CVRM of AstraZeneca and the Executive Vice President and Chief Corporate Development Officer of Ionis (the "***Senior Executives***") for resolution. The Senior Executives will meet as soon as reasonably possible thereafter and use their good faith efforts to mutually agree upon an alternative timeframe applicable to such Product Milestone Event Payment. Notwithstanding anything herein to the contrary, under no circumstances will the Product Milestone Event Payment corresponding to [***] be due later than the due date for achievement of [***] for [***] as determined pursuant to Section 6.5.5 of the Agreement.

c. Notwithstanding the provisions of Section 6.4 of the Agreement, in respect of the Licensed Program that is the [***] Program, if the following Product Milestone Events are first achieved by a [***] Product, then the corresponding Product Milestone Event Payments in TABLE 1 shall be amended to read as:

TABLE 1	
Product Milestone Event	**Product Milestone Event Payment (Applicable only if first achieved by a [***] Product)**
[***]	$[***]
[***]	$[***]

For clarity, in respect of the Licensed Program that is the [***] Program, if the foregoing Product Milestone Events are first achieved by a [***] Product, then the corresponding Product Milestone Event Payments shall be as set forth in TABLE 1 of Section 6.4 of the Agreement without amendment.

d. Notwithstanding that both [***] Products and [***] Products arise from the [***] Program, for purposes of Section 6.7 (Royalty Payments) of the Agreement, [***] Products shall be treated as arising from one Licensed Program (and royalties will be due on [***] Products in accordance with Section 2(e) below) and [***] Products shall be treated as arising from another Licensed Program (and royalties will be due on [***] Products in accordance with Section 6.7 of the Agreement).

e. Solely with respect to such Licensed Program applicable to [***] Products, TABLE 2 in Section 6.7.1 (AstraZeneca Full Royalty) of the Agreement shall be amended to read as follows:

TABLE 2		
Royalty Tier	**Annual Worldwide Net Sales of Products from a Licensed Program (Applicable onlyto[***] Products)**	**Royalty Rate**
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

f. The following shall be added as Section 6.14 to the Agreement:

"6.14. **Commercial Milestones for [***] Products**.

As partial consideration for the rights granted to AstraZeneca hereunder, in accordance with Section 6.5.5, AstraZeneca will pay to Ionis the milestone payments as set forth in TABLE 3 below when a milestone event listed in TABLE 3 is first achieved by AstraZeneca, its Affiliates or Sublicensees with respect to a [***] Product:

TABLE 3	
Commercial Milestone Event **If aggregate Net Sales of all [***] Products sold by AstraZeneca, its Affiliates or Sublicensees in a given Calendar Year exceeds the amount stated below for such Calendar Year:**	**Commercial Milestone Event Payment then AstraZeneca will pay to Ionis:**
US$ [***]	US$ [***]
US$ [***]	US$ [***]
US$ [***]	US$ [***]
US$ [***]	US$ [***]
US$ [***]	US$ [***]
US$ [***]	US$ [***]
US$ [***]	US$ [***]

In the event that in a given Calendar Year more than one of the foregoing thresholds set forth in TABLE 3 is exceeded, AstraZeneca will pay to Ionis a separate milestone payment with respect to each such threshold that is exceeded in such Calendar Year. Each milestone payment in this Section 6.14 will be payable only upon the first achievement of such milestone event in a given Calendar Year and no amounts shall be due for subsequent or repeated achievements of such milestone in subsequent Calendar Years."

3. Amendment Effective Date

This Amendment shall become effective on the Amendment Effective Date.

4. Entire Agreement

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreement. The Agreement together with this Amendment supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreement, as amended. Each Party confirms that it is not relying on any representations, warranties, or covenants of the Party except as specifically set out in the Agreement as amended. Nothing in this Amendment is intended to limit or exclude any liability or fraud. The Parties hereby agree that subject to the modifications specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

[*Remainder of page intentionally blank. Signatures follow.*]

Execution

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

ASTRAZENECA AB (publ.)		**IONIS PHARMACEUTICALS, INC.**	
Signature:	/s/ Regina Fritsche-Danielson	Signature:	/s/ Brett Monia
Name:	Regina Fritsche-Danielson	Name:	Brett Monia
Title:	SVP and Head of Research and Early Development, Cardiovascular, Renal and Metabolic	Title:	CEO

EXHIBIT 31.1

CERTIFICATION

I, Brett P. Monia, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 5, 2020

/s/ BRETT P. MONIA
Brett P. Monia, Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 5, 2020

/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, Brett P. Monia, the Chief Executive Officer of Ionis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended June 30, 2020, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: August 5, 2020

/s/ BRETT P. MONIA
Brett P. Monia, Ph.D.
Chief Executive Officer

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

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