UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 2021

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 April 29, 2021 was 140,963,028.

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TRADEMARKS

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

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

	March 31, 2021	December 31, 2020 (as revised*)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 414,155	$ 397,664
Short-term investments	1,405,840	1,494,711
Contracts receivable	23,397	76,204
Inventories	22,199	21,965
Other current assets	123,827	140,163
Total current assets	1,989,418	2,130,707
Property, plant and equipment, net	180,413	181,077
Patents, net	28,795	27,937
Deposits and other assets	49,925	50,034
Total assets	$ 2,248,551	$ 2,389,755
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 9,506	$ 17,199
Accrued compensation	29,263	65,728
Accrued liabilities	78,766	90,161
Income taxes payable	1,326	1,324
Current portion of 1 percent convertible senior notes, net	61,816	308,809
Current portion of long-term obligations	7,688	7,301
Current portion of deferred contract revenue	106,740	108,376
Total current liabilities	295,105	598,898
Long-term deferred contract revenue	401,966	424,046
0.125 percent convertible senior notes, net	540,679	540,136
1 percent convertible senior notes, net	247,292	–
Long-term obligations, less current portion	22,943	23,409
Long-term mortgage debt	60,002	59,984
Total liabilities	1,567,987	1,646,473
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 140,924,356 and 140,365,594 shares issued and outstanding at March 31, 2021 (unaudited) and December 31, 2020, respectively	141	140
Additional paid-in capital	1,925,801	1,895,519
Accumulated other comprehensive loss	(24,203)	(21,071)
Accumulated deficit	(1,221,175)	(1,131,306)
Total stockholders' equity	680,564	743,282
Total liabilities and stockholders' equity	$ 2,248,551	$ 2,389,755

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended March 31,	
	2021	**2020 (as revised*)**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 59,986	$ 66,008
TEGSEDI and WAYLIVRA revenue, net	19,838	15,159
Licensing and other royalty revenue	4,624	2,794
Total commercial revenue	84,448	83,961
Research and development revenue under collaborative agreements	27,159	49,406
Total revenue	111,607	133,367
Expenses:		
Cost of sales	2,578	2,548
Research, development and patent	139,801	116,952
Selling, general and administrative	61,199	74,994
Total operating expenses	203,578	194,494
Loss from operations	(91,971)	(61,127)
Other income (expense):		
Investment income	4,643	10,479
Interest expense	(2,414)	(2,207)
Other income (expenses)	3	(99)
Loss before income tax (expense) benefit	(89,739)	(52,954)
Income tax (expense) benefit	(130)	3,072
Net loss	(89,869)	(49,882)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	10,254
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (89,869)	$ (39,628)
Basic and diluted net loss per share	$ (0.64)	$ (0.28)
Shares used in computing basic and diluted net loss per share	140,770	139,429

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended March 31,	
	2021	**2020 (as revised*)**
Net loss	$ (89,869)	$ (49,882)
Unrealized losses on debt securities, net of tax	(3,006)	(1,954)
Currency translation adjustment	(126)	9
Comprehensive loss	(93,001)	(51,827)
Comprehensive loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	(10,254)
Comprehensive loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (93,001)	$ (41,573)

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Three Months Ended March 31, 2020 and 2021
(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, 2019 (as revised*)	140,340	$ 140	$ 1,985,650	$ (25,290)	$ (596,495)	$ 1,364,005	$ 213,453	$ 1,577,458
Net loss	—	—	—	—	(39,628)	(39,628)	—	(39,628)
Change in unrealized losses, net of tax	—	—	—	(1,954)	—	(1,954)	—	(1,954)
Foreign currency translation	—	—	—	9	—	9	—	9
Issuance of common stock in connection with employee stock plans	606	—	7,652	—	—	7,652	—	7,652
Repurchases and retirements of common stock	(1,478)	(1)	—	—	(90,549)	(90,550)	—	(90,550)
Stock-based compensation expense	—	—	40,790	—	—	40,790	—	40,790
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(186)	—	(11,603)	—	—	(11,603)	—	(11,603)
Noncontrolling interest in Akcea Therapeutics, Inc	—	—	(6,973)	—	—	(6,973)	(3,281)	(10,254)
Balance at March 31, 2020 (as revised*)	139,282	$ 139	$ 2,015,516	$ (27,235)	$ (726,672)	$ 1,261,748	$ 210,172	$ 1,471,920
Balance at December 31, 2020 (as revised*)	140,366	$ 140	$ 1,895,519	$ (21,071)	$ (1,131,306)	$ 743,282	$ —	$ 743,282
Net loss	—	—	—	—	(89,869)	(89,869)	—	(89,869)
Change in unrealized loss, net of tax	—	—	—	(3,006)	—	(3,006)	—	(3,006)
Foreign currency translation	—	—	—	(126)	—	(126)	—	(126)
Issuance of common stock in connection with employee stock plans	809	1	7,758	—	—	7,759	—	7,759
Stock-based compensation expense	—	—	37,861	—	—	37,861	—	37,861
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(251)	—	(15,337)	—	—	(15,337)	—	(15,337)
Balance at March 31, 2021	140,924	$ 141	$ 1,925,801	$ (24,203)	$ (1,221,175)	$ 680,564	$ —	$ 680,564

* We revised our 2019 and 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended March 31,	
	2021	**2020 (as revised*)**
Operating activities:		
Net loss	$ (89,869)	$ (49,882)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	3,917	3,233
Amortization of right-of-use operating lease assets	394	393
Amortization of patents	544	486
Amortization of premium (discount) on investments, net	4,023	1,062
Amortization of debt issuance costs	860	647
Stock-based compensation expense	37,861	40,790
Gain on investments	(13)	(246)
Non-cash losses related to patents	221	159
Provision for deferred income taxes	—	(2,288)
Changes in operating assets and liabilities:		
Contracts receivable	52,807	34,429
Inventories	(234)	(2,181)
Other current and long-term assets	16,481	9,532
Income taxes payable	2	(532)
Accounts payable	(9,569)	411
Accrued compensation	(36,465)	(20,920)
Accrued liabilities and other current liabilities	(11,905)	(3,006)
Deferred contract revenue	(23,717)	(19,679)
Net cash used in operating activities	(54,662)	(7,592)
Investing activities:		
Purchases of short-term investments	(330,051)	(544,375)
Proceeds from sale of short-term investments	411,907	459,352
Purchases of property, plant and equipment	(1,772)	(9,080)
Acquisition of licenses and other assets, net	(1,228)	(904)
Net cash provided by (used in) investing activities	78,856	(95,007)
Financing activities:		
Proceeds from equity, net	7,760	7,652
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(15,337)	(11,603)
Repurchases and retirements of common stock	—	(90,550)
Net cash used in financing activities	(7,577)	(94,501)
Effects of exchange rates on cash	(126)	8
Net increase (decrease) in cash and cash equivalents	16,491	(197,092)
Cash and cash equivalents at beginning of period	397,664	683,287
Cash and cash equivalents at end of period	$ 414,155	$ 486,195
Supplemental disclosures of cash flow information:		
Interest paid	$ 594	$ 601
Income taxes paid	$ 2	$ 3
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,876	$ 4,903

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three months ended March 31, 2021 and 2020 on the same basis as the audited financial statements for the year ended December 31, 2020, with the exception of our retrospective adoption of Accounting Standards Update, or ASU, 2020-06, which simplifies the accounting for convertible debt instruments. See Note 2, *Significant Accounting Polices*, *Convertible Debt*, for details of our adoption of this guidance. 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, 2020 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In our condensed consolidated financial statements, we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our wholly owned subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries ("we", "us" or "our"). We formed Akcea in December 2014. In July 2017, Akcea completed an initial public offering, or IPO, which reduced our ownership of Akcea's common stock below 100 percent. In October 2020, we acquired the shares of Akcea's common stock we did not own. We will refer to this transaction as the Akcea Acquisition throughout the remainder of this document. We reflected changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the change occurred.

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 under our other partnerships.

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

In the United States, or U.S., through the first quarter of 2021, we sold TEGSEDI through an exclusive distribution agreement with a third-party logistics company, or 3PL, that took title to TEGSEDI. The 3PL was our sole customer in the U.S. The 3PL then distributed TEGSEDI to a specialty pharmacy and a specialty distributor, which we collectively refer to as wholesalers, who then distributed TEGSEDI to health care providers and patients. In Europe, through 2020, we sold TEGSEDI and WAYLIVRA to hospitals and pharmacies, which were our customers, using 3PLs as distributors. In January 2021, we began commercializing TEGSEDI and WAYLIVRA in Europe through a distribution agreement with Swedish Orphan Biovitrum AB, or Sobi. In April 2021, we expanded our distribution agreement with Sobi to also include commercializing TEGSEDI in North America. Under our agreements, we are responsible for supplying finished goods inventory to Sobi and Sobi is responsible for selling each medicine to the end customer. As a result of these agreements, we earn a distribution fee on net sales from Sobi for each medicine.

Under our collaboration agreement with PTC, PTC is responsible for commercializing TEGSEDI and WAYLIVRA in Latin America and Caribbean countries.

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.

See Note 5, *Collaborative Arrangements and Licensing Agreements*, for collaborations with substantive changes that occurred in 2021. Additionally, see 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, 2020 for a summary of each of our material collaborative agreements.

Steps to Recognize Revenue

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

1. Identify the contract

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

- We and our partner approved the contract and we are both committed to perform our obligations;
- We have identified our rights, our partner's rights and the payment terms;
- We have concluded that the contract has commercial substance, meaning that the risk, timing, or amount of our future cash flows is expected to change as a result of the contract; and
- We believe collectability 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 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 and are not priced at a significant discount. 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/ or are usually based on scientific progress which is inherently uncertain. For example, in the fourth quarter of 2020, we earned a $20 million milestone payment from AstraZeneca when AstraZeneca initiated a Phase 2b study for ION449, our medicine in development targeting PCSK9 to lower LDL-cholesterol. We did not consider the milestone payment probable until AstraZeneca achieved the milestone event because advancing ION449 was contingent on AstraZeneca initiating a Phase 2b study and 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;
- Estimated 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.

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: TEGSEDI and WAYLIVRA revenue, net

Prior to our distribution agreement with Sobi, we recognized TEGSEDI and WAYLIVRA commercial revenue in the period when our customer obtained control of our products, which occurred at a point in time upon transfer of title to the customer. We classified payments to customers or other parties in the distribution channel for services that were distinct and priced at fair value as selling, general and administrative, or SG&A, expenses in our condensed consolidated statements of operations. We classified payments to customers or other parties in the distribution channel that did not meet those criteria as a reduction of revenue, as discussed further below. We excluded from revenues taxes collected from customers relating to TEGSEDI and WAYLIVRA commercial revenue and remitted these amounts to governmental authorities.

Under our distribution agreement with Sobi we concluded that our performance obligation is to supply finished goods inventory to Sobi. This performance obligation is a series of distinct activities that are substantially the same because we transfer title using the same criteria each time we ship inventory to Sobi. Therefore, we recognize as revenue the price Sobi pays us for the inventory when we deliver the finished goods inventory to Sobi. We also recognize distribution fee revenue based on Sobi's net sales of TEGSEDI and WAYLIVRA. Additionally, Sobi does not generally have a right of return.

Reserves for TEGSEDI and WAYLIVRA commercial revenue

Prior to our distribution agreement with Sobi, we recorded TEGSEDI and WAYLIVRA commercial revenue at our net sales price, or transaction price. We included in our transaction price estimated reserves for discounts, returns, chargebacks, rebates and other allowances that we offered within contracts between us and our customers, wholesalers, distributors, health care providers and other indirect customers. We estimated our reserves using the amounts we have earned or we could claim on the associated sales. We classified our reserves as a reduction of accounts receivable when we were not required to make a payment or as a current liability when we were required to make a payment. In certain cases, our estimates included a range of possible outcomes that were 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 reflected our best estimates under the terms of our respective contracts. When calculating our reserves and related TEGSEDI and WAYLIVRA commercial revenue, we only recognized amounts to the extent that we considered it probable that we would not have to reverse a significant amount of the cumulative sales we previously recognized in a future period. The actual amounts we receive may ultimately differ from our reserve estimates. If actual amounts in the future vary from our estimates, we will adjust these estimates, which would affect our net TEGSEDI and WAYLIVRA revenue in the corresponding period. See our revenue recognition policy in Note 1, *Organization and Significant Accounting Policies*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2020 for additional details regarding how we accounted for the reserves related to TEDSEDI and WAYLIVIRA product sales.

Under our distribution agreement with Sobi, Sobi is financially responsible for any applicable reserves.

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 typically 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 fourth quarter of 2020, we achieved a $7.5 million milestone payment from Biogen when we advanced a target under our 2018 strategic collaboration. We added this payment to the transaction price and allocated it to our R&D services performance obligation. 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 third quarter of 2020, we recognized $18 million in milestone payments when Biogen initiated a Phase 1/2 trial for ION464, our medicine in development targeting alpha-synuclein to treat patients with multiple system atrophy. We concluded that the milestone payments were not related to our R&D services performance obligation. Therefore, we recognized the milestone payments in full in the third 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 fourth quarter of 2020, we earned a $30 million license fee from AstraZeneca when AstraZeneca licensed ION455, an investigational medicine in development to treat nonalcoholic steatohepatitis, or NASH.

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.

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 sold 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 are sold at a 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, 2020 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 contracts receivable to be unconditional. We typically receive payment within one quarter of billing our partner or customer.

As of March 31, 2021, approximately 46.8 percent of our contracts receivables were from three significant customers. As of December 31, 2020, approximately 99.5 percent of our contracts receivables were from two significant customers.

Unbilled SPINRAZA Royalties

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

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our condensed consolidated balance sheet. During the three months ended March 31, 2021 and 2020, we recognized $26.0 million and $28.0 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 Sales

Our cost of sales 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 sales.

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 in our condensed consolidated statement of operations. We use the specific identification method to determine the cost of securities sold.

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At March 31, 2021, 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 seven privately held companies, Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, 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 and fourth quarters of 2020, we revalued our investments in three privately held companies, Dynacure, Suzhou-Ribo and Aro Biotherapeutics because the companies sold additional equity securities that were similar to the equity we own. These observable price changes resulted in us recognizing a $6.3 million gain on our investment in Dynacure, a $3.0 million gain on our investment in Suzhou-Ribo and a $5.5 million gain on our investment in Aro Biotherapeutics in our condensed consolidated statement of operations during 2020 because the sales were at higher prices compared to our recorded value.

Inventory Valuation

We reflect our inventory on our condensed consolidated balance sheet at the lower of cost or net realizable 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 March 31, 2021, 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 recorded an insignificant amount of inventory write-offs for the three months ended March 31, 2021 and 2020.

Our inventory consisted of the following (in thousands):

	March 31, 2021	December 31, 2020
Raw materials:		
Raw materials- clinical	$ 10,695	$ 9,206
Raw materials- commercial	7,502	7,502
Total raw materials	18,197	16,708
Work in process	2,096	2,252
Finished goods	1,906	3,005
Total inventory	$ 22,199	$ 21,965

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 determine the lease term at the inception of each 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. When we exercise a lease option that was not previously included in the initial lease term, we reassess our right-of-use asset and lease liabilities for the new lease term.

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), as of the lease inception date or at the lease option extension 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 we expect to realize.

We evaluate our deferred tax assets regularly to determine whether adjustments to the valuation allowance are appropriate due to changes in facts or circumstances, such as changes in expected future pre-tax earnings, tax law, interactions with taxing authorities and developments in case law. In making this evaluation, we rely on our recent history of pre-tax earnings. Our material assumptions are our forecasts of future pre-tax earnings and the nature and timing of future deductions and income represented by the deferred tax assets and liabilities, all of which involve the exercise of significant judgment.

We assessed our valuation allowance requirements and recorded a valuation allowance against all of Ionis' U.S. federal net deferred tax assets in the fourth quarter of 2020, due to uncertainties related to our ability to realize the tax benefits associated with these assets. We based our determination largely on Akcea rejoining the Ionis U.S. consolidated federal tax group in the fourth quarter of 2020. Due to Akcea's historical and projected financial statement losses, and the negative impact we expect this to have on Ionis' consolidated taxable income, there is uncertainty of generating sufficient consolidated pre-tax income in future periods to realize the Ionis deferred tax benefits. We also expect that Ionis' pre-tax income in future periods may be lower due to increased research and development expenses associated with our pipeline of wholly owned medicines. We continue to maintain a valuation allowance against all our consolidated U.S. federal and state net deferred tax assets.

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

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the U.S. that require us to make estimates and assumptions that affect the amounts reported in our condensed consolidated financial statements and accompanying notes. Actual results could differ from our estimates.

Basic and Diluted Net Loss Per Share

Basic net loss per share

In the first quarter of 2021, we computed basic net loss per share by dividing our net loss by our weighted-average number of common shares outstanding during the period. For the first quarter of 2021, we did not have to consider Akcea results separately in our calculation because we owned 100 percent of Akcea for the entire period. Our basic net loss per share for the three months ended March 31, 2021 was $0.64.

In the first quarter of 2020, prior to the Akcea Acquisition, we calculated our net loss for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period to determine our total net loss attributable to our common stockholders. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's net loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net loss available to Ionis common stockholders for the calculation of net loss per share is different than our net 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 March 31, 2020, was calculated as follows (in thousands, except per share amounts):

Three months ended March 31, 2020	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Loss Per Share**	**Basic Net Loss Per Share Calculation (as revised*)**
Ionis' portion of Akcea's net loss	77,095	$ (0.42)	$ (32,674)
Akcea's net loss attributable to our ownership			$ (32,674)
Ionis' stand-alone net loss			(7,032)
Net loss available to Ionis common stockholders			$ (39,706)
Weighted average shares outstanding			139,429
Basic net loss per share			$ (0.28)

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

Diluted net loss per share

For the three months ended March 31, 2021 and 2020, 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;
- Note hedges related to the 0.125 percent convertible senior notes;
- 1 percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

Additionally as of March 31, 2021, we had warrants related to our 0.125 percent convertible senior notes outstanding. We will include the shares issuable under these 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.

Convertible Debt

Adoption of ASU 2020-06

In August 2020, the FASB issued ASU 2020-06, which simplifies the accounting for convertible debt instruments, amends the guidance on derivative scope exceptions for contracts in an entity's own equity, and modifies the guidance on diluted earnings per share calculations. We adopted ASU 2020-06 on January 1, 2021 under the full retrospective approach, which required us to revise our prior period financial statements. This guidance impacted our accounting for outstanding convertible debt. As of March 31, 2021, we had two outstanding convertible notes, our 0.125 percent senior convertible notes, or 0.125% Notes, which mature in December 2024, and our 1 percent senior convertible notes, or 1% Notes, which mature in November 2021.

The updated guidance eliminates the cash conversion accounting model we previously followed in Accounting Standard Codification, or ASC, 470-20, which required us to separate each of our convertible debt instruments at issuance into two units of accounting, a liability component, based on our nonconvertible debt borrowing rate at issuance, and an equity component. Under ASU 2020-06, we now account for each of our convertible debt instruments as a single unit of accounting, a liability, because we concluded that the conversion features do not require bifurcation as a derivative under ASC 815-15 and our convertible debt instruments were not issued at a substantial premium. Since we adopted ASU 2020-06 using the full retrospective approach, we were required to apply the guidance to all convertible debt instruments we had outstanding as of January 1, 2019. We recomputed the basis of each convertible debt instrument as if we accounted for each as a single unit of accounting at issuance. This update included recalculating the amortization of debt issuance costs using an updated effective interest rate. As a result of adopting ASU 2020-06, we recorded a cumulative adjustment to decrease our additional paid in capital and our accumulated deficit at January 1, 2019. We have updated these financial statements to reflect the cumulative adjustment for the periods presented. We have labeled our prior period financial statements "as revised" to indicate the change required under the new accounting guidance. Below is a summary of the change in our balance sheet at December 31, 2020 and statement of operations from our first quarter 2020 under the ASC 470-20 legacy guidance compared to the new ASU 2020-06 guidance we adopted:

The following table summarizes the adjustments we made to the condensed consolidated balance sheet we originally reported at December 31, 2020 to adopt ASU 2020-06 (in thousands):

	December 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
1 percent convertible senior notes	$ 293,161	$ 15,648	$ 308,809
0.125 percent convertible senior notes	$ 455,719	$ 84,417	$ 540,136
Additional paid-in-capital	$ 2,113,646	$ (218,127)	$ 1,895,519
Accumulated deficit	$ (1,249,368)	$ 118,062	$ (1,131,306)

Under ASU 2020-06, our revised ending balances for our 1% Notes and 0.125% Notes as of December 31, 2020 represent the principal balance of each convertible debt instrument less debt issuance costs. Additionally, because we have deferred tax assets related to our convertible debt instruments, we also adjusted these amounts as part of our adoption of ASU 2020-06. However, because we have a full valuation allowance on our deferred tax assets, there was no impact to our condensed consolidated balance sheet related to our deferred tax assets.

The following table summarizes the adjustments we made to the condensed consolidated statement of operations we originally reported at March 31, 2020 to adopt ASU 2020-06 (in thousands):

	Three Months Ended March 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Interest expense	$ (10,990)	$ 8,783	$ (2,207)
Loss before income tax benefit	$ (61,737)	$ 8,783	$ (52,954)
Income tax benefit	$ 3,257	$ (185)	$ 3,072
Net loss	$ (58,480)	$ 8,598	$ (49,882)
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (48,226)	$ 8,598	$ (39,628)
Basic and diluted net loss per share	$ (0.35)	$ 0.07	$ (0.28)

Under ASU 2020-06, our revised interest expense is lower as we are no longer recording non-cash interest expense related to a debt discount. This decrease was partially offset by the increase in interest expense related to the amortization of debt issuance costs because we no longer allocate a portion of our debt issuance costs to stockholders' equity at issuance. Instead, the entire debt issuance costs were recorded as a contra-liability on our condensed consolidated balance sheet at issuance and we are amortizing them over the contractual term using an updated effective interest rate. Our updated effective interest rates for our 1% Notes and 0.125% Notes were 1.4 percent and 0.5 percent, respectively.

The following tables summarize the adjustments we made to our condensed consolidated statements of stockholders' equity we originally reported at December 31, 2020 and 2019 to adopt ASU 2020-06 (in thousands):

	December 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Additional paid-in-capital	$ 2,113,646	$ (218,127)	$ 1,895,519
Accumulated deficit	$ (1,249,368)	$ 118,062	$ (1,131,306)
Total stockholders' equity	$ 843,347	$ (100,065)	$ 743,282

	December 31, 2019		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Additional paid-in-capital	$ 2,203,778	$ (218,128)	$ 1,985,650
Accumulated deficit	$ (707,534)	$ 111,039	$ (596,495)
Total stockholders' equity	$ 1,684,547	$ (107,089)	$ 1,577,458

Call Spread

In conjunction with the issuance of our 0.125% Notes in December 2019, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants. We account for the note hedges and warrants as separate freestanding financial instruments and treat each instrument as a separate unit of accounting. We determined that the note hedges and warrants do not meet the definition of a liability using the guidance contained in ASC Topic 480, therefore we account for the note hedges and warrants using the Derivatives and Hedging – Contracts in Entity's Own Equity accounting guidance contained in ASC Topic 815. We determined that the note hedges and warrants meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders' equity. We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants as additional paid-in capital in our condensed consolidated balance sheet. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Segment Information

In 2021, we began operating as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment. Previously, we had operated as two operating segments, Ionis Core and Akcea Therapeutics. In October 2020, we acquired the remaining common stock of Akcea that we did not own and fully integrated Akcea's operations into ours as of January 1, 2021.

Stock-based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, 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.

On the grant date, we use our stock price and assumptions regarding a number of variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors.

We recognize compensation expense for stock options granted, RSUs, PRSUs and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

In December 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. As a result, all employees are now under an Ionis stock plan and subject to the same Black-Scholes assumptions. During the three months ended March 31, 2021 and 2020, we did not grant any stock options or RSUs to our Board of Directors. For the three months ended March 31, 2021 and 2020, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2021	**2020**
Risk-free interest rate	0.5%	1.6%
Dividend yield	0.0%	0.0%
Volatility	55.1%	58.9%
Expected life	4.9 years	4.7 years

ESPP:

	Three Months Ended March 31,	
	2021	**2020**
Risk-free interest rate	0.1%	1.1%
Dividend yield	0.0%	0.0%
Volatility	39.1%	47.2%
Expected life	6 months	6 months

RSU's:

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted to employees vest annually over a four-year period. The RSUs we granted to our board of directors prior to June 2020 vest annually over a four-year period. RSUs granted after June 2020 to our board of directors fully vest after one year. The weighted-average grant date fair value of RSUs granted to employees for the three months ended March 31, 2021 was $62.02 per share.

PRSU's:

Beginning in 2020, we added performance-based restricted stock units, or PRSU, awards to the compensation for our Chief Executive Officer, Dr. Brett Monia. Under the terms of the grants, one third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (i.e., the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on our relative total shareholder return, or TSR, as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. Under the terms of the grants no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero percentto 150 percent of the target number depending on our relative TSR.

We determined the fair value of Dr. Monia's PRSUs using a Monte Carlo model because the performance target is based on our relative TSR, which represents a market condition. We are recognizing the grant date fair value of these awards as stock-based compensation expense using the accelerated multiple-option approach over the vesting period. The weighted-average grant date fair value of PRSUs granted to Dr. Monia for the three months ended March 31, 2021 was $77.17 per share.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2021 and 2020 (in thousands).

	Three Months Ended March 31,	
	2021	2020
Cost of sales	$ 182	$ 237
Research, development and patent expense	25,899	25,556
Selling, general and administrative expense	11,780	14,997
Total	$ 37,861	$ 40,790

As of March 31, 2021, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $101.8 million, $109.6 million and $3.8 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 our non-vested stock options, RSUs and PRSUs over a weighted average amortization period of 1.4 years, 1.8 years and 1.7 years, respectively.

Impact of Recently Issued Accounting Standards

As disclosed in the “Convertible Debt” policy above within this footnote, we adopted the simplified accounting for convertible debt instrument guidance (ASU 2020-06) on January 1, 2021. Refer to the section above for the impact of adoption. We do not expect any other recently issued accounting standards to have a material impact to our financial results.

3. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2021:

One year or less	67%
After one year but within two years	20%
After two years but within three and a half years	13%
Total	100%

As illustrated above, at March 31, 2021, 87 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 March 31, 2021, we had an ownership interest of less than 20 percent in seven private companies and two public companies with which we conduct business. The privately held companies are Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd. The publicly traded companies are Antisense Therapeutics Ltd. and ProQR Therapeutics N.V.

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

March 31, 2021	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 446,816	$ 1,838	$ (76)	$ 448,578
Debt securities issued by U.S. government agencies	80,703	292	(2)	80,993
Debt securities issued by the U.S. Treasury (2)	234,164	126	—	234,290
Debt securities issued by states of the U.S. and political subdivisions of the states	121,776	220	(22)	121,974
Other municipal debt securities	5,137	—	(7)	5,130
Total securities with a maturity of one year or less	888,596	2,476	(107)	890,965
Corporate debt securities	325,335	3,108	(245)	328,198
Debt securities issued by U.S. government agencies	96,698	36	(164)	96,570
Debt securities issued by the U.S. Treasury	59,030	326	(35)	59,321
Debt securities issued by states of the U.S. and political subdivisions of the states	34,515	81	(25)	34,571
Other municipal debt	6,233	—	(20)	6,213
Total securities with a maturity of more than one year	521,811	3,551	(489)	524,873
Total available-for-sale securities	$ 1,410,407	$ 6,027	$ (596)	$ 1,415,838
Equity securities:				
Total equity securities included in other current assets (3)	$ 4,712	$ —	$ (1,514)	$ 3,198
Total equity securities included in deposits and other assets (4)	15,062	15,938	—	31,000
Total equity securities	19,774	15,938	(1,514)	34,198
Total available-for-sale and equity securities	$ 1,430,181	$ 21,965	$ (2,110)	$ 1,450,036

December 31, 2020	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 514,182	$ 2,194	$ (41)	$ 516,335
Debt securities issued by U.S. government agencies	94,234	354	(2)	94,586
Debt securities issued by the U.S. Treasury (2)	307,576	233	(9)	307,800
Debt securities issued by states of the U.S. and political subdivisions of the states	104,271	196	(12)	104,455
Other municipal debt securities	5,191	—	(7)	5,184
Total securities with a maturity of one year or less	1,025,454	2,977	(71)	1,028,360
Corporate debt securities	325,079	4,941	(40)	329,980
Debt securities issued by U.S. government agencies	80,099	185	(9)	80,275
Debt securities issued by the U.S. Treasury	50,318	383	(4)	50,697
Debt securities issued by states of the U.S. and political subdivisions of the states	31,779	91	(16)	31,854
Other municipal debt securities	1,041	—	—	1,041
Total securities with a maturity of more than one year	488,316	5,600	(69)	493,847
Total available-for-sale securities	$ 1,513,770	$ 8,577	$ (140)	$ 1,522,207
Equity securities:				
Total equity securities included in other current assets (3)	$ 4,712	$ —	$ (2,681)	$ 2,031
Total equity securities included in deposits and other assets (4)	15,062	15,938	—	31,000
Total equity securities	19,774	15,938	(2,681)	33,031
Total available-for-sale and equity securities	$ 1,533,544	$ 24,515	$ (2,821)	$ 1,555,238

(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.

The following is a summary of our investments we consider to be temporarily impaired at March 31, 2021 (in thousands). All of these investments have less than 12 months of temporary impairment. 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.

	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	101	$ 233,665	$ (321)
Debt securities issued by U.S. government agencies	7	60,681	(166)
Debt securities issued by the U.S. Treasury	6	52,838	(35)
Debt securities issued by states of the U.S. and political subdivisions of the states	297	76,712	(47)
Other municipal debt securities	3	11,343	(27)
Total temporarily impaired securities	414	$ 435,239	$ (596)

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 March 31, 2021 and December 31, 2020 that we regularly measure and carry at fair value. As of March 31, 2021 and December 31, 2020, we did not have any investments that we valued using Level 3 inputs. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At March 31, 2021	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 372,050	$ 372,050	$ —
Corporate debt securities (2)	776,776	—	776,776
Debt securities issued by U.S. government agencies (3)	177,563	—	177,563
Debt securities issued by the U.S. Treasury (3)	293,611	293,611	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	156,545	—	156,545
Other municipal debt securities (3)	11,343	—	11,343
Investment in ProQR Therapeutics N.V. (4)	3,198	3,198	—
Total	$ 1,791,086	$ 668,859	$ 1,122,227

	At December 31, 2020	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 221,125	$ 221,125	$ —
Corporate debt securities (2)	846,315	—	846,315
Debt securities issued by U.S. government agencies (3)	174,861	—	174,861
Debt securities issued by the U.S. Treasury (5)	358,497	358,497	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	136,309	—	136,309
Other municipal debt securities (3)	6,225	—	6,225
Investment in ProQR Therapeutics N.V. (4)	2,031	2,031	—
Total	$ 1,745,363	$ 581,653	$ 1,163,710

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

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

(2) $10.0 million was included in cash and cash equivalents, with the difference included in short-term investments.

(3) Included in short-term investments.

(4) Included in other current assets on our condensed consolidated balance sheet.

(5) $17.5 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

Convertible Notes

Our 1% Notes and 0.125% Notes had a fair value of $314.6 million and $527.3 million at March 31, 2021, 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. Collaborative Arrangements and Licensing Agreements

Below, we have included our Biogen collaboration, which is our only collaboration with substantive changes during 2021 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, 2020.

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. We and Biogen are currently developing eight investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development 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 March 31, 2021, we have received $2.9 billion from our Biogen collaborations.

During the three months ended March 31, 2021 and 2020, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended March 31,	
	2021	2020
SPINRAZA royalties (commercial revenue)	$ 60.0	$ 66.0
R&D revenue	18.1	21.4
Total revenue from our relationship with Biogen	$ 78.1	$ 87.4
Percentage of total revenue	70%	66%

Our condensed consolidated balance sheet at March 31, 2021 and December 31, 2020 included deferred revenue of $447.7 million and $465.8 million, respectively, related to our relationship with Biogen.

During the first three months of 2021, we did not have any changes to our performance obligations, transaction price or the timing in which we expect to recognize revenue under our Biogen collaborations.

In April 2021, we achieved a $10 million milestone payment from Biogen when Biogen advanced ION541, an investigational medicine targeting ataxin 2 to treat patients with ALS. We will achieve the next payment of $8 million if Biogen advances one of the medicines under our 2013 strategic neurology collaboration.

6. Convertible Debt

0 Percent Convertible Senior Notes and Call Spread

In April 2021, we completed a $632.5 million offering of convertible senior notes. We used a portion of the net proceeds from the issuance of the 0 percent convertible senior notes, or 0% Notes, to repurchase $247.9 million in principal of our 1% Notes for $257.0 million.

Following the closing of the debt transaction in April 2021, we had the following 0% Notes outstanding (amounts in millions except interest rate and price per share data):

	0% Notes
Outstanding principal balance	$ 632.5
Maturity date	April 2026
Interest rate	0 percent
Conversion price per share	$ 57.84
Effective conversion price per share with call spread	$ 76.39
Total shares of common stock subject to conversion	10.9

In conjunction with the April 2021 offering, 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% Notes by increasing the effective conversion price on our 0% Notes. We increased our effective conversion price to $76.39 with the same number of underlying shares as our 0% Notes. The call spread cost us $46.9 million, of which $136.7 million was for the note hedge purchase, offset by $89.8 million we received for selling the warrants. Similar to our 0% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0% Notes. The note hedges will expire upon maturity of the 0% Notes, or April 2026. The note hedges and warrants are separate transactions and are not part of the terms of our 0% Notes. The holders of the 0% Notes do not have any rights with respect to the note hedges and warrants.

0.125 Percent Convertible Senior Notes and Call Spread

At March 31, 2021, we had the following 0.125% Notes outstanding with interest payable semi-annually (amounts in millions except interest rate and 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
Effective conversion price per share with call spread	$ 123.38
Total shares of common stock subject to conversion	6.6
Unamortized debt issuance costs	$ 8.1

In conjunction with the issuance of our 0.125% Notes in December 2019, 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 effective conversion price on our 0.125% Notes. We increased our effective conversion price to $123.38 with the same number of underlying shares as our 0.125% Notes. 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. 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 the 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 amount paid for the note hedges and the amount received for the warrants in additional paid-in capital in our condensed consolidated balance sheet. See our Call Spread accounting policy in Note 2, *Significant Accounting Policies*, in the Notes to the Condensed Consolidated Financial Statements. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

1 Percent Convertible Senior Notes

At March 31, 2021, we had the following 1% Notes outstanding with interest payable semi-annually (amounts in millions except interest rate and 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
Unamortized debt issuance costs	$ 0.8

In April 2021, we repurchased $247.9 million in aggregate principal amount of our 1% Notes in privately negotiated transactions. As a result, in April 2021, the remaining principal outstanding for our 1% Notes was $62.0 million, resulting in 0.9 million shares of common stock subject to conversion. As a result of the repurchase, we reclassified the repurchased portion of our 1% Notes from current to non-current liabilities on our condensed consolidated balance sheet as of March 31, 2021 because we replaced this portion of our outstanding debt with long-term debt.

Other Terms of Convertible Senior Notes

The 0%, 0.125% and 1% Notes are convertible under certain conditions, at the option of the note holders. We can settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the notes prior to maturity, and we do not have to provide a sinking fund for them. Holders of the notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indentures governing the notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus any accrued and unpaid interest.

7. Severance and Retention Costs

Akcea Acquisition

As a result of the Akcea Acquisition in October 2020, we began recognizing severance and retention expenses in the fourth quarter of 2020. The following table summarizes our total estimated severance and retention expenses related to the Akcea Acquisition (in millions):

	Severance and Retention Expenses
Total estimated expenses	$ 28.5
Expenses incurred in the three months ended December 31, 2020	15.3
Expenses incurred in the three months ended March 31, 2021	5.4
Remaining estimated expenses to be recognized through October 2021	$ 7.8

The following table summarizes our severance and retention expenses related to the Akcea Acquisition that we recognized during the three months ended March 31, 2021 (in millions):

	Three Months Ended March 31, 2021
Research, development and patent expenses	$ 2.5
Selling, general and administrative expenses	2.9
Total	$ 5.4

The following table summarizes the severance and retention reserve amounts related to the Akcea Acquisition that we included in accrued compensation for the period indicated (in millions):

	Three Months Ended March 31, 2021
Beginning balance	$ 14.7
Amounts expensed during the period	6.1
Reserve adjustments during the period	(0.7)
Net amount expensed during the period	5.4
Amounts paid during the period	(9.0)
Ending balance	$ 11.1

The reserve adjustments during the period primarily related to forfeitures of severance and retention payments as a result of employee terminations before they earned the amounts.

Restructured European Operations

As a result of restructuring our European operations, or Restructured European Operations, in December 2020, we began recognizing severance and retention expenses in the fourth quarter of 2020. The following table summarizes our total severance and retention expenses related to our Restructured European Operations (in millions):

	Severance and Retention Expenses
Total estimated expenses	$ 13.6
Expenses incurred in the three months ended December 31, 2020	12.5
Expenses incurred in the three months ended March 31, 2021	0.7
Remaining estimated expenses through October 2021	$ 0.4

The following table summarizes the severance and retention expenses related to our Restructured European Operations that we recognized during the three months ended March 31, 2021 (in millions):

	Three Months Ended March 31, 2021
Research, development and patent expenses	$ 0.1
Selling, general and administrative expenses	0.6
Total	$ 0.7

The following table summarizes the severance and retention reserve amounts related to our Restructured European operations that we included in accrued compensation for the periods indicated (in millions):

	Three Months Ended March 31, 2021
Beginning balance	$ 12.4
Amounts expensed during the period	2.2
Reserve adjustments during the period	(1.5)
Net amount expensed during the period	0.7
Amounts paid during the period	(11.9)
Ending balance	$ 1.2

The reserve adjustments during the period primarily related to tax expense adjustments.

Restructured North American TEGSEDI Operations

In April 2021, we entered into a distribution agreement with Sobi for TEGSEDI in North America. Under the terms of the distribution agreement, we will retain the marketing authorizations for TEGSEDI in the U.S. and Canada. We will continue to supply commercial product to Sobi and manage regulatory and manufacturing processes, as well as relationships with key opinion leaders. We will also continue to lead the TEGSEDI global commercial strategy. Sobi will otherwise have responsibility for commercializing TEGSEDI in the U.S. and Canada and will assume these activities by August 2021.

In connection with restructuring our North American TEGSEDI operations, or Restructured North American TEGSEDI Operations, we enacted a plan to reorganize our Akcea workforce in North America to better align with the needs of our business, or the Reorganization Plan, and to focus on our wholly owned pipeline. Under the Reorganization Plan, we expect to incur restructuring charges in the range of $11 million to $14 million principally in the second quarter of 2021.

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

In this Report on Form 10-Q, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us," means Ionis Pharmaceuticals, Inc. and its wholly owned 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. 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 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, 2020, 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 RNA-targeted therapy and believe our medicines are pioneering new markets, changing standards of care and transforming the lives of people with devastating diseases. Our clinical pipeline of potential first-in-class and/or best-in-class medicines address a broad range of diseases. We are primarily focused on two core franchises: neurology and cardiometabolic. Our commercial products SPINRAZA, TEGSEDI and WAYLIVRA, are approved in major markets around the world. Within our late-stage pipeline, we have six Phase 3 studies ongoing with five medicines: tofersen for SOD1-ALS, IONIS-TTR-L_{Rx} for transthyretin, or TTR, amyloidosis, IONIS-APOCIII-L_{Rx} for familial chylomicronemia syndrome, or FCS, pelacarsen for lipoprotein(a), or Lp(a), driven cardiovascular disease and ION363 for amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or FUS.

Our multiple sources of revenue provide us with substantial financial strength. Our financial strength enables us to execute on our capital allocation strategy, which is focused on internal investment in three key areas: our wholly owned pipeline, building our commercial capabilities and broadening the reach of our technology. We believe investing in these areas moves us closer to our goal of 12 or more marketed products in 2026 and will drive the greatest value for patients and shareholders.

In April 2021, we entered into a distribution agreement with Sobi for TEGSEDI in North America. Under the terms of the distribution agreement, we retained the marketing authorizations for TEGSEDI in the U.S. and Canada. We will continue to supply commercial product to Sobi and manage regulatory and manufacturing processes, as well as relationships with key opinion leaders. We will also continue to lead the TEGSEDI global commercial strategy. In connection with the agreement, we enacted the Reorganization Plan to reorganize our Akcea workforce in North America to better align with the needs of our business and to focus on our wholly owned pipeline. Under the Reorganization Plan, we expect to incur restructuring charges in the range of $11 million to $14 million principally in the second quarter of 2021.

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 March 31, 2021, more than 11,000 patients were on SPINRAZA therapy in markets around the world. Through March 31, 2021, we have earned more than $1.4 billion in revenues from our SPINRAZA collaboration, including approximately $1 billion in royalties on sales of SPINRAZA.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis, or hATTR, a debilitating, progressive, and fatal disease. We launched TEGSEDI in the U.S. and the European Union, or EU, in late 2018. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Sobi. Additionally, in the second quarter of 2021, Sobi also began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC Therapeutics International Limited, or PTC, through its exclusive license agreement with us, is commercializing TEGSEDI in Brazil and is working towards access in additional Latin American countries.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine that received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. Through our exclusive license agreement with PTC, we are 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 the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária), or ANVISA.

Medicines in Phase 3 Studies

We advanced our pipeline of medicines that we believe will pioneer new markets and change standards of care.
Our Phase 3 medicines include:

- Tofersen: Biogen completed enrollment in the VALOR Phase 3 study in patients with SOD1-ALS in December 2020
- IONIS-TTR-L_{Rx}: Enrollment is ongoing in both the NEURO-TTRansform and the CARDIO-TTRansform Phase 3 studies
- IONIS-APOCIII-L_{Rx}: Enrollment is ongoing in the BALANCE Phase 3 study in patients with FCS
- Pelacarsen: Enrollment is ongoing in Novartis Pharma AG's Lp(a)HORIZON Phase 3 cardiovascular outcome study
- ION363: We recently initiated a Phase 3 study in patients with FUS-ALS, the most common cause of juvenile-onset ALS

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 minimizing the impact to timelines. While the COVID-19 pandemic has impacted some areas of our business, we believe our mitigation efforts and financial strength will enable us to continue to manage through the pandemic and 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 the impact on our commercial products and the medicines in our pipeline.

Financial Highlights

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

	Three Months Ended March 31,	
	2021	**2020**
		(as revised*)
Total revenue	$ 111.6	$ 133.4
Total operating expenses	$ 203.6	$ 194.5
Loss from operations	$ (92.0)	$ (61.1)
Net loss	$ (89.9)	$ (49.9)

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

Our revenue for the first quarter of 2021 was $111.6 million. Our commercial revenue in the first quarter of 2021 was consistent with the same period last year. As we complete the transition of TEGSEDI operations in North America to Sobi, our commercial revenue from product sales will shift to distribution fee revenue.

We earn our R&D revenue from multiple sources that can fluctuate depending on the timing of events. Our R&D revenue decreased in the first quarter of 2021 compared to the same period in 2020 primarily because we earned more milestone payments in the first quarter of 2020 than in the first quarter of 2021. We expect our R&D revenue to increase in the second half of 2021 compared to the first half.

Our operating expenses for the first quarter of 2021 were $203.6 million and increased over the same period in 2020, principally due to our investments in advancing our late-stage wholly owned pipeline. In addition, we incurred approximately $7 million in costs related to the Akcea Acquisition and Restructured European Operations, primarily comprised of severance and retention costs.

We expect our operating expenses to continue to increase during the rest of 2021 as we continue to advance our strategic priorities. Additionally, we expect to incur an additional $11 million to $14 million of restructuring costs, principally in the second quarter of 2021, related to the Restructured North American TEGSEDI Operations to better align with the immediate needs of our business and to focus on our wholly owned pipeline. We also expect to recognize the majority of the remaining severance and retention costs related to the Akcea Acquisition and Restructured European Operations transactions in the second quarter of 2021. See Note 7, *Severance and Retention Costs*, for additional details.

We ended the first quarter of 2021 with $1.8 billion in cash and short-term investments. In April 2021, we issued $632.5 million of 0% senior convertible notes due in April 2026 and repurchased $247.9 million of our 1% senior convertible notes. In conjunction with these transactions, we also executed a call spread to increase the effective conversion price of the 0% senior convertible notes to $76.39. After giving effect to these transactions, our pro forma cash, cash equivalents and short-term investments was $2.1 billion. We believe our strong financial position should enable us to continue to execute on our corporate goals throughout this year and beyond, including developing and commercializing medicines within our wholly owned pipeline.

Recent Business Updates

First Quarter 2021 Marketed Products Highlights

- SPINRAZA: a global foundation-of-care for the treatment of SMA patients of all ages
  - $521 million in worldwide sales in the first quarter
  - More than 11,000 patients worldwide were on therapy at the end of the first quarter across post-marketing, expanded access and clinical trial settings
  - Higher-dose SPINRAZA demonstrated safety and tolerability consistent with the currently approved dose in the open-label safety cohort of the DEVOTE study, enabling enrollment in the blinded, pivotal cohort to get underway
- TEGSEDI and WAYLIVRA: important medicines approved for the treatment of patients with severe rare diseases
  - Completed the transition of European operations to Sobi and expanded the distribution agreement to include North American TEGSEDI operations

First Quarter 2021 and Recent Pipeline Events

- Phase 3 Pipeline: growing and positioned for 12 or more products on the market in 2026
  - Advanced ION363 into a Phase 3 study in patients with FUS-ALS
  - Advanced tofersen into the Phase 3 ATLAS study in presymptomatic SOD1-ALS patients
  - Roche reported tominersen data related to the dosing halt in the Phase 3 program
- Mid-stage Pipeline: advancing multiple medicines with potential to change the standard of care for patients with severe diseases
  - Reported positive topline IONIS-PKK-L_{Rx} results in patients with hereditary angioedema
  - Advanced ION373 into the Phase 2 portion of a pivotal study in patients with Alexander disease
  - Advanced the IONIS-AGT-L_{Rx} development program:
    - Reported positive Phase 2 data in *JACC: Basic to Translational Science*
    - Advanced into a Phase 2b study in patients with hypertension uncontrolled with three or more antihypertensive medications
    - Advanced into a Phase 2 study in patients with chronic heart failure with reduced injection fraction
  - Advanced the ongoing Phase 2 study of ION541 in patients with ALS regardless of family history, resulting in a $10 million payment from Biogen

Business Segment

In 2021, we began operating as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment. Previously, we had operated as two operating segments, Ionis Core and Akcea Therapeutics. In October 2020, we acquired the remaining common stock of Akcea that we did not own and fully integrated Akcea's operations into ours as of January 1, 2021.

Critical Accounting Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the U.S. 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. 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

In the first quarter of 2021, we determined the estimation of our income taxes was no longer a critical accounting estimate because we recorded a valuation allowance against the entirety of our net deferred tax assets in the fourth quarter of 2020. We recorded the expected impact from the valuation allowance on our tax provision for 2021.

There have been no other 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, 2020.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2021 was $111.6 million compared to $133.4 million for the same period in 2020 and was comprised of the following (amounts in millions):

	Three Months Ended March 31,	
	2021	**2020**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 60.0	$ 66.0
TEGSEDI and WAYLIVRA revenue, net	19.8	15.2
Licensing and other royalty revenue	4.6	2.8
Total commercial revenue	84.4	84.0
R&D revenue:		
Amortization from upfront payments	20.1	21.1
Milestone payments	5.2	23.1
Other services	1.9	5.2
Total R&D revenue	27.2	49.4
Total revenue	$ 111.6	$ 133.4

Our commercial revenue in the first quarter of 2021 was consistent with the same period last year. As we complete the transition of TEGSEDI operations in North America to Sobi, our commercial revenue from product sales will shift to distribution fee revenue.

We earn our R&D revenue from multiple sources that can fluctuate depending on the timing of events. Our R&D revenue decreased in the first quarter of 2021 compared to the same period in 2020 primarily because we earned more milestone payments in the first quarter of 2020 than in the first quarter of 2021. We anticipate our R&D revenue to increase in the second half of 2021 compared to the first half of 2021 as many of our partnered programs advance.

Operating Expenses

Our operating expenses were as follows (in millions):

	Three Months Ended March 31,	
	2021	2020
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 159.0	$ 153.7
Restructuring expenses	6.7	—
Non-cash compensation expense related to equity awards	37.9	40.8
Total operating expenses	$ 203.6	$ 194.5

Operating expenses, excluding non-cash compensation expense related to equity awards, for the three months ended March 31, 2021 increased compared to the same period in 2020. The increase was due to our investments in the Phase 3 program for IONIS-TTR-L_{Rx} and other medicines in our wholly owned pipeline. Additionally, we incurred approximately $7 million in costs related to the Akcea Acquisition and Restructured European Operations, primarily comprised of severance and retention costs. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the rest of 2021 as we continue to advance our strategic priorities. Additionally, we expect to incur an additional $11 million to $14 million of restructuring costs, principally in the second quarter of 2021, related to our the Restructured North American TEGSEDI Operations to better align with the immediate needs of our business and to focus on our wholly owned pipeline. We also expect to recognize the majority of the remaining severance and retention costs related to the Akcea Acquisition and Restructured European Operations transactions in the second quarter of 2021. See Note 7, *Severance and Retention Costs*, for additional details.

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 related to equity awards 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 Sales

Our cost of sales 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 we are using in the commercial launches. We expect cost of sales to increase as we deplete these inventories.

Our cost of sales were as follows (in millions):

	Three Months Ended March 31,	
	2021	2020
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 2.4	$ 2.3
Non-cash compensation expense related to equity awards	0.2	0.2
Total cost of sales	$ 2.6	$ 2.5

Our cost of sales, excluding non-cash compensation expense related to equity awards, for the three months ended March 31, 2021 were consistent with the same period in 2020.

Research, Development and Patent Expenses

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

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

	Three Months Ended March 31,	
	2021	2020
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 111.3	$ 91.4
Restructuring expenses	2.6	—
Non-cash compensation expense related to equity awards	25.9	25.6
Total research, development and patent expenses	$ 139.8	$ 117.0

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 pipeline.

Our antisense drug discovery expenses were as follows (in millions):

	Three Months Ended March 31,	
	2021	2020
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 26.6	$ 18.4
Non-cash compensation expense related to equity awards	6.3	6.3
Total antisense drug discovery expenses	$ 32.9	$ 24.7

Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2021 compared to the same period in 2020 due to expenses we incurred related to advancing our research programs and investments we made to expand the reach of our antisense technology.

Antisense Drug Development

The following table sets forth drug development expenses, including expenses for our marketed medicines and those in Phase 3 development for which we have incurred significant costs (in millions):

	Three Months Ended March 31,	
	2021	2020
TEGSEDI	$ 1.8	$ 4.3
WAYLIVRA	0.6	1.0
IONIS-TTR-L_{Rx}	13.3	5.9
IONIS-APOCIII-L_{Rx}	1.4	0.8
ION363	2.1	—
Other antisense development projects	20.3	21.0
Development overhead expenses	22.5	17.9
Restructuring expenses	2.3	—
Total antisense drug development, excluding non-cash compensation expense related to equity awards	64.3	50.9
Non-cash compensation expense related to equity awards	12.4	11.8
Total antisense drug development expenses	$ 76.7	$ 62.7

Our development expenses, excluding non-cash compensation expense related to equity awards, increased for the three months ended March 31, 2021 compared to the same period in 2020 primarily due to our broad Phase 3 program for IONIS-TTR-L_{Rx}, which we initiated in late 2019. Additionally, we advanced other medicines in our wholly owned pipeline, including ION363, which we recently initiated a Phase 3 study for in patients with FUS-ALS.

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 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 millions):

	Three Months Ended March 31,	
	2021	2020
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 11.8	$ 12.0
Restructuring expenses	0.3	—
Non-cash compensation expense related to equity awards	3.1	2.8
Total manufacturing and development chemistry expenses	$ 15.2	$ 14.8

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, were essentially flat for the three months ended March 31, 2021 compared to the same period in 2020.

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 millions):

	Three Months Ended March 31,	
	2021	2020
Personnel costs	$ 4.3	$ 3.8
Occupancy	3.2	2.4
Patent expenses	0.8	0.7
Insurance	0.8	0.6
Computer software and licenses	0.5	0.6
Other	1.3	2.0
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	10.9	10.1
Non-cash compensation expense related to equity awards	4.1	4.6
Total R&D support expenses	$ 15.0	$ 14.7

R&D support expenses, excluding non-cash compensation expense related to equity awards, for the three months ended March 31, 2021 increased slightly compared to the same period in 2020.

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 millions):

	Three Months Ended March 31,	
	2021	2020
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 45.3	$ 60.0
Restructuring expenses	4.1	—
Total selling, general and administrative expenses, excluding non-cash compensation related to equity awards	49.4	60.0
Non-cash compensation expense related to equity awards	11.8	15.0
Total selling, general and administrative expenses	$ 61.2	$ 75.0

SG&A expenses, excluding non-cash compensation expense related to equity awards, were lower for the three months ended March 31, 2021 compared to the same period in 2020 due to operating efficiencies attained from our integration of Akcea and our updated European distribution model. These decreases were slightly offset by restructuring costs related to the Akcea Acquisition and Restructured European Operations.

Investment Income

Investment income for the three months ended March 31, 2021 was $4.6 million compared to $10.5 million for 2020. The decrease in investment income was primarily due to a decline in interest rates and a lower cash balance during the three months ended March 31, 2021 compared to the same period in 2020.

Interest Expense

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

	Three Months Ended March 31,	
	2021	2020 (as revised*)
Convertible notes:		
Non-cash amortization of debt issuance costs	$ 0.9	$ 0.7
Interest expense payable in cash	0.9	0.9
Interest on mortgage for primary R&D and manufacturing facilities	0.6	0.6
Total interest expense	$ 2.4	$ 2.2

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

Income Tax Expense (Benefit)

We recorded negligible income tax expense for the three months ended March 31, 2021 primarily due to our valuation allowance and our expected taxable losses for the year. We recorded an income tax benefit of $3.1 million for the same period in 2020 primarily due to our pre-tax loss for the period and a $1.7 million tax benefit related to utilization of additional net operating loss carryforwards provided by the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, enacted by the U.S. Congress in March 2020.

Net Loss

We had a net loss of $89.9 million for the three months ended March 31, 2021 compared to net loss of $49.9 million for the same period in 2020, which reflects the fluctuations discussed above.

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

During the first quarter of 2020, we owned approximately 76 percent of Akcea. The shares of Akcea third parties owned represented an interest in Akcea's equity that we did not control. However, because we maintained overall control of Akcea through our voting interest, we reflected Akcea's results of operations in our condensed consolidated financial statements. We reflected the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line called "Net loss attributable to noncontrolling interest in Akcea" on our statement of operations. Our noncontrolling interest in Akcea on our statement of operations for the three months ended March 31, 2020, was a loss of $10.3 million. After our acquisition of Akcea in October 2020, we no longer recorded any adjustment related to noncontrolling interest for Akcea's net loss.

Net Loss Attributable to Our Common Stockholders and Net Loss per Share

We had a net loss attributable to our common stockholders of $89.9 million for the three months ended March 31, 2021 compared to net loss of $39.6 million for the same period in 2020. Basic and diluted net loss per share for the three months ended March 31, 2021 were $0.64. Our basic and diluted net loss per share for the three months ended March 31, 2020 were $0.28.

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 TEGSEDI and WAYLIVRA commercial revenue. From our inception through March 31, 2021, we have earned approximately $5.1 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through March 31, 2021, we have raised net proceeds of approximately $2.0 billion from the sale of our equity securities. Additionally, from our inception through March 31, 2021, we have borrowed approximately $1.5 billion under long-term debt arrangements to finance a portion of our operations.

Our key liquidity metrics and capital resources, including our cash, cash equivalents and short-term investments and debt obligations did not change significantly at March 31, 2021 compared to December 31, 2020, except working capital. Our working capital increased because we reclassified a portion of our 1% Notes as a non-current liability on our condensed consolidated balance sheet in the first quarter of 2021.

In April 2021, we issued $632.5 million of 0% Notes due in April 2026 and repurchased $247.9 million of our 1% Notes. Therefore, as of March 31, 2021, we classified the repurchased portion of our 1% Notes as a non-current liability on our condensed consolidated balance sheet.

The following table summarizes our contractual obligations as of March 31, 2021. 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**	**More than 1 year**
0.125% Notes (principal and interest payable)	$ 551.6	$ 0.7	$ 550.9
1% Notes (principal and interest payable)*	313.0	313.0	—
Building mortgage payments	75.5	2.4	73.1
Operating leases	22.4	3.3	19.1
Other obligations (principal and interest payable)	0.9	0.1	0.8
Total	$ 963.4	$ 319.5	$ 643.9

* In April 2021, we repurchased $247.9 million in aggregate principal amount of our 1% Notes in privately negotiated transactions. As a result, in April 2021, the remaining principal outstanding for our 1% Notes was $62.0 million. As a result of the repurchase, we reclassified the repurchased portion of our 1% Notes from current to non-current liabilities on our condensed consolidated balance sheet as of March 31, 2021 because we replaced this portion of our outstanding debt with long-term debt.

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. We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

Convertible Debt and Call Spread

Refer to our Convertible Debt and Call Spread accounting policies in Note 2, *Significant Accounting Policies*, and Note 6, *Convertible Debt*, in the Notes to our condensed consolidated financial statements for the significant terms of each convertible debt instrument.

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 March 31, 2021 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.

ITEM 4. CONTROLS AND PROCEDURES

We maintain disclosure controls and procedures that are designed to ensure that information we are required to disclose in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We design and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2021. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2021.

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 IONIS-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.

In light of the August 31, 2020 public announcement of the Akcea Acquisition, the parties to the Delaware Action entered into a stipulation whereby the Defendants need not respond to the complaint filed on July 16, 2020, and the plaintiff will file an amended complaint. The amended complaint has not yet been filed.

ITEM 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider 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, 2020.

Summary of Risk Factors

There are a number of risks related to our business and our securities. Some of the principal risks related to our business include the following:

- the impact on our operations and financial condition from the effects of the current COVID-19 pandemic;
- our ability to generate substantial revenue from the sale of our medicines;
- our and our partners' ability to compete effectively;
- the availability of adequate coverage and payment rates for our medicines;
- our ability to successfully manufacture our medicines;
- our ability to successfully develop and obtain marketing approvals for our medicines;
- our ability to secure and maintain effective corporate partnerships;
- our ability to sustain cash flows and achieve consistent profitability;
- our ability to protect our intellectual property;
- our ability to maintain the effectiveness of our personnel; and
- the other factors set forth below.

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 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 offices 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 globally and generally suspended business-related travel. 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. We believe 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 our and our partners' 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 our commercialization efforts for TEGSEDI and WAYLIVRA. Additionally, Biogen has reported that as a result of the COVID-19 Pandemic, SPINRAZA sales revenues have decreased in part because SPINRAZA doses have been delayed due, directly or indirectly, to the COVID-19 Pandemic, and that future SPINRAZA sales revenues may be adversely affected by continued dosing delays. These and similar, and perhaps more severe, disruptions in our or our partner's 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, we instituted a temporary suspension of enrollment for new subjects in our Phase 3 studies of IONIS-TTR-L_{Rx} based on advice from our trial advisory committee; however, enrollment has resumed.
- some patients have not been able to meet protocol requirements, as quarantines have impeded patient movement and interrupted healthcare services;
- we have experienced some delays in site initiations due to principle investigators and site staff focusing on and prioritizing COVID-19 patient care; 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 Related to the Commercialization of our Medicines

We have limited experience as a company in commercializing medicines, and we may have to invest significant resources to develop these capabilities. If we are unable to establish effective marketing, sales and distribution capabilities or enter into agreements with third parties to market, sell and distribute our medicines, we may not be able to generate revenue from our medicines.

We have limited experience as a company in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure to effectively manage our internal sales, marketing and distribution capabilities would adversely impact the commercialization of our medicines. In addition, we may not be able to enter into collaborations or hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms, or at all. Even if we are able to engage third parties to market, sell and distribute our medicines, our product revenues and profitability may be lower if we rely on such third parties for these functions than if we were to perform them on our own. We also will likely have little control over such third parties, and any of them may fail to devote the necessary resources and attention to market, sell and distribute our medicines effectively. If we are not successful in commercializing our medicines, either on our own or through arrangements with one or more third parties, we may not be able to generate revenue from our medicines.

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. Furthermore, 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 patisiran, marketed by Alnylam Pharmaceuticals, Inc. Although patisiran 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 EU 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 mitigate safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we can better maintain patients on TEGSEDI and WAYLIVRA through our patient-centric commercial approach where we or our partner plan to have greater involvement with physicians and patients, if we or our partner cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on the 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 are engaged 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.

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:

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Patisiran, tafamidis and tafamidis meglumine compete with TEGSEDI;
- Vutrisiran and acoramidis could compete with TEGSEDI and IONIS-TTR-L_{Rx};
- ARO-APOC3, lomitapide and gemcabene could compete with WAYLIVRA and IONIS-APOCIII-L_{Rx}; and
- Arimoclomol, ultomiris, mastinib and trehalose could compete with tofersen and ION363.

Specifically, SPINRAZA faces competition from onasemnogene abeparvovec, a new gene therapy product that was approved in the U.S. in May 2019 and in the EU in May 2020 for the treatment of SMA, as well as risdiplam, a new oral product for the treatment of SMA that was approved in the U.S. in August 2020. Biogen has disclosed that SPINRAZA revenue has decreased due in part to lower sales volumes as a result of increased competition and that future sales of SPINRAZA may be adversely affected by the commercialization of competing products. SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries.

Additionally, companies that are developing medicines that target the same patient populations as our medicines in development may compete with us to enroll participants in the clinical trials for such medicines, which could make it more difficult for us to complete enrollment for these clinical trials.

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 IONIS-APOCIII-L_{Rx} and TEGSEDI inhibits the production of the same protein as IONIS-TTR-L_{Rx}. We believe the enhancements we incorporated into IONIS-APOCIII-L_{Rx} and IONIS-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 IONIS-APOCIII-L_{Rx} or IONIS-TTR-L_{Rx} instead of WAYLIVRA or TEGSEDI, respectively, it will reduce the revenue we derive from those medicines. In addition, while vupanorsen, IONIS-APOCIII-L_{Rx} and WAYLIVRA use different mechanisms of action, if vupanorsen and IONIS-APOCIII- L_{Rx} can effectively lower triglyceride levels in patients, including patients with FCS, WAYLIVRA, vupanorsen and IONIS-APOCIII-L_{Rx} may compete with each other.

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; and
- in the U.S., TEGSEDI is available only through a REMS program.

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 EU, we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA, 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, manufacture 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, manufacture 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.

We are relying on third parties to market, sell and distribute TEGSEDI and WAYLIVRA.*

We have entered into agreements with third parties to commercialize TEGSEDI and WAYLIVRA as follows:

- In April 2021, we entered into a distribution agreement with Sobi to commercialize TEGSEDI in the U.S. and Canada;
- In December 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe; and
- In August 2018, we granted PTC the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries.

We are relying on Sobi and PTC to effectively market, sell and distribute TEGSEDI and WAYLIVRA and have less control over sales efforts and may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. If Sobi or PTC does not successfully commercialize TEGSEDI or WAYLIVRA, including as a result of delays or disruption caused by the current COVID-19 Pandemic, we may receive limited revenue for TEGSEDI or WAYLIVRA in the U.S., Canada, Europe, Latin America or certain Caribbean countries, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

Our operations are subject to additional healthcare laws.

Our operations are subject to additional healthcare laws, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws. Efforts to ensure that our operations comply with applicable healthcare laws and regulations involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings.

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 EU, 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 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. In November 2020, the U.S. Supreme Court heard oral arguments and is expected to rule on the case in its current session, which began in October 2020. Although the U.S. Supreme Court has not yet ruled on the constitutionality of the Affordable Care Act, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace. It is unclear how the Supreme Court ruling, or other such litigation and healthcare reform measures, 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. Such restrictions may include legislative proposals seeking to reduce drug prices (e.g., by placing limits on pharmaceutical price increases and tying Medicare Part B drug prices to international drug prices), increase competition (e.g., by allowing for personal importation of drugs from Canada), lower out-of-pocket drug costs for patients (e.g., by capping Medicare Part D beneficiary out-of-pocket pharmacy expenses) and increase patient access to lower-cost generic and biosimilar drugs. In November 2020, the U.S. Department of Health and Human Services issued a final rule modifying the anti-kickback law safe harbors for plans, pharmacies, and pharmaceutical benefit managers. 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 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 would need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and drug product for 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 or our partners 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 cGMP 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 cGMP, 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.

Risks Related to the Development and Regulatory Approval of our Medicines

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

We cannot guarantee that any of our medicines will be considered safe and effective or will be approved for commercialization. In addition, 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 we received a complete response letter from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018.

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, or may delay the inspection of such facilities due to restrictions related to the COVID-19 Pandemic; 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, 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 or have been discontinued for other reasons. For example, in March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington's disease based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. Similar results could occur in clinical studies for our other medicines, including the studies of tofersen, pelacarsen, IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx} and ION363. If any of our medicines in clinical studies, including tofersen, pelacarsen, IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx} and ION363, do not show sufficient efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, 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 tofersen, pelacarsen, IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx} and ION363. For example, in March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington's disease based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. 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 or lack of efficacy 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 EU, as the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. We have 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 WAYLIVRA. Adverse events or results from these studies or the EAPs could negatively impact our 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 tofersen, pelacarsen, IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx} and ION363, could reduce the commercial potential or viability of our medicines.

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 tofersen, pelacarsen, IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx} and ION363. 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.

Since corporate partnering is a significant part of our strategy to fund the advancement 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 many of 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 pelacarsen; 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 authorizations; 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, pelacarsen 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 we or 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, pelacarsen, IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx} and ION363, the price of our securities could decrease.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition and business strategy

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2021, we had an accumulated deficit of approximately $1.2 billion and stockholders' equity of approximately $0.7 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 medicines or achieve or sustain future profitability.

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 authorizations, preclinical activities and commitment of significant additional resources prior to their successful commercialization. These activities will require significant cash. As of March 31, 2021, we had cash, cash equivalents and short-term investments equal to $1.8 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.

Risks related to our intellectual property

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.

Risks related to our business strategy and personnel

If we fail to successfully integrate Akcea's business and operations, it may adversely affect our future results.

We believe our Akcea Acquisition will result in certain benefits, including a single vision and set of strategic priorities, led by one team, accelerating our next phase of growth and positioning us to more effectively deliver our medicines to patients. Under this transaction, Ionis will now retain more value from Akcea's pipeline and commercial medicines, further strengthening our financial position and supporting continued investments in our future. The success of the transaction will depend on our ability to realize these anticipated benefits. We may fail to realize the anticipated benefits of the Akcea Acquisition for a variety of reasons, including the following:

- failure to successfully manage relationships with partners, customers, distributors and suppliers;
- disruptions to Akcea's commercial operations;
- potential incompatibility of technologies and systems;
- failure to leverage the capabilities of the combined company quickly and effectively;
- potential difficulties integrating and harmonizing business systems and processes;
- tax benefits of the combined structure may not be available or in the expected amounts; and
- the loss of key employees.

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. Following the 2021 Annual Meeting of Stockholders, Dr. Crooke will step down from the Board and will serve as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's 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, we are dependent on the principal members of our staff responsible for marketing, sales and distribution activities. If we are not able to recruit and retain qualified marketing and sales personnel, the sales of TEGSEDI and WAYLIVRA may be adversely affected.

Risks related to taxes

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. AB 85 did not have a material impact on our 2020 tax provision, and we do not expect that it will materially impact our 2021 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. As a result of the Akcea Acquisition, we are subject to the Separate Return Limitation Year, or SRLY, rules. Under SRLY, our utilization of Akcea's pre-acquisition net operating loss and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-acquisition tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income. 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.

Our future taxable income could be impacted by changes in tax laws, regulations and treaties.

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.

General Risk Factors

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2021, the market price of our common stock ranged from $64.37 to $41.42 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.

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 April 2021, we completed a $632.5 million offering of 0% Notes. 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% Notes and 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 18.4 million shares of our common stock upon conversion of our 0% Notes, 0.125% Notes, and 1% Notes, up to 10.9 million shares in connection with the warrant transactions we entered into in connection with the issuance of our 0% Notes, and up to 6.6 million shares 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% Notes and 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% Notes or 0.125% Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0% Notes or 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.

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.

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

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

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

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole 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.

A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business.

In addition to our U.S. operations, we are commercializing TEGSEDI in the EU, Canada, Latin America and certain Caribbean countries, and WAYLIVRA in the EU, Latin America and certain Caribbean countries. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations we are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines and foreign employees;
- complexities associated with managing multiple payer reimbursement regimes, government payers or patient self-pay systems;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions;
- economic weakness, including inflation, natural disasters, war, events of terrorism, political instability or public health issues or pandemics, such as the current COVID-19 Pandemic, in particular foreign countries or globally;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country;
- compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.; and
- changes in diplomatic and trade relationships.

The United Kingdom’s exit from the E.U. could increase these risks.

Our business activities outside of the U.S. are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom’s Bribery Act 2010. In many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have an adverse impact on our business and financial condition.

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

The withdrawal of the UK from the EU, commonly referred to as “Brexit,” may adversely impact our ability to obtain regulatory approvals of our medicines in the EU, result in restrictions or imposition of taxes and duties for importing our medicines into the EU, and may require us to incur additional expenses in order to develop, manufacture and commercialize our medicines in the EU.

Following the result of a referendum in 2016, the UK left the EU on January 31, 2020. Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period that ended December 31, 2020, or the Transition Period, during which EU rules continued to apply. A trade and cooperation agreement, or the Trade and Cooperation Agreement, that outlines the future trading relationship between the UK and the EU was agreed in December 2020.

Since a significant proportion of the regulatory framework in the UK applicable to our business and our medicines is derived from EU directives and regulations, Brexit has had, and may continue to have, a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our medicines in the UK or the EU. For example, Great Britain is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our medicines in Great Britain. It is currently unclear whether the Medicines & Healthcare products Regulatory Agency in the UK is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would delay or prevent us from commercializing our medicines in the UK or the EU.

While the Trade and Cooperation Agreement provides for the tariff-free trade of medicinal products between the UK and the EU, there may be additional non-tariff costs to such trade which did not exist prior to the end of the Transition Period. Further, should the UK diverge from the EU from a regulatory perspective in relation to medicinal products, tariffs could be put into place in the future. We could therefore, both now and in the future, face significant additional expenses (when compared to the position prior to the end of the Transition Period) to operate our business.

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
3.1	Amended and Restated Bylaws, filed as an exhibit to Registrant's Form 8-K filed with the SEC on March 29, 2021 and incorporated herein by reference.
10.1	Letter agreement dated October 21, 2020 to the License Agreement by and among Akcea Therapeutics, Inc. and Pfizer Inc. dated October 4, 2019. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.2	Board Compensation Policy.
14.1	Code of Ethics, filed as an exhibit to Registrant's Form 8-K filed with the SEC on March 29, 2021 and incorporated herein by reference.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended March 31, 2021, 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)	May 5, 2021
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 5, 2021

Exhibit 10.1

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

October 21, 2020

Pfizer Inc.
235 East 42nd Street
New York, NY 10017
Attention: James Rusnak, M.D., Ph.D.

Re: AKCEA-ANGPTL3-L$_{Rx}$ License Agreement

Dear Dr. Rusnak:

This letter agreement ("***Letter Agreement***") is in reference to the License Agreement (the "***Agreement***"), dated October 4, 2019, by and between Akcea Therapeutics, Inc. ("***Akcea***") and Pfizer Inc. ("***Pfizer***"). Any capitalized terms not defined in this Letter Agreement will have the meanings set forth in the Agreement, unless expressly specified otherwise.

1. Akcea's Right to Participate in Funding of Development of the Product. Akcea and Pfizer desire to modify Section 2.3.4 of the Agreement. Accordingly, Section 2.3.4 of the Agreement is deleted in its entirety and replaced with the following provision:

2.3.4 **Akcea's Right to Participate in the Funding of Development of the Product**. At any time beginning on the Closing Date until [***], Akcea will have the conditional right to elect to participate in the funding of the Development of the Product with Pfizer under the Development Plan pursuant to this Section 2.3.4. If Akcea provides written notice of such election to Pfizer prior to [***] (a "***Notice of Interest***"), then the Parties will negotiate in good faith the terms and conditions of Akcea's participation in the funding of the Development of the Product with Pfizer under the Development Plan for a period of [***], including certain [***] terms for [***]. If Akcea (a) gives notice that it does not wish to participate in the funding of the Development of the Product with Pfizer under the Development Plan, (b) fails to give a timely Notice of Interest, or (c) gives a timely Notice of Interest but the Parties cannot mutually agree on the terms upon which Akcea will participate in the funding of the Development of the Product with Pfizer under the Development Plan by the [***] following the delivery of such notice, then (i) Akcea's right to participate in the funding of the Development of the Product with Pfizer under the Development Plan pursuant to this Section 2.3.4 will automatically terminate, and (ii) Pfizer will continue to be solely responsible for the Development of the Product, including all funding, in accordance with the Development Plan.

For purposes of this Section 2.3.4, [***].

2. This Letter Agreement may be executed in any number of counterparts, each of which shall be deemed an original and all of which taken together shall be deemed to constitute one and the same agreement. The Parties agree that execution of this Letter Agreement by industry standard electronic signature software and/or by exchanging executed signature pages in .pdf format via e-mail shall have the same legal force and effect as the exchange of original signatures, and that in any proceeding arising under or related to this Letter Agreement, each Party hereby waives any right to raise any defense or waiver based upon execution of this Letter Agreement by means of such electronic signatures or maintenance of the executed agreement electronically.

3. Except as otherwise expressly set forth in this Letter Agreement, the Agreement remains in full force and effect in accordance with its terms.

[*Signature page to follow****]***

If the terms of this Letter Agreement are acceptable, please so indicate by executing a copy of this Letter Agreement and returning it to Akcea.

Very truly yours,

AKCEA THERAPEUTICS, INC.

/s/Damien McDevitt

Damien McDevitt, Ph.D.
Chief Executive Officer

AGREED TO AND CONFIRMED BY PFIZER INC.:

By: /s/James Rusnak
Name: James Rusnak
Title: SVP, Chief Development Officer

Exhibit 10.2

Adopted by the Board of Directors March 26, 2021

Non-Employee Director Compensation Policy

Ionis Pharmaceuticals, Inc. ("***Ionis***") values the contributions made by its Board of Directors. In recognition of these valuable contributions, Ionis will provide each non-employee Director with the compensation described in this policy.

Cash Compensation

Each non-employee Director will receive cash compensation based on his or her role on the Board and Board committees as follows:

Role	Cash Compensation
Board Member (base retainer)	$60,000[(1)]
Non-Executive Chairman of the Board (additional)	$40,000
Independent Lead Director (additional)	$40,000
Committee Chair (additional):	
-Audit	$24,000
-Commercial Compliance	$10,000
-Compensation	$20,000
-Finance	$20,000
-Nominating, Governance and Review	$20,000
-Science/Medical	$20,000
Committee Member (additional):	
-Audit	$12,000
-Commercial Compliance	$5,000
-Compensation	$10,000
-Finance	$10,000
-Nominating, Governance and Review	$10,000
-Science/Medical	$10,000

(1) Before March 31, 2024 this annual base cash retainer for each non-employee Director (not including fees for Non-Executive Chair, Independent Lead Director, Committee Chair or Committee Member) is limited to a maximum of $70,000 per year.

Equity Compensation

Each non-employee Director will receive an initial stock option award and restricted stock unit award upon joining the Board and an annual stock option award and restricted stock unit award for each year of continued service as follows (subject to the aggregate grant date value limit described below):

Type of Grant	Number of Shares*
Initial Stock Option Grant	24,000
Initial Restricted Stock Unit Grant	10,667
Annual Stock Option Grant	12,000
Annual Restricted Stock Unit Grant	5,333

*These equity awards are to be automatically granted pursuant to the terms of the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors Stock Option Plan as approved by our stockholders on June 4, 2020 (the ***"NED Plan"***). Notwithstanding the terms of the NED Plan, (1) the Compensation Committee, with input from its independent consultant, may reduce the number of shares to be automatically issued on a grant date for each such award so that the awards granted have an aggregate grant date fair value (as determined in accordance with FASB Topic ASC 718 or its successor) that is aligned with the set of peer companies the Compensation Committee uses to evaluate compensation, and (2) the initial equity awards for new directors will be adjusted downward such that they are 1.5X the annual equity awards for any given year.

The exercise price of each stock option will be the Fair Market Value (as defined in the NED Plan) of Ionis' common stock on the date of grant.

As set forth in the NED Plan, initial grants vest on the annual anniversary of the date of grant and annual grants vest on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.

While serving on the Board, each non-employee Director may not sell Ionis shares obtained pursuant to vesting of restricted stock unit awards if selling such shares would reduce the shares owned by such non-employee Director (not including stock options or unvested restricted stock units) below an amount that is equal to four times his or her annual base cash retainer.

Review of Non-Employee Director Compensation Policy

This policy will be reviewed annually by Ionis' Compensation Committee and Board of Directors.

On at least an annual basis, Ionis will retain an independent consultant to (1) advise the Compensation Committee on recent developments and best practices concerning director compensation, and (2) compare Ionis' director compensation levels, policies, practices, and procedures to a set of peer companies selected by the Compensation Committee with input from the independent consultant.

Ionis reserves the right to amend this compensation policy at any time so long as the issuance of the equity awards comply with the terms of the NED Plan or any successor thereto.

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: May 5, 2021

/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: May 5, 2021

/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 March 31, 2021, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: May 5, 2021

/s/ BRETT P. MONIA	/s/ ELIZABETH L. HOUGEN
Brett P. Monia, Ph.D. Chief Executive Officer	Elizabeth L. Hougen Chief Financial Officer

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