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, 2022

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 28, 2022 was 141,797,854.

IONIS PHARMACEUTICALS, INC.
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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)

	March 31, 2022 (unaudited)	December 31, 2021
ASSETS		
Current assets:		
Cash and cash equivalents	$ 542,513	$ 869,191
Short-term investments	1,509,880	1,245,782
Contracts receivable	26,122	61,896
Inventories	24,032	24,806
Other current assets	150,577	143,374
Total current assets	2,253,124	2,345,049
Property, plant and equipment, net	177,724	178,069
Patents, net	29,295	29,005
Deposits and other assets	58,949	59,567
Total assets	$ 2,519,092	$ 2,611,690
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 16,125	$ 11,904
Accrued compensation	16,525	38,810
Accrued liabilities	99,256	88,560
Income taxes payable	901	36
Current portion of long-term obligations	4,206	3,526
Current portion of deferred contract revenue	91,437	97,714
Total current liabilities	228,450	240,550
Long-term deferred contract revenue	333,138	351,879
0 percent convertible senior notes, net	619,898	619,119
0.125 percent convertible senior notes, net	542,860	542,314
Long-term obligations, less current portion	25,710	26,378
Long-term mortgage debt	59,462	59,713
Total liabilities	1,809,518	1,839,953
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 141,753,122 and 141,210,015 shares issued and outstanding at March 31, 2022 (unaudited) and December 31, 2021, respectively	142	141
Additional paid-in capital	1,983,078	1,964,167
Accumulated other comprehensive loss	(48,578)	(32,668)
Accumulated deficit	(1,225,068)	(1,159,903)
Total stockholders' equity	709,574	771,737
Total liabilities and stockholders' equity	$ 2,519,092	$ 2,611,690

See accompanying notes.

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

	Three Months Ended March 31,	
	2022	**2021**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 53,818	$ 59,986
TEGSEDI and WAYLIVRA revenue, net	6,160	19,838
Licensing and other royalty revenue	12,307	4,624
Total commercial revenue	72,285	84,448
Research and development revenue:		
Collaborative agreement revenue	49,784	27,159
Eplontersen joint development revenue	19,850	—
Total research and development revenue	69,634	27,159
Total revenue	141,919	111,607
Expenses:		
Cost of sales	4,170	2,578
Research, development and patent	161,126	139,801
Selling, general and administrative	34,127	61,199
Total operating expenses	199,423	203,578
Loss from operations	(57,504)	(91,971)
Other income (expense):		
Investment income	1,993	4,643
Interest expense	(2,122)	(2,414)
Loss on investments	(6,625)	—
Other income	187	3
Loss before income tax expense	(64,071)	(89,739)
Income tax expense	(1,094)	(130)
Net loss	$ (65,165)	$ (89,869)
Basic and diluted net loss per share	$ (0.46)	$ (0.64)
Shares used in computing basic and diluted net loss per share	141,599	140,770

See accompanying notes.

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

	Three Months Ended March 31,	
	2022	**2021**
Net loss	$ (65,165)	$ (89,869)
Unrealized losses on debt securities, net of tax	(15,756)	(3,006)
Currency translation adjustment	(154)	(126)
Comprehensive loss	$ (81,075)	$ (93,001)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Three Months Ended March 31, 2021 and 2022
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2020	140,366	$ 140	$ 1,895,519	$ (21,071)	$ (1,131,306)	$ 743,282
Net loss	—	—	—	—	(89,869)	(89,869)
Change in unrealized losses, net of tax	—	—	—	(3,006)	—	(3,006)
Foreign currency translation	—	—	—	(126)	—	(126)
Issuance of common stock in connection with employee stock plans	809	1	7,758	—	—	7,759
Stock-based compensation expense	—	—	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)
Balance at March 31, 2021	140,924	$ 141	$ 1,925,801	$ (24,203)	$ (1,221,175)	$ 680,564
Balance at December 31, 2021	141,210	$ 141	$ 1,964,167	$ (32,668)	$ (1,159,903)	$ 771,737
Net loss	—	—	—	—	(65,165)	(65,165)
Change in unrealized losses, net of tax	—	—	—	(15,756)	—	(15,756)
Foreign currency translation	—	—	—	(154)	—	(154)
Issuance of common stock in connection with employee stock plans	847	1	1,848	—	—	1,849
Stock-based compensation expense	—	—	26,236	—	—	26,236
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(304)	—	(9,173)	—	—	(9,173)
Balance at March 31, 2022	141,753	$ 142	$ 1,983,078	$ (48,578)	$ (1,225,068)	$ 709,574

See accompanying notes.

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

	Three Months Ended March 31,	
	2022	**2021**
Operating activities:		
Net loss	$ (65,165)	$ (89,869)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	3,701	3,917
Amortization of right-of-use operating lease assets	602	394
Amortization of patents	592	544
Amortization of premium on investments, net	4,175	4,023
Amortization of debt issuance costs	1,343	860
Stock-based compensation expense	26,236	37,861
Gain on investments	(10)	(13)
Non-cash losses related to disposal of property, plant and equipment	527	—
Non-cash losses related to patents	110	221
Changes in operating assets and liabilities:		
Contracts receivable	35,774	52,807
Inventories	774	(234)
Other current and long-term assets	(7,222)	16,481
Income taxes receivable	865	2
Accounts payable	2,878	(9,569)
Accrued compensation	(22,285)	(36,465)
Accrued liabilities and other current liabilities	10,473	(11,905)
Deferred contract revenue	(25,018)	(23,717)
Net cash used in operating activities	(31,650)	(54,662)
Investing activities:		
Purchases of short-term investments	(462,855)	(330,051)
Proceeds from sale of short-term investments	178,837	411,907
Purchases of property, plant and equipment	(2,705)	(1,772)
Acquisition of licenses and other assets, net	(826)	(1,228)
Net cash (used in) provided by investing activities	(287,549)	78,856
Financing activities:		
Proceeds from equity, net	1,848	7,760
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(9,173)	(15,337)
Net cash used in financing activities	(7,325)	(7,577)
Effects of exchange rates on cash	(154)	(126)
Net (decrease) increase in cash and cash equivalents	(326,678)	16,491
Cash and cash equivalents at beginning of period	869,191	397,664
Cash and cash equivalents at end of period	$ 542,513	$ 414,155
Supplemental disclosures of cash flow information:		
Interest paid	$ 594	$ 594
Income taxes paid	$ 2	$ 2
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,344	$ 1,876

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2022
(Unaudited)

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three months ended March 31, 2022 and 2021 on the same basis as the audited financial statements for the year ended December 31, 2021. 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, 2021 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").

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.

At contract inception, we analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of Accounting Standards Codification, or ASC, Topic 808, *Collaborative Arrangements*, or ASC 808. ASC 808 does not address the recognition and measurement of collaborative arrangements and instead refers companies to use other authoritative accounting literature. If there is no appropriate analogous authoritative accounting literature, ASC 808 suggests companies consistently apply a reasonable and rational accounting policy election. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration reflect a vendor-customer relationship and therefore are within the scope of ASC 606, *Revenue from Contracts with Customers*. When we determine elements of a collaboration do not reflect a vendor-customer relationship, we consistently apply the reasonable and rational policy election we made by analogizing to authoritative accounting literature.

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 January 2021 and April 2021, we entered into distribution agreements with Swedish Orphan Biovitrum AB, or Sobi, in which Sobi began commercializing TEGSEDI and WAYLIVRA in Europe and TEGSEDI in North America, respectively. 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.

Prior to the second quarter of 2021 in North America, we sold TEGSEDI through exclusive distribution agreements with third-party logistics companies, or 3PLs, that took title to TEGSEDI. The 3PLs 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 the United States, or U.S., we had a single 3PL as our sole customer and in Canada we also had a single 3PL as our sole customer. Prior to 2021 in Europe, we sold TEGSEDI and WAYLIVRA to hospitals and pharmacies, which were our customers, using 3PLs as distributors.

Under our collaboration agreement with PTC Therapeutics International Limited, or PTC, PTC is responsible for commercializing TEGSEDI and WAYLIVRA in Latin America and Caribbean countries. Under our agreement, we started receiving royalties from PTC for TEGSEDI sales in December 2021.

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 6, *Collaborative Arrangements and Licensing Agreements*, for collaborations with substantive changes that occurred in 2022. 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, 2021 for a summary of each of our material collaborative agreements.

Steps to Recognize Revenue

For elements of our contractual relationships that we account for under ASC 606, 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.

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 first quarter of 2022, we earned a $10 million milestone payment from Biogen when Biogen advanced the Phase 1/2 study for ION859, an investigational antisense medicine targeting leucine rich repeat kinase 2, or LRRK2, in patients with Parkinson's disease. We did not consider the milestone payment probable until Biogen achieved the milestone event because advancing ION859 was contingent on Biogen advancing a Phase 1/2 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;
- Estimated expenses we may 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 estimated number of internal hours we will spend performing these services;
- The estimated cost of work we will perform;
- The estimated cost of work that we will contract with third parties to perform; and
- The estimated cost of API we will use.

For purposes of determining 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

Under our distribution agreements with Sobi we concluded that our performance obligation is to provide services to Sobi over the term of the agreement, which includes supplying finished goods inventory to Sobi. We are also responsible for maintaining the marketing authorization for TEGSEDI and WAYLIVRA in major markets and for leading the global commercial strategy for each medicine. We view this performance obligation as a series of distinct activities that are substantially the same. 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. Under our agreements with Sobi, Sobi does not generally have a right of return.

Prior to our distribution agreements 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.

Reserves for TEGSEDI and WAYLIVRA commercial revenue

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

Prior to our distribution agreements 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. Under our agreements with Sobi, we transferred all reserves to Sobi. 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, 2021 for additional details regarding how we accounted for the reserves related to TEDSEDI and WAYLIVIRA product sales prior to our agreements with Sobi.

Research and development revenue under collaboration agreements:

Upfront payments

When we enter into a collaboration agreement and receive 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 2021, 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 first quarter of 2022, we recognized $18 million in milestone payments when Biogen advanced two targets under our 2013 strategic collaboration. 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 first quarter of 2022.

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 2021, we earned a $60 million license fee from Biogen when Biogen licensed ION306, an investigational medicine in development to treat SMA.

Sublicense fees

We recognize sublicense fee revenue in the period in which a party, who has already licensed our technology, further licenses the technology to another party because we do not have any performance obligations related to the sublicense. For example, in the fourth quarter of 2020, we earned a $41.2 million sublicense fee from Alnylam Pharmaceuticals for its sublicense of our technology to Sanofi Genzyme.

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.

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.

Eplontersen Collaboration with AstraZeneca

In December 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of transthyretin amyloidosis, or ATTR. We are jointly developing and preparing to commercialize eplontersen with AstraZeneca in the U.S. We granted AstraZeneca exclusive rights to commercialize eplontersen outside the U.S., except certain countries in Latin America. Under the terms of the agreement, we received a $200 million upfront payment in 2021.

We evaluated our eplontersen collaboration under ASC 808 and identified four material components: (i) the license we granted to AstraZeneca in 2021, (ii) the co-development activities that we and AstraZeneca are performing, (iii) the co-commercialization activities that we and AstraZeneca are performing and (iv) the co-medical affairs activities that we and AstraZeneca are performing.

We determined that we had a vendor-customer relationship within the scope of ASC 606 for the license we granted to AstraZeneca and as a result we had one performance obligation. For our sole performance obligation, we determined the transaction price was the $200 million upfront payment we received. We recognized the upfront payment in full in 2021 because we did not have any remaining performance obligations after we delivered the license to AstraZeneca.

We also concluded that the co-development activities, the co-commercialization activities and the co-medical affairs activities are within the scope of ASC 808 because we and AstraZeneca are active participants exposed to the risks and benefits of the activities under the collaboration and therefore do not have a vendor-customer relationship. AstraZeneca is responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. As we continue to lead the Phase 3 development program, we made an accounting policy election to recognize as non-customer revenue the cost-share funding from AstraZeneca in the same period we incur the related development expenses. As AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing eplontersen to market outside the U.S., we made an accounting policy election to recognize cost-share funding we receive from AstraZeneca related to commercial and medical affairs activities as reductions of our SG&A expense and R&D expense, respectively. Refer to Item 2, *Management's Discussion and Analysis of Financial Condition and Results of Operations*, for further details on the financial statement impacts of our eplontersen collaboration with AstraZeneca.

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, 2022, approximately 82.2 percent of our contracts receivables were from two significant customers. As of December 31, 2021, approximately 93.8 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, 2022 and 2021, we recognized $26.2 million and $26.0 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, 2022, we held equity investments in three publicly held companies, Antisense Therapeutics Limited, or ATL, Bicycle Therapeutics plc, or Bicycle, and ProQR Therapeutics N.V., or ProQR. We also held equity investments in seven privately held companies, Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, YourBio Health, Inc. (formerly 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 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. As a result of these observable price changes, we recognized a total gain of $14.8 million on our investments in these companies 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. Our raw materials - commercial inventory includes API for our commercial medicines. We capitalize material, labor and overhead costs as part of our raw materials - commercial inventory.

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 immaterial amount of inventory write-offs for the three months ended March 31, 2022 and 2021.

Our inventory consisted of the following (in thousands):

	March 31, 2022	December 31, 2021
Raw materials:		
Raw materials- clinical	$ 15,764	$ 14,507
Raw materials- commercial	2,165	4,139
Total raw materials	17,929	18,646
Work in process	5,637	5,770
Finished goods	466	390
Total inventory	$ 24,032	$ 24,806

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 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.

In January 2022, we entered into a sublease agreement for our office space located in Boston, Massachusetts. The sublease commenced in January 2022 when the office space was ready for our tenant's occupancy. We are subleasing this space under a non-cancelable operating sublease with a sublease term ending in November 2028 with no option to extend the sublease. Under the sublease agreement we provided a seven-month free rent period, which commenced in January 2022. We will receive lease payments over the sublease term totaling $9.6 million. We are recognizing sublease payments as other income on a straight-line, gross basis over the term of our sublease.

Research, Development and Patent Expenses

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

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

Income Taxes

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

We apply the authoritative accounting guidance prescribing a threshold and measurement attribute for the financial recognition and measurement of a tax position taken or expected to be taken in a tax return. We recognize liabilities for uncertain tax positions based on a two-step process. The first step is to evaluate the tax position for recognition by determining if the weight of available evidence indicates that it is more likely than not that the position will be sustained on audit, including resolution of related appeals or litigation processes, if any. The second step requires us to estimate and measure the tax benefit as the largest amount that is more than 50 percent likely to be realized upon ultimate settlement.

We are required to use significant judgment in evaluating our uncertain tax positions and determining our provision for income taxes. Although we believe our reserves are reasonable, we can provide no assurance that the final tax outcome of these matters will not be different from that which we have reflected in our historical income tax provisions and accruals. We adjust these reserves for changing facts and circumstances, such as the closing of a tax audit or the refinement of an estimate. To the extent that the final tax outcome of these matters is different than the amounts recorded, such differences may impact the provision for income taxes in the period in which we make such determination.

We are also required to use significant judgment in determining any valuation allowance recorded against our deferred tax assets. In assessing the need for a valuation allowance, we consider all available evidence, including scheduled reversal of deferred tax liabilities, past operating results, the feasibility of tax planning strategies and estimates of future taxable income. We base our estimates of future taxable income on assumptions that are consistent with our plans. The assumptions we use represent our best estimates and involve inherent uncertainties and the application of our judgment. Should actual amounts differ from our estimates, the amount of our tax expense and liabilities we recognize could be materially impacted. We record a valuation allowance to reduce the balance of our net deferred tax assets to the amount we believe is more-likely-than-not to be realized.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries.

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

We calculated our basic net loss per share for the three months ended March 31, 2022 and 2021 by dividing our net loss by our weighted-average number of common shares outstanding during the period. Our basic net loss per share for the three months ended March 31, 2022 and 2021 were $0.46 and $0.64, respectively.

Diluted net loss per share

For the three months ended March 31, 2022 and 2021, 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, or 0.125% Notes;
- Note hedges related to the 0.125% Notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

For the three months ended March 31, 2021, common stock from our 1 percent convertible senior notes, or 1% Notes, would also have had an anti-dilutive effect on net loss per share.

For the three months ended March 31, 2022, common stock from the following would also have had an anti-dilutive effect on net loss per share:

- 0 percent convertible senior notes, or 0% Notes; and
- Note hedges related to the 0% Notes.

Additionally as of March 31, 2022, we had warrants related to our 0% and 0.125% 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

We 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. We record the entire debt issuance costs as a contra-liability on our condensed consolidated balance sheet at issuance and we amortize them over the contractual term using an updated effective interest rate. As such, the ending balances for our 0% and 0.125% Notes represent the principal balance of each convertible debt instrument less debt issuance costs. We amortize debt issuance costs for our 0% and 0.125% Notes over the respective contractual term using an effective interest rate of 0.5 percent for each note. Refer to Note 7, *Convertible Debt*, for further details on our convertible debt instruments.

Call Spread

In conjunction with the issuance of our 0% Notes and 0.125% Notes in April 2021 and December 2019, respectively, we entered into call spread transactions, which were 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

We operate 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.

Stock-based Compensation Expense

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

For the three months ended March 31, 2022 and 2021, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2022	**2021**
Risk-free interest rate	1.7%	0.5%
Dividend yield	0.0%	0.0%
Volatility	55.2%	55.1%
Expected life*	6.3 years	4.9 years

* In 2021, our Compensation Committee approved an amendment to the 2011 Equity Incentive Plan, or 2011 Plan, and 2020 Plan, that increased the contractual term of stock options granted under these plans from seven years to ten years for stock options granted on January 1, 2022 and thereafter. We determined that we are unable to rely on our historical exercise data as a basis for estimating the expected life of stock options granted to employees following this change because the contractual term changed and we have no other means to reasonably estimate future exercise behavior. We therefore used the simplified method for determining the expected life of stock options granted to employees in the three months ended March 31, 2022. Under the simplified method, we calculate the expected term as the average of the time-to-vesting and the contractual life of the options. As we gain additional historical information, we will transition to calculating our expected term based on our historical exercise patterns.

ESPP:

	Three Months Ended March 31,	
	2022	**2021**
Risk-free interest rate	0.6%	0.1%
Dividend yield	0.0%	0.0%
Volatility	50.2%	39.1%
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, 2022 was $33.08 per share.

PRSU's:

Beginning in 2020, we added PRSU awards to the compensation for our Chief Executive Officer, Dr. Brett Monia. Beginning in 2022, we added PRSU awards to the compensation for our other executive officers. 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 the 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 our executive officers for the three months ended March 31, 2022 and 2021 were $42.28 and $77.17 per share, respectively.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2022 and 2021 (in thousands).

	Three Months Ended March 31,	
	2022	2021
Cost of sales	$ 160	$ 182
Research, development and patent expense	19,082	25,899
Selling, general and administrative expense	6,994	11,780
Total	$ 26,236	$ 37,861

As of March 31, 2022, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $67.7 million, $69.2 million and $5.4 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, 1.7 years and 1.6 years, respectively.

Impact of Recently Issued Accounting Standards

We do not expect any 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, 2022:

One year or less	63%
After one year but within two years	30%
After two years but within three and a half years	7%
Total	100%

As illustrated above, at March 31, 2022, 93 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, 2022, we had an ownership interest of less than 20 percent in seven private companies and three public companies with which we conduct business. The privately held companies are Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, YourBio Health, Inc. and Suzhou-Ribo Life Science Co, Ltd. The publicly traded companies are Antisense Therapeutics Ltd., Bicycle and ProQR.

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

March 31, 2022	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (1)	$ 420,081	$ 131	$ (1,766)	$ 418,446
Debt securities issued by U.S. government agencies	34,407	—	(49)	34,358
Debt securities issued by the U.S. Treasury (1)	330,358	1	(1,133)	329,226
Debt securities issued by states of the U.S. and political subdivisions of the states	158,548	1	(376)	158,173
Other municipal debt securities	6,419	—	(99)	6,320
Total securities with a maturity of one year or less	949,813	133	(3,423)	946,523
Corporate debt securities	345,813	24	(10,275)	335,562
Debt securities issued by U.S. government agencies	72,844	—	(1,974)	70,870
Debt securities issued by the U.S. Treasury	164,040	70	(2,544)	161,566
Debt securities issued by states of the U.S. and political subdivisions of the states	34,995	—	(818)	34,177
Total securities with a maturity of more than one year	617,692	94	(15,611)	602,175
Total available-for-sale securities	$ 1,567,505	$ 227	$ (19,034)	$ 1,548,698
Equity securities:				
Total equity securities included in other current assets (2)	$ 11,897	$ 3,946	$ (4,274)	$ 11,569
Total equity securities included in deposits and other assets (3)	23,115	16,707	—	39,822
Total equity securities	35,012	20,653	(4,274)	51,391
Total available-for-sale and equity securities	$ 1,602,517	$ 20,880	$ (23,308)	$ 1,600,089

December 31, 2021	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (1)	$ 383,870	$ 728	$ (226)	$ 384,372
Debt securities issued by U.S. government agencies	48,493	19	(18)	48,494
Debt securities issued by the U.S. Treasury (1)	45,424	—	(64)	45,360
Debt securities issued by states of the U.S. and political subdivisions of the states	134,770	45	(37)	134,778
Total securities with a maturity of one year or less	612,557	792	(345)	613,004
Corporate debt securities	382,000	331	(2,644)	379,687
Debt securities issued by U.S. government agencies	72,935	—	(561)	72,374
Debt securities issued by the U.S. Treasury	137,635	139	(500)	137,274
Debt securities issued by states of the U.S. and political subdivisions of the states	39,909	1	(224)	39,686
Other municipal debt securities	6,136	—	(37)	6,099
Total securities with a maturity of more than one year	638,615	471	(3,966)	635,120
Total available-for-sale securities	$ 1,251,172	$ 1,263	$ (4,311)	$ 1,248,124
Equity securities:				
Total equity securities included in other current assets (2)	$ 11,897	$ 7,145	$ (837)	$ 18,205
Total equity securities included in deposits and other assets (3)	15,615	16,707	—	32,322
Total equity securities	27,512	23,852	(837)	50,527
Total available-for-sale and equity securities	$ 1,278,684	$ 25,115	$ (5,148)	$ 1,298,651

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

(2) Our equity securities included in other current assets consisted of our investments in two publicly traded companies, ProQR and Bicycle, which we classify as Level 1 and Level 3 investments, respectively. We recognize publicly traded equity securities at fair value. In the three months ended March 31, 2022, we recognized a $3.4 million and a $3.2 million unrealized loss on our condensed consolidated statement of operations related to our investments in ProQR and Bicycle, respectively. In the three months ended March 31, 2021, our equity securities included in other current assets only consisted of ProQR.

(3) 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, 2022 (in thousands, except for number of investments). We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	337	$ 647,390	$ (11,694)	$ 11,300	$ (347)	$ 658,690	$ (12,041)
Debt securities issued by U.S. government agencies	14	95,543	(1,697)	9,685	(326)	105,228	(2,023)
Debt securities issued by the U.S. Treasury	44	406,747	(3,539)	4,860	(138)	411,607	(3,677)
Debt securities issued by states of the U.S. and political subdivisions of the states	619	173,537	(1,096)	5,455	(98)	178,992	(1,194)
Other municipal debt securities	3	1,315	(16)	5,005	(83)	6,320	(99)
Total temporarily impaired securities	1,017	$1,324,532	$ (18,042)	$ 36,305	$ (992)	$1,360,837	$ (19,034)

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, 2022 and December 31, 2021 that we regularly measure and carry at fair value. As of March 31, 2022 and December 31, 2021, our Bicycle investment was subject to trading restrictions that extend to the third quarter of 2022; as a result, we included a lack of marketability discount in valuing this investment, which is a Level 3 input. 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, 2022	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 407,399	$ 407,399	$ —	$ —
Corporate debt securities (2)	754,008	—	754,008	—
Debt securities issued by U.S. government agencies (3)	105,228	—	105,228	—
Debt securities issued by the U.S. Treasury (4)	490,792	490,792	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (5)	192,350	—	192,350	—
Other municipal debt securities (3)	6,320	—	6,320	—
Investment in Bicycle Therapeutics plc (6)	11,131	—	—	11,131
Investment in ProQR Therapeutics N.V. (6)	438	438	—	—
Total	$ 1,967,666	$ 898,629	$ 1,057,906	$ 11,131

	At December 31, 2021	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 541,199	$ 541,199	$ —	$ —
Corporate debt securities (3)	764,059	—	764,059	—
Debt securities issued by U.S. government agencies (3)	120,868	—	120,868	—
Debt securities issued by the U.S. Treasury (3)	182,634	182,634	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (7)	174,464	—	174,464	—
Other municipal debt securities (3)	6,099	—	6,099	—
Investment in Bicycle Therapeutics plc (6)	14,330	—	—	14,330
Investment in ProQR Therapeutics N.V. (6)	3,875	3,875	—	—
Total	$ 1,807,528	$ 727,708	$ 1,065,490	$ 14,330

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) $13.5 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(3) Included in short-term investments.

(4) $15.0 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(5) $10.3 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

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

(7) $2.3 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

Convertible Notes

Our 0.125% Notes and 0% Notes had a fair value of $494.4 million and $595.4 million at March 31, 2022, respectively. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

5. Income Taxes

Beginning in 2022, the Tax Cuts and Jobs Act of 2017, or TCJA, requires taxpayers to amortize research and development expenditures over five years pursuant to Internal Revenue Code, or IRC, Section 174. Although the U.S. Congress is considering legislation that would defer the amortization requirement to later years, we have no assurance that the provision will be repealed or otherwise modified. As a result, we recorded a $1.1 million income tax expense for the three months ended March 31, 2022 compared to $0.1 million income tax expense for the same period in 2021.

6. Collaborative Arrangements and Licensing Agreements

Below, we have included our Biogen collaboration, which is our only collaboration with substantive changes during 2022 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, 2021.

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 numerous investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with ALS, SMA, Angelman Syndrome, 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, 2022, we have received $3.3 billion from our Biogen collaborations.

During the three months ended March 31, 2022 and 2021, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended March 31,	
	2022	2021
SPINRAZA royalties (commercial revenue)	$ 53.8	$ 60.0
R&D revenue	40.1	18.1
Total revenue from our relationship with Biogen	$ 93.9	$ 78.1
Percentage of total revenue	66%	70%

Our condensed consolidated balance sheet at March 31, 2022 and December 31, 2021 included deferred revenue of $385.5 million and $407.5 million, respectively, related to our relationship with Biogen.

During the first quarter of 2022, we did not have any material changes to our performance obligations, transaction price or the timing in which we expect to recognize revenue under our Biogen collaborations.

In the first quarter of 2022, we earned $18 million in milestone payments from Biogen when Biogen advanced two targets under our 2013 strategic collaboration. We recognized the milestone payments in full in the first quarter of 2022 because we did not have any remaining performance obligations related to the milestone payments. We will achieve the next payment of up to $10 million if Biogen advances a medicine under our 2013 strategic neurology collaboration.

7. 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% Notes to repurchase $247.9 million in principal of our 1% Notes for $257.0 million.

At March 31, 2022, 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
Unamortized debt issuance costs	$ 12.6
Maturity date	April 2026
Interest rate	0 percent
Effective interest rate	0.5 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.

We recorded the amount we paid for the note hedges and the amount we 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.

0.125 Percent Convertible Senior Notes and Call Spread

At March 31, 2022, 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
Unamortized debt issuance costs	$ 6.0
Maturity date	December 2024
Interest rate	0.125 percent
Effective interest rate	0.5 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

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 we paid for the note hedges and the amount we 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

In April 2021, we repurchased $247.9 million in aggregate principal amount of our 1% Notes in privately negotiated transactions. As a result of the repurchase, we recognized an $8.6 million non-cash loss on early retirement of debt in the second quarter of 2021, reflecting the early retirement of a significant portion of our 1% Notes. The non-cash loss on the early retirement of our debt is the difference between the amount paid to retire our 1% Notes and the net carrying balance of the liability at the time that we retired the debt. We paid the remaining principal balance of our 1% Notes with $62.0 million of cash at maturity in November 2021.

Other Terms of Convertible Senior Notes

The 0% and 0.125% 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. The 1% Notes were subject to similar terms.

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), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, tofersen 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, 2021, 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 therapeutics. We believe our medicines have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases. We currently have three marketed medicines- SPINRAZA, TEGSEDI and WAYLIVRA. We also have a rich late-stage pipeline of medicines, primarily focused on our cardiovascular and neurology franchises. Our late-stage pipeline consists of six medicines in Phase 3 development for eight indications.

Our multiple sources of revenue and strong balance sheet enable us to invest in our strategic priorities to build our commercial pipeline, expand and diversify our technology and deliver new medicines to the market. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to deliver increasing value for patients and shareholders.

Marketed Medicines

SPINRAZA is the global market leader 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, 2022, new patient starts in the U.S. reached a two-year high and initial uptake in China was strong as this was the first full quarter since receiving national reimbursement in China. Through March 31, 2022, we have earned more than $1.6 billion in revenues from our SPINRAZA collaboration, including more than $1.2 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 polyneuropathy, or ATTRv-PN, 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 began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC Therapeutics International Limited, or PTC, is commercializing TEGSEDI in Brazil. PTC is pursuing access in additional Latin American countries under its exclusive license agreement with us. In the first quarter of 2022, we continued to progress into new and existing markets in Europe and Latin America through Sobi and PTC, respectively.

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 familial chylomicronemia syndrome, or 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. Under our exclusive license agreement with PTC, PTC is working to provide access to WAYLIVRA across Latin America, beginning in Brazil. In the third quarter of 2021, the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária), or ANVISA, approved WAYLIVRA in Brazil. In December 2021, PTC submitted an application to ANVISA for approval of WAYLIVRA for the treatment of familial partial lipodystrophy, or FPL, in Brazil. If approved, Waylivra will be the first approved treatment for patients with FPL in Brazil.

Under our distribution agreements with Sobi, we retained the marketing authorizations for TEGSEDI and WAYLIVRA in major markets. 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 and WAYLIVRA global commercial strategy. In connection with the agreements, we restructured our European operations in the first quarter of 2021, and we restructured our North American TEGSEDI operations in the second quarter of 2021.

Medicines in Phase 3 Studies

We currently have six medicines in Phase 3 studies for eight indications, which include:

- Eplontersen: our medicine in development for ATTR
  - In the second quarter of 2022, we achieved our original enrollment goal and increased the study size and duration in the Phase 3 CARDIO-TTRansform study in patients with ATTR cardiomyopathy, or ATTR-CM, with the aim to ensure a highly positive outcome and generate an even more robust data set to successfully compete in this growing and dynamic market. We expect data from this study in the first half of 2025
  - Enrollment is complete in the NEURO-TTRansform Phase 3 study in patients with ATTRv-PN. We expect data from this study in mid-2022
  - In the first quarter of 2022, the U.S. FDA granted orphan drug designation to eplontersen for the treatment of patients with ATTR
- Olezarsen: our medicine in development for familial chylomicronemia syndrome, or FCS, and severe hypertriglyceridemia, or SHTG
  - Enrollment is ongoing in the BALANCE Phase 3 study in patients with FCS and the CORE Phase 3 study in patients with SHTG
  - We published positive data from the Phase 2 study of olezarsen in patients with hypertriglyceridemia and either at high risk for or with established cardiovascular disease in the *European Heart Journal*
  - We initiated a study of olezarsen in patients with hypertriglyceridemia to support the broad Phase 3 program
- Donidalorsen: our medicine in development for hereditary angioedema, or HAE
  - Enrollment is ongoing in the Phase 3 OASIS-HAE study
  - We published positive data from the Phase 2 study of donidalorsen in patients with HAE in the *New England Journal of Medicine*
  - We presented positive data from the Phase 2 study of donidalorsen in patients with HAE at the American Academy of Allergy, Asthma and Immunology annual meeting
- ION363: our medicine in development for amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or FUS. FUS-ALS is the most common cause of juvenile-onset ALS
  - Enrollment is ongoing in the Phase 3 study in patients with FUS-ALS
- Pelacarsen: our medicine in development for lipoprotein(a), or Lp(a), driven cardiovascular disease
  - Enrollment is ongoing in Novartis' Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with established cardiovascular disease and elevated lipoprotein(a), or Lp(a)
- Tofersen: our medicine in development for superoxide dismutase 1 ALS, or SOD1-ALS
  - Biogen plans to present new data from the ongoing VALOR open-label extension, or OLE, study at the European Network to Cure ALS meeting in June 2022
  - Biogen remains engaged with regulators to identify a potential path forward for tofersen

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 monitor 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,	
	2022	**2021**
Total revenue	$ 141.9	$ 111.6
Total operating expenses	$ 199.4	$ 203.6
Loss from operations	$ (57.5)	$ (92.0)
Net loss	$ (65.2)	$ (89.9)

Our financial results for the first quarter of 2022 reflected the cost-sharing provisions related to our eplontersen collaboration with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. Under the terms of the collaboration agreement, AstraZeneca is paying 55 percent of the costs associated with the ongoing global Phase 3 development program. As we are leading the Phase 3 development program, we are recognizing as R&D revenue the 55 percent of cost-share funding AstraZeneca is responsible for in the same period we incur the related development expenses. As a result of the cost-sharing provisions in our collaboration, we will receive payments of $20 million from AstraZeneca related to development expenses incurred in the first quarter of 2022.

As AstraZeneca is responsible for the majority of the medical affairs and commercial costs in the U.S. and all costs associated with bringing eplontersen to market outside the U.S., we are recognizing cost-share funding we receive from AstraZeneca related to these activities as a reduction of our medical affairs and commercialization expenses, which we classify as R&D and SG&A expenses, respectively. In the first quarter of 2022, we recognized $0.4 million and $0.2 million of medical affairs expenses and commercialization expenses for eplontersen, respectively, net of cost-share funding from AstraZeneca. We expect our medical affairs and commercialization expenses to increase as our collaboration with AstraZeneca progresses.

The following is a summary of the financial impacts on our statement of operations of the joint development activities under our eplontersen collaboration with AstraZeneca:

Collaboration Activities	Financial Statement Line		Impact of Cost-Sharing Provisions on our Statement of Operations
Phase 3 Development: Ionis leads and conducts	Eplontersen Joint Development Revenue (R&D Revenue)	$20M	55% of Ionis' Phase 3 development expenses, including internal+external costs & CMC costs
	Development Expenses (R&D expenses)	$36M	100% of Ionis' Phase 3 development expenses

Our revenue in the first quarter of 2022 increased more than 25 percent compared to the same period last year. The increase was driven by significant partner payments across multiple partnered programs, including $20 million from AstraZeneca for its share of the global Phase 3 program costs for eplontersen and $40 million from Biogen for advancing several neurology disease programs, including investigational medicines to treat patients with spinocerebellar ataxia type 3 and Parkinson's disease, among others.

We completed the transition to Sobi of our TEGSEDI and WAYLIVRA commercial operations in Europe and our TEGSEDI commercial operations in North America in the first and second quarters of 2021, respectively. The decrease in TEGSEDI and WAYLIVRA revenue in the first quarter of 2022 compared to the same period last year was due to the shift from product sales to distribution fees based on net sales generated by Sobi. As part of the transition, we restructured our commercial operations in 2021, resulting in substantial cost savings.

Our operating expenses, excluding non-cash compensation expense related to equity awards, increased in the first quarter of 2022 compared to the same period in 2021. Our R&D expenses increased due to our investments in advancing our late-stage pipeline, including our expanding number of Phase 3 studies, which doubled over the course of 2021 from three to six studies. Our SG&A expenses included our investments in advancing our go-to-market activities for our near-term commercial opportunities. However, these expenses were offset by the savings we realized from the operating efficiencies we achieved from integrating Akcea and restructuring our commercial operations for TEGSEDI and WAYLIVRA. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the rest of 2022 as we continue to build our commercial pipeline, invest in expanding and diversifying our technology and advance our go-to-market activities.

As of March 31, 2022, we had $2.1 billion in cash and short-term investments and remain well capitalized with the resources we need to continue investing to drive future growth.

Recent Business Updates

First Quarter 2022 Marketed Products Highlights

SPINRAZA®: the global market leader for the treatment of SMA patients of all ages

- $473 million in worldwide SPINRAZA sales in the first quarter of 2022
- Biogen provided updates from the ASCEND, RESPOND and NURTURE studies of SPINRAZA at the Muscular Dystrophy Association (MDA) Clinical and Scientific conference and the American Academy of Neurology (AAN) annual meeting

TEGSEDI® and WAYLIVRA®: important medicines approved for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis and familial chylomicronemia syndrome, respectively

- Continued to progress into new and existing markets in Europe and Latin America in the first quarter through Sobi and PTC, respectively

First Quarter 2022 and Recent Events

Advancing our near-term commercial opportunities toward the market

- Increased study size and duration in the Phase 3 CARDIO-TTRansform study of eplontersen in patients with ATTR-CM with the aim to generate even more robust data and ensure a highly positive study outcome to successfully compete in this growing and dynamic market. Data from this study are expected in the first half of 2025
- The U.S. FDA granted orphan drug designation to eplontersen for the treatment of patients with ATTR
- Published positive data from the Phase 2 study of olezarsen in patients with hypertriglyceridemia and either at high risk for or with established cardiovascular disease in the *European Heart Journal*
- Initiated a study of olezarsen in patients with hypertriglyceridemia to support the broad Phase 3 program
- Published positive data from the Phase 2 study of donidalorsen in patients with HAE in the *New England Journal of Medicine*
- Presented additional positive data from the Phase 2 study of donidalorsen in patients with HAE at the American Academy of Allergy, Asthma and Immunology annual meeting

Advancing our leading cardiovascular disease franchise

- AstraZeneca presented positive data from the Phase 2b ETESIAN study of ION449 (AZD8233) targeting PCSK9 in statin treated patients with dyslipidemia at the American College of Cardiology (ACC) annual scientific session
- Achieved full enrollment in the Phase 2b study of IONIS-AGT-L_{Rx} for patients with treatment-resistant hypertension, with data expected in the second half of 2022

Advancing our leading neurological disease franchise

- Roche plans to initiate a new Phase 2 study of tominersen in patients with Huntington's disease based on findings from a post-hoc analysis of the GENERATION-HD1 study
- Biogen initiated the Phase 1/2 study for ION260 (BIIB132) targeting ataxin-3 (ATXN3) in patients with spinocerebellar ataxia type 3 (SCA3), resulting in an $8 million milestone payment from Biogen
- Biogen advanced the Phase 1/2 study for ION859 (BIIB094) targeting LRRK2 in patients with Parkinson's disease, resulting in a $10 million milestone payment from Biogen
- Announced the discontinuation of IONIS-$C9_{Rx}$ (BIIB078) due to lack of patient benefit demonstrated in the Phase 1/2 study in patients with C9orf72-ALS

Business Segment

We operate 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.

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; and
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities

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, 2021.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2022 was $141.9 million compared to $111.6 million for the same period in 2021 and was comprised of the following (amounts in millions):

	Three Months Ended March 31,	
	2022	**2021**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 53.8	$ 60.0
TEGSEDI and WAYLIVRA revenue, net	6.2	19.8
Licensing and other royalty revenue	12.3	4.6
Total commercial revenue	72.3	84.4
R&D revenue:		
Amortization from upfront payments	17.4	20.1
Milestone payments	27.2	5.2
License fees	2.0	—
Other services	3.1	1.9
Collaborative agreement revenue	49.7	27.2
Eplontersen joint development revenue	19.9	—
Total R&D revenue	69.6	27.2
Total revenue	$ 141.9	$ 111.6

Our revenue in the first quarter of 2022 increased more than 25 percent compared to the same period last year. The increase in our R&D revenue was driven by significant partner payments across multiple partnered programs, including $20 million from AstraZeneca for its share of the global Phase 3 program costs for eplontersen and $40 million from Biogen for advancing several neurology disease programs, including investigational medicines to treat patients with spinocerebellar ataxia type 3 and Parkinson's disease, among others.

Our commercial revenue in the first quarter of 2022 decreased compared to the same period last year. We completed the transition to Sobi of our TEGSEDI and WAYLIVRA commercial operations in Europe and our TEGSEDI commercial operations in North America in the first and second quarters of 2021, respectively. As a result of our distribution agreements with Sobi for TEGSEDI and WAYLIVRA, our commercial revenue from product sales shifted to commercial revenue from distribution fees based on net sales generated by Sobi. As part of the transition, we restructured our commercial operations in 2021, resulting in substantial cost savings.

Operating Expenses

Our operating expenses were as follows (in millions):

	Three Months Ended March 31,	
	2022	2021
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 173.1	$ 159.0
Restructuring expenses	—	6.7
Total operating expenses, excluding non-cash compensation expense related to equity awards	173.1	165.7
Non-cash compensation expense related to equity awards	26.3	37.9
Total operating expenses	$ 199.4	$ 203.6

Operating expenses, excluding non-cash compensation expense related to equity awards, for the three months ended March 31, 2022 increased compared to the same period in 2021. Our R&D expenses increased due to our investments in advancing our late-stage pipeline, including our expanding number of Phase 3 studies, which doubled over the course of 2021 from three to six studies. Our SG&A expenses included our investments to prepare for the launches of eplontersen, olezarsen and donidalorsen. However, these expenses were offset by the savings we realized from integrating Akcea and restructuring our TEGSEDI and WAYLIVRA commercial operations. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the rest of 2022 as we continue to advance our mid- and late-stage medicines in development, invest in expanding and diversifying our technology and prepare for commercialization.

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.

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

	Three Months Ended March 31,	
	2022	2021
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 4.0	$ 2.4
Non-cash compensation expense related to equity awards	0.2	0.2
Total cost of sales	$ 4.2	$ 2.6

Our cost of sales, excluding non-cash compensation expense related to equity awards, increased slightly during the three months ended March 31, 2022 compared to the same period in 2021.

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,	
	2022	2021
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 142.0	$ 111.3
Restructuring expenses	—	2.6
Total research, development and patent expenses, excluding non-cash compensation expense related to equity awards	142.0	113.9
Non-cash compensation expense related to equity awards	19.1	25.9
Total research, development and patent expenses	$ 161.1	$ 139.8

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.

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

	Three Months Ended March 31,	
	2022	2021
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 19.1	$ 26.6
Non-cash compensation expense related to equity awards	4.1	6.3
Total antisense drug discovery expenses	$ 23.2	$ 32.9

Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards, decreased in the three months ended March 31, 2022 compared to the same period in 2021. In the first quarter of 2021, we incurred in-licensing expenses under our agreement with Genuity. We expect antisense drug discovery expenses to increase in the remainder of 2022 as we continue to invest in 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,	
	2022	2021
TEGSEDI and WAYLIVRA	$ 2.1	$ 1.4
Eplontersen	27.0	13.3
Olezarsen	8.7	1.4
Donidalorsen	1.7	1.8
ION363	1.7	2.1
Other antisense development projects	29.5	20.8
Development overhead expenses	19.3	18.3
Restructuring expenses	—	2.3
Total antisense drug development, excluding non-cash compensation expense related to equity awards	90.0	61.4
Non-cash compensation expense related to equity awards	8.6	12.4
Total antisense drug development expenses	$ 98.6	$ 73.8

Our development expenses, excluding non-cash compensation expense related to equity awards, increased for the three months ended March 31, 2022 compared to the same period in 2021 primarily due to our advancing late-stage pipeline, including our expanding number of Phase 3 studies, which doubled over the course of 2021 from three to six studies.

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.

Medical Affairs

Our medical affairs function is responsible for communicating scientific and clinical information to healthcare providers, medical professionals and patients.

Our medical affairs expenses were as follows (in millions):

	Three Months Ended March 31,	
	2022	2021
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 2.8	$ 2.9
Non-cash compensation expense related to equity awards	0.3	—
Total medical affairs expenses	$ 3.1	$ 2.9

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, were essentially flat in the three months ended March 31, 2022 compared to the same period in 2021. We expect medical affairs expenses to increase throughout 2022 as we advance our late-stage pipeline.

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,	
	2022	2021
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 16.3	$ 11.8
Restructuring expenses	—	0.3
Total manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	16.3	12.1
Non-cash compensation expense related to equity awards	2.7	3.1
Total manufacturing and development chemistry expenses	$ 19.0	$ 15.2

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2022 compared to the same period in 2021 due to increased costs we incurred in preparation for our near-term commercial launches, including manufacturing costs and activities for eplontersen and donidalorsen.

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,	
	2022	2021
Personnel costs	$ 5.1	$ 4.3
Occupancy	4.0	3.2
Patent expenses	0.7	0.8
Insurance	0.9	0.8
Computer software and licenses	0.6	0.5
Other	2.5	1.3
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	13.8	10.9
Non-cash compensation expense related to equity awards	3.4	4.1
Total R&D support expenses	$ 17.2	$ 15.0

R&D support expenses, excluding non-cash compensation expense related to equity awards, for the three months ended March 31, 2022 increased compared to the same period in 2021. The increase was primarily related to increased personnel and occupancy costs to support advancing our pipeline and our technology.

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,	
	2022	2021
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 27.1	$ 45.3
Restructuring expenses	—	4.1
Total selling, general and administrative expenses, excluding non-cash compensation related to equity awards	27.1	49.4
Non-cash compensation expense related to equity awards	7.0	11.8
Total selling, general and administrative expenses	$ 34.1	$ 61.2

SG&A expenses, excluding non-cash compensation expense related to equity awards, decreased in the three months ended March 31, 2022 compared to the same period in 2021 due to operating efficiencies achieved from the Akcea Merger and the restructuring of our commercial operations, partially offset by increased pre-commercialization expenses resulting from our go-to-market preparations for our near-term commercial opportunities. Non-cash compensation expense related to equity awards decreased in 2022 compared to 2021 due to reduced headcount as a result of the Akcea Merger and our restructured commercial operations.

Investment Income

Investment income for the three months ended March 31, 2022 was $2.0 million compared to $4.6 million for the same period in 2021. Our investment income decreased because we earned a lower average return on our investments due to market conditions during the three months ended March 31, 2022 compared to the same period in 2021.

Interest Expense

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

	Three Months Ended March 31,	
	2022	2021
Convertible notes:		
Non-cash amortization of debt issuance costs	$ 1.3	$ 0.9
Interest expense payable in cash	0.2	0.9
Interest on mortgage for primary R&D and manufacturing facilities	0.6	0.6
Total interest expense	$ 2.1	$ 2.4

Income Tax Expense

Beginning in 2022, the Tax Cuts and Jobs Act of 2017, or TCJA, requires taxpayers to amortize research and development expenditures over five years pursuant to IRC Section 174. Although the U.S. Congress is considering legislation that would defer the amortization requirement to later years, we have no assurance that the provision will be repealed or otherwise modified. As a result, we recorded a $1.1 million income tax expense for the three months ended March 31, 2022, compared to $0.1 million for the same period in 2021.

Net Loss and Net Loss per Share

We had a net loss of $65.2 million for the three months ended March 31, 2022 compared to net loss of $89.9 million for the same period in 2021, which reflects the fluctuations discussed above. Our basic and diluted net loss per share for the three months ended March 31, 2022 and 2021 were $0.46 and $0.64, respectively.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and TEGSEDI and WAYLIVRA commercial revenue. From our inception through March 31, 2022, we have earned approximately $6.0 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through March 31, 2022, we have raised net proceeds of approximately $2.0 billion from the sale of our equity securities. Additionally, from our inception through March 31, 2022, we have borrowed approximately $2.1 billion under long-term debt arrangements to finance a portion of our operations.

Our cash, cash equivalents and short-term investments, debt obligations and working capital did not change significantly from December 31, 2021 to March 31, 2022.

The following table summarizes our contractual obligations as of March 31, 2022. 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 (selected balances described below)	Payments Due by Period (in millions) Total	Less than 1 year	More than 1 year
0 % Notes (principal payable)	$ 632.5	$ —	$ 632.5
0.125% Notes (principal and interest payable)	550.9	0.7	550.2
Building mortgage payments (principal and interest payable)	72.8	3.0	69.8
Operating leases	26.6	4.3	22.3
Other obligations (principal and interest payable)	0.8	0.1	0.7
Total	$ 1,283.6	$ 8.1	$ 1,275.5

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility mortgages, facility leases, equipment financing arrangements and other obligations. Due to the uncertainty with respect to the timing of future cash flows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded our gross unrecognized tax benefits from our contractual obligations table above. 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 7, *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, 2022 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, 2022. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2022.

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 August 5, 2021, four purported former stockholders of Akcea filed an action in the Delaware Court of Chancery captioned John Makris, et al. v. Ionis Pharmaceuticals, Inc., et al., C.A. No. 2021-0681, or the "Delaware Action." The plaintiffs in the Delaware Action assert claims against (i) former members of Akcea's board of directors; and (ii) Ionis, or collectively, the "Defendants." The plaintiffs assert putatively direct claims on behalf of a purported class of former Akcea stockholders. The plaintiffs in the Delaware Action assert that the Defendants breached their fiduciary duties in connection with the October 2020 take-private transaction that we and Akcea entered into, in which Akcea became a wholly-owned subsidiary of Ionis. We believe that the claims asserted in the Delaware Action are without merit and we filed a motion to dismiss the claims in November 2021. Briefing and argument on the motion to dismiss is complete and we are awaiting the court's ruling on the motion.

On January 19, 2022, a purported stockholder of Ionis filed a stockholder derivative complaint in the Delaware Court of Chancery captioned Leo Shumacher, et al. v. Joseph Loscalzo, et al., C.A. No. 2022-0059, or the "Action." The complaint names as defendants the current members of Ionis' board of directors, collectively the "Directors". The company is a nominal defendant. Plaintiff asserts a breach of fiduciary duty claim against the Directors for awarding and receiving allegedly excessive compensation. Plaintiff also asserts an unjust enrichment claim against the non-employee Directors as a result of the compensation they received. The complaint seeks, among other things, damages, restitution, attorneys' fees and costs, and such other relief as deemed just and proper by the court. The defendants have indicated they intend to file a motion to dismiss the claim, however no briefing schedule has been set.

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, 2021.

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, 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, in March 2020, we implemented work-from-home policies for most of our employees globally and generally suspended business-related travel. In the U.S., as vaccinations have become more widely available, states have lifted restrictions implemented as part of the pandemic response and reopened their economies. In June 2021, the Governor of California terminated the vast majority of executive actions that were put in place beginning in March 2020, leaving only a subset of provisions that facilitate the ongoing recovery. In May 2021, the Commonwealth of Massachusetts also lifted most of its pandemic restrictions. We continue to modify our policies for our employees in California, Massachusetts, and internationally to align with current local guidance. We believe the effects of these work-from-home and travel policies have had a limited impact on our business.

These public health directives and orders have 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 it is monitoring the demand for SPINRAZA, including the duration and degree to which it might see delays in starting new patients on SPINRAZA due to hospitals diverting resources necessary to administer SPINRAZA to care for COVID-19 patients. 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. Recently there have been major disruptions to the global supply chain due to the COVID-19 Pandemic. To date, we have not experienced any significant consequences to our business as a result of the current supply chain disruptions, but could in the future if such disruptions persist or worsen.

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:

- delays in clinical site initiation, site monitoring 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 eplontersen 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;
- delays in site initiations due to principle investigators and site staff focusing on and prioritizing COVID-19 patient care; and
- 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.

In addition, some of our partners have experienced impacts to their clinical trial operations as a result of the COVID-19 Pandemic. For example, in December 2021, Novartis announced that enrollment for the Phase 3 HORIZON study had been delayed due to the COVID-19 Pandemic.

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 will have to invest significant resources to develop these capabilities. If we are unable to establish effective marketing, sales, market access, distribution, and related functions, or enter into agreements with third parties to commercialize our medicines, we may not be able to generate revenue from our medicines.

We have limited experience as a company in commercializing medicines and we will have to invest significant financial and management resources to develop the infrastructure required to successfully commercialize our medicines. 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. We will also need to scale-up existing internal support functions to aid our commercialization efforts, in particular, regulatory affairs and medical affairs. Any failure to effectively build or maintain the infrastructure required to successfully commercialize our medicines, including our sales, marketing, market access, distribution, and related capabilities, or scale-up our existing support functions, could adversely impact the revenue we generate from our medicines. In addition, if we choose to rely on third parties to assist us in commercializing our medicines, we may not be able to enter into collaborations or hire consultants or external service providers on acceptable financial terms, or at all. If we do engage third parties to assist us in the commercialization of our medicines, our product revenues and profitability may be lower than if we commercialized such medicines ourselves.

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, 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. If the pricing of any of our medicines decreases for any reason, it will reduce our revenue for such medicine. For example, Biogen has disclosed that SPINRAZA revenue has decreased in part due to lower pricing in the U.S. and certain rest of world markets.

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, TEGSEDI requires periodic blood and urine monitoring, is available in the U.S. only through a REMS program, and the product label in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. 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 nor is it available only through a REMS program. Additionally, the product label for WAYLIVRA in the EU requires regular blood monitoring. In each case, these label requirements have negatively affected our ability to attract and retain patients for these medicines. 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 generate 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 and could compete with eplontersen;
- Vutrisiran and acoramidis could compete with TEGSEDI and eplontersen;
- ARO-APOC3, lomitapide, evinacumab, BIO89-100, and gemcabene could compete with WAYLIVRA and olezarsen;
- AMG890 could compete with pelacarsen;
- Arimoclomol, ultomiris, mastinib and trehalose could compete with tofersen; and
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, KVD824, and NTLA-2002 could compete with donidalorsen.

SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries. Specifically, SPINRAZA faces competition from onasemnogene abeparvovec, a 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, an oral product for the treatment of SMA that was approved in the U.S. in August 2020 and in the EU in March 2021. Biogen has disclosed that SPINRAZA revenue has decreased primarily due to a reduction in demand as a result of increased competition and that future sales of SPINRAZA may be adversely affected by competing products.

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.

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 uses 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, generate additional clinical data 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 depend on our collaboration with AstraZeneca for the joint development and commercialization of eplontersen.

We have entered into a collaborative arrangement with AstraZeneca to develop and commercialize eplontersen. Under the terms of the collaboration agreement, Ionis and AstraZeneca will co-develop and co-commercialize eplontersen in the U.S. and AstraZeneca will have the sole right to commercialize eplontersen in all other countries, except for certain Latin American countries. Prior to co-commercializing eplontersen in the U.S., we will need to negotiate a co-commercialization agreement with AstraZeneca to govern the parties' performance of co-commercialization, which agreement will include a commercial plan and budget. As a company we do not have experience with co-commercialization arrangements. We also do not have control over the amount and timing of resources that AstraZeneca devotes to our collaboration, particularly outside of the U.S. If the co-commercialization arrangement for eplontersen is not successful for any reason, eplontersen may not meet our commercial objectives and our revenues for eplontersen may be limited.

In addition, a Joint Steering Committee, or JSC, having equal membership from us and AstraZeneca, and various subcommittees oversee and coordinate the development, manufacturing, commercialization and other exploitation activities for eplontersen in the U.S. by mutual agreement. If any subcommittee cannot reach unanimous agreement on any matter within its respective scope of authority, such matter may be referred to the JSC for resolution. If the JSC cannot come to a mutual agreement on any particular matter, this could delay our ability to develop or commercialize eplontersen.

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, which are subject to change at any time. For example, in November 2020, the U.S. Department of Health and Human Services issued a final rule modifying the anti-kickback law safe harbors for Medicare Part D plans, pharmacies, and pharmaceutical benefit managers. Efforts to ensure that our operations comply with current 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. Even if favorable coverage status and adequate reimbursement rates are attained, less favorable coverage policies and reimbursement rates may be implemented in the future. Accordingly, SPINRAZA, TEGSEDI and WAYLIVRA, 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 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 have been 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. It is unclear how future litigation and healthcare reform measures will impact the Affordable Care Act and our business.

Further, we believe that future coverage, reimbursement and pricing will likely be subject to increased restrictions both in the U.S. and in international markets. 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, legislation and executive orders designed to, among other things, reduce drug prices (e.g., by supporting drug price negotiation in Medicare Parts B and D, with those negotiated prices also available to commercial plans, and progressing legislation to slow price increases over time on existing drugs), increase competition (e.g., by supporting legislation to speed the entry of biosimilar and generic drugs, including shortening the period of exclusivity, policies in Medicare Part B to increase the prescribing of biosimilars by physicians, and a prohibition on "pay-for-delay" agreements and anti-competitive practices by drug manufacturers), lower out-of-pocket drug costs for patients (e.g., by capping Medicare Part D beneficiary out-of-pocket pharmacy expenses), and foster scientific innovation to promote better health care and improved health (e.g., by investing in public and private research and incentivizing the market to promote discovery of valuable and accessible new treatments). 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 or the ongoing war between Russia and Ukraine, could limit the commercial success of our medicines. In addition, as our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. For example, we have plans to expand our manufacturing infrastructure to support our wholly owned pipeline. If we are not successful in executing this expansion, it could limit our ability to meet our manufacturing requirements and commercial objectives in the future.

Additionally, 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 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.

We may not be able to benefit from orphan drug designation for our medicines.

In the U.S., under the Orphan Drug Act, the FDA may designate a medicine as an orphan drug if it is intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the U.S. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods. The FDA has granted orphan drug designation to eplontersen for the treatment of patients with transthyretin-mediated amyloidosis. The FDA and EMA have granted orphan drug designation to TEGSEDI for the treatment of patients with ATTRv-PN, to WAYLIVRA for the treatment of patients with FCS, and to tominersen for the treatment of patients with HD. In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. Even if approval is obtained on a medicine that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA or EMA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable medicine to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same medicine in a safer or more effective form or that makes a major contribution to patient care. If we lose orphan drug exclusivity on any of our medicines, we may face increased competition and lose market share for such medicine.

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.

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. If any of our medicines in Phase 3 clinical studies, including the studies of eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen, 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.

In the past, we have invested in clinical studies of medicines that have not met the primary clinical endpoints in their Phase 3 studies or have been discontinued for other reasons. For example, in October 2021, Biogen reported that tofersen did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring tofersen were seen across multiple secondary and exploratory measures of disease activity and clinical function. In addition, 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 eplontersen, olezarsen, donidalorsen, ION363 and pelacarsen.

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 or 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 ongoing post-marketing studies for WAYLIVRA and TEGSEDI and an 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 ATTRv-PN, respectively, or the commercial opportunity for WAYLIVRA or TEGSEDI.

Any failure or delay in our clinical studies, including the studies of tofersen, pelacarsen, eplontersen, olezarsen, donidalorsen, 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 Icon Clinical Research Limited, Syneos Health, Inc., Thermo Fisher Scientific Inc. and Medpace for the clinical studies for our medicines, including eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen. 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. For example, some of our key vendors are experiencing labor shortages, which could impact their ability to perform services for us for certain of our clinical trials. 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.

In addition, while we do not have any clinical trial sites in Ukraine, we do have a limited number of clinical trial sites in Russia and surrounding countries that may be impacted by the ongoing war between Russia and Ukraine, and could result in difficulties enrolling or completing our clinical trials in such areas on schedule. Furthermore, the U.S. and its European allies have imposed significant new sanctions against Russia, including regional embargoes, full blocking sanctions, and other restrictions targeting major Russian financial institutions. The U.S. government has also indicated it will consider imposing additional sanctions and other similar measures in the near future. Our ability to conduct clinical trials in Russia may become restricted under applicable sanctions laws, which would require us to identify alternative trial sites, and could increase our costs and delay the clinical development of certain of our medicines.

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:

- AstraZeneca for the joint development and funding of eplontersen;
- Novartis for development and funding of pelacarsen;
- Biogen for development and funding of tofersen; and
- Roche for development and funding of tominersen.

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, after a review of data from the global Phase 2b study of vupanorsen, Pfizer decided to discontinue the clinical development program for vupanorsen.

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

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

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

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

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, eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen, the price of our securities could decrease.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

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, 2022, 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, 2022, we had cash, cash equivalents and short-term investments equal to $2.1 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 eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- our manufacturing requirements and capacity to fulfill such requirements.

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, even 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 personnel

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, and Dr. Monia, who was our Chief Operating Officer and a member of our team since our founding over 30 years ago, began serving as our Chief Executive Officer. Following the 2021 Annual Meeting of Stockholders, Dr. Crooke stepped down from the Board and now serves as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. In June 2021, Dr. Loscalzo, a member of our Board since February 2014, was appointed Chairman of the Board. 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.

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 the Code, 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 current U.S. federal income tax law, U.S. federal NOLs generated in taxable years beginning after December 31, 2017 may be carried forward indefinitely, but the deductibility of such U.S. federal NOLs in taxable years beginning after December 31, 2020 is limited to 80 percent of taxable income. It is uncertain if and to what extent various states will conform to current U.S. federal income tax law, and there may be periods during which states suspend or otherwise limit the use of NOLs for state income tax purposes.

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 percentage-point cumulative change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL 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 NOL 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 Merger, we are subject to the separate return limitation year, or SRLY, rules. Under the SRLY rules, our utilization of Akcea's pre-merger NOL and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-merger 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 foreign income taxes, sales taxes in the U.S., 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 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, 2022, the market price of our common stock ranged from $47.87 to $25.04 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.

Broad market factors may materially harm the market price of our common stock irrespective of our operating performance. For example, 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. The global credit and financial markets may also be adversely affected by the ongoing war between Russia and Ukraine and measures taken in response thereto. In addition, industry factors may materially harm the market price of our common stock. NASDAQ, and the market for biotechnology companies in particular, have historically 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 that 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 and used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million of our 1% Notes for $257.0 million. 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 17.5 million shares of our common stock upon conversion of our 0% Notes and 0.125% 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 during the COVID-19 Pandemic. In addition, the number and frequency of cybersecurity events globally may be heightened during times of geopolitical tension or instability between countries, including, for example, the ongoing war between Russia and Ukraine, as a result of which several companies (not including Ionis) have reported recent cybersecurity events.

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.

Our business may be adversely affected by climate change, extreme weather events, earthquakes, pandemics, war, civil or political unrest, terrorism or other catastrophic events.

In recent years, extreme weather events and changing weather patterns have become more common. As a result, we are potentially exposed to varying natural disaster or extreme weather risks such as hurricanes, tornadoes, fires, droughts, floods, or other events that may result from the impact of climate change on the environment. The potential impacts of climate change may also include increased operating costs associated with additional regulatory requirements and investments in reducing energy, water use and greenhouse gas emissions. In addition, 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 disasters or other events outside our control, such as earthquakes, pandemics, war, civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, 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 control systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

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

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have recently experienced substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government in response to the COVID-19 Pandemic. In addition, the global credit and financial markets may be adversely affected by the ongoing war between Russia and Ukraine and measures taken in response thereto. 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. In addition, due to the rapidly rising inflation rate, we may experience increased costs of goods and services for our business.

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 signed 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
10.1	Amended and Restated Ionis Pharmaceuticals, Inc. Severance Benefit Plan.
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, 2022, 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 4, 2022
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 4, 2022

Exhibit 10.1

AMENDED AND RESTATED

IONIS PHARMACEUTICALS, INC.

SEVERANCE BENEFIT PLAN

1. INTRODUCTION. This Amended and Restated Ionis Pharmaceuticals, Inc. Severance Benefit Plan (the "***Plan***") is adopted by Ionis Pharmaceuticals, Inc. (the "***Company***") on March 17, 2022 (the "***Effective Date***") and amends and restates the Severance Benefit Plan established by the Company on October 18, 2018. The Plan provides for severance benefits to selected employees of the Company. This document constitutes the Summary Plan Description for the Plan.

2. DEFINITIONS. For purposes of the Plan, the following terms are defined as follows:

(a) "***Affiliate***" shall have the meaning given to such term in the Equity Plan.

(b) "***Board***" means the Board of Directors of the Company.

(c) "***Cause***" means the occurrence of any one or more of the following: (i) any material breach of any written agreement between the Participant and the Company, if such breach causes material harm to the Company or reasonably threatens to cause such harm; (ii) any material failure to comply with the Company's written policies or rules, as they may be in effect from time to time during the Participant's employment or any statutory duty to the Company, if such failure causes material harm to the Company or reasonably threatens to cause such harm, and to the extent it is curable by the Participant, is not cured within 30 days after written notice thereof is given to the Participant by the Company; (iii) commission, conviction of, or a plea of "guilty" or "no contest" to, a felony under the laws of the United States or any State; or (iv) any willful, intentional or grossly negligent act having the effect of materially injuring (whether financially or otherwise) the business or reputation of the Company, which to the extent it is curable by the Participant, is not cured within 30 days after written notice thereof is given to the Participant by the Company.

(d) "***Change in Control***" or "***CiC***" for purposes of this Plan shall mean the sale of all or substantially all the assets of the Company; any merger, consolidation or acquisition of the Company with, by or into another corporation, entity or person; or any change in the ownership of more than 50% of the voting capital stock of the Company in one or more related transactions, *provided*, none of the following events will be a Change in Control: (1) acquisitions of capital stock directly from the Company for cash, whether in a public or private offering, (2) distributions of capital stock by the Company's stockholders, (3) acquisitions of capital stock by or from any employee benefit plan or related trust, or (4) a merger for which the sole purpose is to change the Company's name and/or state of incorporation.

(e) "***Change in Control Protection Period***" means the period commencing three months prior to, and ending 12 months following, the effective date of a Change in Control.

(f) "***Change in Control Termination***" means a Participant's Qualifying Termination that occurs during the Change in Control Protection Period.

(g) "***CiC Severance Period***" means the number of months of severance payable under this Plan to the Participant with respect to the applicable Change in Control Termination, as indicated in the Participant's Participation Notice, which will be (i) 24 months for the Chief Executive Officer, (ii) 18 months for Executive Vice Presidents, (iii) 12 months for Senior Vice Presidents, and (iv) 9 months for Vice Presidents.

(h) "***Code***" means the Internal Revenue Code of 1986, as amended.

(i) "***Common Stock***" means the common stock of the Company.

(j) "***Continuous Service***" shall have the meaning given to such term in the Equity Plan.

(k) "***Disability***" shall have the meaning given to such term in the Equity Plan.

(l) ***"Employment Agreement"*** means any individual employment offer letter, contract or agreement that a Participant has with the Company.

(m) "***Equity Award***" means each compensatory equity award granted to a Participant, whether under the Equity Plan, or otherwise.

(n) "***Equity Plan***" means the Company's 2011 Equity Incentive Plan or the Company's 2020 Equity Incentive Plan, as applicable, in each case as amended from time to time.

(o) "***ERISA***" means the Employee Retirement Income Security Act of 1974, as amended.

(p) "***Good Reason***" means the occurrence of any of the following events without the Participant's consent: (i) a material reduction by the Company of the Participant's base salary as in effect immediately prior to the reduction; (ii) a material reduction by the Company of the Participant's annual bonus target as in effect immediately prior to the reduction, provided a compensation plan change that affects similarly all employees at similar levels will not constitute Good Reason; (iii) a material reduction in the Participant's authority, duties or responsibilities, provided a change in job title or reporting relationship without a reduction in the Participant's base salary or annual bonus target will not constitute Good Reason; or (iv) relocation of the offices at which the Participant is required to work to a location that is outside San Diego county or would increase the Participant's one-way commute by more than 40 miles; *provided*, that any resignation by the Participant due to any of the above conditions will only be deemed for Good Reason if: (1) the Participant gives the Company written notice of the intent to terminate for Good Reason within 90 days following the first occurrence of the condition(s) that the Participant believes constitutes Good Reason, which notice will describe such condition(s); (2) the Company fails to remedy, if remediable, such condition(s) within 30 days following receipt of the Participant's written notice (the "***Cure Period***") of such condition(s) from the Participant; and (3) the Participant actually resigns his or her employment within the first 15 days after expiration of the Cure Period.

(q) "***Individual Severance Arrangement***" means any Employment Agreement providing for severance or change in control benefits to a Participant or any other severance arrangement between the Participant and the Company other than the Plan, in each case that remains in effect through the date of a Qualifying Termination.

(r) "***Non-CiC Severance Period***" means the number of months of severance payable under this Plan to the Participant with respect to the applicable Non-CiC Termination, as indicated in the Participant's Participation Notice, which will be (i) 18 months for the Chief Executive Officer, (ii) 12 months for Executive Vice Presidents, (iii) 9 months for Senior Vice Presidents, and (iv) 6 months for Vice Presidents.

(s) "***Non-CiC Termination***" means a Participant's Qualifying Termination that does not occur during the Change in Control Protection Period.

(t) "***Participant***" means each individual who is employed by the Company, has been designated as a Participant by the Plan Administrator, and has received and returned a signed Participation Notice.

(u) "***Participation Notice***" means the latest notice delivered by the Company to a Participant informing the Participant that he or she is eligible to participate in the Plan, substantially in the form attached hereto as **Exhibit A**.

(v) "***Plan Administrator***" means the Board or any committee of the Board duly authorized to administer the Plan, including the Compensation Committee of the Board, or any member of senior management of the Company designated by the Board (including, for example, the head of Human Resources). The Board may at any time administer the Plan, in whole or in part, notwithstanding that the Board has previously appointed a committee or other person to act as the Plan Administrator. Notwithstanding the foregoing, upon and after the consummation of a Change in Control, the Plan Administrator shall mean the Representative.

(w) ***"Person"*** means a "person" as such term is used in Sections 13(d) and 14(d) of the United States Securities Exchange Act of 1934, as amended

(x) "***Pro-rated Target Bonus***" means with respect to a Participant, the portion of the Participant's target annual bonus under the Company's annual cash bonus plan or policy then in effect (and without giving effect to any reduction in target bonus that would give rise to the Participant's right to resign for Good Reason) pro-rated based on the number of days from the beginning of the calendar year through the date of the Participant's Non-CiC Termination.

(y) "***Qualifying Termination***" means a termination of the Participant's Continuous Service either (i) by the Company without Cause or (ii) by the Participant with Good Reason. Termination of Continuous Service due to the Participant's death or Disability will not constitute a Qualifying Termination. Transferring from the Company to an Affiliate where such transfer does not constitute Good Reason will not constitute a Qualifying Termination. For clarity, if the Participant terminates his or her employment without Good Reason, and the Company unilaterally accelerates the Participant's date of termination in connection therewith, such acceleration will not result in a termination by the Company without Cause or a Qualifying Termination hereunder. Further, if the Participant is offered an identical or substantially equivalent or comparable position with the Company or an Affiliate, such Participant will not be deemed to have been terminated without Cause. For purposes of the foregoing, a "substantially equivalent or comparable position" is one that provides the Participant substantially the same level of responsibility and compensation.

(z) "***Release Effective Date***" means the date, which must occur during the Release Period, on which the Release becomes effective and is no longer revocable by the Participant.

(aa) "***Release***" has the meaning set forth in Section 6.

(bb) "***Release Period***" means the sixty-day period following a Participant's Qualifying Termination during which the Release must be executed (and not revoked) by the Participant.

(cc) "***Representative***" means one or more members of the Board or other persons designated by the Board (including a member of senior management such as the head of Human Resources) prior to or in connection with a Change in Control to administer the Plan.

(dd) "***Separation from Service***" means a "separation from service" within the meaning of Treasury Regulations Section 1.409A-1(h), without regard to any alternative definition thereunder.

(ee) "***Target Bonus***" means with respect to a Participant, 100% of the Participant's target annual bonus under the Company's annual cash bonus plan or policy then in effect (and without giving effect to any reduction in target bonus that would give rise to the Participant's right to resign for Good Reason or which is implemented following a Change in Control); *provided that*, if the Company does not maintain such a plan or policy, then the last target bonus prior to the Change in Control.

3. Eligibility for Benefits. Subject to the terms and conditions of the Plan, the Company will provide the benefits described in Section 5 to the affected Participant. A Participant will not receive benefits under the Plan (or will receive reduced benefits under the Plan) in the following circumstances, as determined by the Plan Administrator, in its sole discretion:

(a) The Participant's employment is terminated by either the Company or the Participant for any reason other than a Qualifying Termination;

(b) The Participant is rehired by the Company or an Affiliate and recommences employment prior to the date benefits under the Plan are scheduled to commence.

(c) The Participant has not entered into the Company's standard form of Employee Invention Assignment and Confidentiality Agreement or any similar or successor document (the "***Confidentiality Agreement***");

(d) The Participant has failed to execute and allow to become effective the Release within the Release Period; and

(e) The Participant has failed to return all Company Property. For this purpose, "***Company Property***" means all paper and electronic Company documents (and all copies thereof) created and/or received by the Participant during his or her period of employment with the Company and other Company materials and property that the Participant has in his or her possession or control, including, without limitation, Company files, notes, drawings, records, plans, forecasts, reports, studies, analyses, proposals, agreements, financial information, research and development information, sales and marketing information, operational and personnel information, specifications, code, software, databases, computer-recorded information, tangible property and equipment (including, without limitation, leased vehicles, computers, computer equipment, software programs, facsimile machines, mobile telephones, servers), credit and calling cards, entry cards, identification badges and keys, and any materials of any kind that contain or embody any proprietary or confidential information of the Company (and all reproductions thereof, in whole or in part). As a condition to receiving benefits under the Plan, a Participant must not make or retain copies, reproductions or summaries of any such Company Property. However, a Participant is not required to return his or her personal copies of documents evidencing the Participant's hire, termination, compensation, benefits and stock options and any other documentation received as a stockholder of the Company.

4. No Duplicative Benefits Provided Under Plan. This Plan does not supersede the terms of any Individual Severance Arrangement or Equity Award in effect as of the Effective Date. Unless otherwise determined by the Plan Administrator in its sole discretion, if a Participant is otherwise eligible to receive severance benefits under this Plan that are of the same category and would otherwise duplicate the benefits available under the terms of any Individual Severance Arrangement ("***Duplicative Benefits***"), such Participant will receive severance benefits under the Individual Severance Arrangement in lieu of any Plan benefits to the extent such benefits are Duplicative Benefits, and severance benefits will be provided under the Plan only to the extent, if any, that Plan benefits are not Duplicative Benefits.

5. Payments & Benefits Upon a Qualifying Termination. Except as may otherwise be provided in the Participant's Participation Notice, in the event of a Qualifying Termination, the Company will provide the payments and benefits described in this Section 5, subject to the terms and conditions of the Plan.

(a) Payment of Accrued Obligations. The Company shall pay to each eligible Participant who incurs a Qualifying Termination a lump sum payment in cash, paid in accordance with applicable law, equal to the sum of (i) the Participant's accrued but unpaid base salary and any accrued but unpaid vacation pay through the date of the Qualifying Termination, and (ii) any earned but unpaid annual bonus for any fiscal year preceding the fiscal year in which the termination occurs.

(b) Non-CiC Termination.

(i) Cash Severance. Subject to the execution (and non-revocation) of the Release, upon a Non-CiC Termination, the Participant will receive as severance an amount equal to the Participant's Non-CiC Severance Base Pay (as defined below), and for the Chief Executive Officer only, the Pro-rated Target Bonus. Such amounts will be payable in accordance with Section 5(b)(i)(2) below.

(1) ***Non-CiC Severance Base Pay***. For this purpose, "***Non-CiC Severance Base Pay***" means an amount equal to the product of (A) the Participant's annual base salary or annualized wages (excluding incentive pay, premium pay, commissions, overtime, bonuses and other forms of variable compensation) as in effect on the date of the Qualifying Termination and (B) a fraction, the numerator of which is the number of months represented by the Non-CiC Severance Period and the denominator of which is twelve (12).

(2) ***Payment Schedule***. The Company will pay the Non-CiC Severance Base Pay and, for the Chief Executive Officer only, the Pro-rated Target Bonus in a lump sum on the first payroll date that occurs more than five (5) days after the Release Effective Date. Notwithstanding the foregoing, to the extent required to comply with Section 409A (as defined below), if the Release Period spans two calendar years such that the Release Effective Date could occur in either of such calendar years, the Non-CiC Severance Base Pay and, if applicable, the Pro-rated Target Bonus to be paid to the Participant will be made in the second calendar year.

(ii) COBRA Payments; Special Severance Payments.

(1) ***COBRA Payment Period***. If the Participant is eligible for and has made the necessary elections for continuation coverage pursuant to COBRA under a group health, dental or vision plan sponsored by the Company, the Company will pay, as and when due directly to the COBRA carrier, the premiums sufficient to continue the Participant's COBRA coverage for the Participant and the Participant's eligible dependents from the date of the Non-CIC Termination until the earliest to occur of (i) the end of the Non-CiC Severance Period, (ii) the expiration of the Participant's eligibility for the continuation coverage under COBRA, and (iii) the date on which the Participant becomes eligible for health insurance coverage in connection with new employment or self-employment (such period, the "***Non-CiC COBRA Payment Period***"). The Participant agrees to promptly notify the Company as soon as the Participant becomes eligible for health insurance coverage in connection with new employment or self-employment.

(2) ***Special Severance Payment***. Notwithstanding Section 5(b)(ii)(1) above, if at any time the Company determines, in its sole discretion, that the payment of the COBRA premiums would result in a violation of the nondiscrimination rules of Section 105(h)(2) of the Code or any statute or regulation of similar effect (including, without limitation, the 2010 Patient Protection and Affordable Care Act, as amended by the 2010 Health Care and Education Reconciliation Act and any other subsequent amendments), then in lieu of providing the benefit set forth in Section 5(b)(ii)(1) above, the Company will instead pay the Participant, on the first day of each month of the remainder of the Non-CiC COBRA Payment Period, a fully taxable cash payment equal to the COBRA premiums for that month, subject to applicable tax withholdings and deductions (such amount, the "***Non-CiC Special Severance Payment***").

(3) ***Payment Schedule.*** The Company will make the first payment under this Section 5(b)(ii) (and, in the case of the Non-CiC Special Severance Payment, such payment will be made to the Participant, in a lump sum) within five (5) business days after the Release Effective Date. Notwithstanding the foregoing, to the extent required to comply with Section 409A (as defined below), if the Release Period spans two calendar years such that the Release Effective Date could occur in either of such calendar years, the first payment to be made under this Section 5(b)(ii) will be made in the second calendar year (and, if applicable, will include any amounts that the Company otherwise would have paid through such date), with the balance of the payments (if applicable) paid thereafter on the original schedule.

(iii) Accelerated Vesting. Subject to the Participant's execution (and non-revocation) of the Release, upon a Non-CiC Termination, the vesting and exercisability (if applicable) of all outstanding unvested time-based equity awards granted under the Company's equity incentive plans that are held by a Participant on the date of the Non-CiC Termination that otherwise would have vested with the passage of time over the entirety of the Non-CiC Severance Period had the Participant remained in Continuous Service with the Company will be accelerated.

(c) Change in Control Termination.

(i) Cash Severance. Subject to the execution (and non-revocation) of the Release, upon a Change in Control Termination, the Participant will receive as severance an amount equal to the Participant's CiC Severance Base Pay and Target Bonus Multiple (both as defined below). Such amount will be payable in accordance with Section 5(c)(i)(3) below.

(1) ***CiC Severance Base Pay***. For this purpose, "***CiC Severance Base Pay***" means an amount equal to the product of (A) the Participant's annual base salary or annualized wages (excluding incentive pay, premium pay, commissions, overtime, bonuses and other forms of variable compensation) as in effect on the date of the Change in Control and (B) a fraction, the numerator of which is the number of months represented by the CiC Severance Period and the denominator of which is twelve (12).

(2) ***Target Bonus Multiple***. For this purpose, "***Target Bonus Multiple***" means an amount equal to the product of (A) the Participant's Target Bonus as in effect on the date of the Change in Control and (B) a fraction, the numerator of which is the number of months represented by the CiC Severance Period and the denominator of which is twelve (12).

(3) ***Payment Schedule***. The Company will pay the CiC Severance Base Pay and Target Bonus Multiple in a lump sum on the first payroll date that occurs more than five (5) days after the Release Effective Date. Notwithstanding the foregoing, to the extent required to comply with Section 409A (as defined below), if the Release Period spans two calendar years such that the Release Effective Date could occur in either of such calendar years, the CiC Severance Base Pay and Target Bonus Multiple to be paid to the Participant will be made in the second calendar year.

(ii) COBRA Payments; Special Severance Payments.

(1) ***COBRA Payment Period***. If the Participant is eligible for and has made the necessary elections for continuation coverage pursuant to COBRA under a group health, dental or vision plan sponsored by the Company, the Company will pay, as and when due directly to the COBRA carrier, the premiums sufficient to continue the Participant's COBRA coverage for the Participant and the Participant's eligible dependents from the date of the Change in Control Termination until the earliest to occur of (A) the end of the CiC Severance Period, (B) the expiration of the Participant's eligibility for the continuation coverage under COBRA, and (C) the date on which the Participant becomes eligible for health insurance coverage in connection with new employment or self-employment (such period, the "***CiC COBRA Payment Period***"). The Participant agrees to promptly notify the Company as soon as the Participant becomes eligible for health insurance coverage in connection with new employment or self-employment.

(2) ***Special Severance Payment***. Notwithstanding Section 5(c)(ii)(1) above, if at any time the Company determines, in its sole discretion, that the payment of the COBRA premiums would result in a violation of the nondiscrimination rules of Section 105(h)(2) of the Code or any statute or regulation of similar effect (including, without limitation, the 2010 Patient Protection and Affordable Care Act, as amended by the 2010 Health Care and Education Reconciliation Act and any other subsequent amendments), then in lieu of providing the benefit set forth in Section 5(c)(ii)(1) above, the Company will instead pay the Participant, on the first day of each month of the remainder of the CiC COBRA Payment Period, a fully taxable cash payment equal to the COBRA premiums for that month, subject to applicable tax withholdings and deductions (such amount, the "***CiC Special Severance Payment***").

(3) ***Payment Schedule.*** The Company will make the first payment under this Section 5(c)(ii) (and, in the case of the CiC Special Severance Payment, such payment will be made to the Participant, in a lump sum) within five (5) business days after the Release Effective Date. Notwithstanding the foregoing, to the extent required to comply with Section 409A (as defined below), in the event that the Release Period spans two calendar years such that the Release Effective Date could occur in either of such calendar years, the first payment to be made under this Section 5(c)(ii) will be made in the second calendar year (and, if applicable, will include any amounts that the Company otherwise would have paid through such date), with the balance of the payments (if applicable) paid thereafter on the original schedule.

(iii) **Accelerated Vesting.** Subject to the Participant's execution (and non-revocation) of the Release, upon a Change in Control Termination, the vesting and exercisability (if applicable) of all outstanding unvested time-based equity awards granted under the Company's equity incentive plans that are held by a Participant on the date of the Change in Control Termination will be accelerated in full. Notwithstanding the foregoing, if, in connection with a Change in Control, an equity award will terminate and will not be so assumed or continued by the successor or acquiror entity in such Change in Control or substituted for a similar award of the successor or acquiror entity, then, the Participant will become vested, with respect to 100 percent of any then unvested portion of any applicable equity award, effective immediately prior to, but subject to the consummation of such Change in Control.

6. **Conditions and Limitations on Benefits.**

(a) **Release.** To be eligible to receive any benefits under the Plan, a Participant must sign a general waiver and release in substantially the form attached hereto as **Exhibit B**, **Exhibit C**, or **Exhibit D**, as appropriate (the "***Release***"), and such release must be executed (and not revoked) by the Participant in accordance with its terms, in each case within the Release Period. The Plan Administrator, in its sole discretion, may modify the form of the required Release to comply with applicable law, and any such Release may be incorporated into a termination agreement or other agreement with the Participant.

(b) Prior Agreements; Certain Reductions. The Plan Administrator will reduce a Participant's benefits under the Plan by any other statutory severance obligations or contractual severance benefits, obligations for pay in lieu of notice, and any other similar benefits payable to the Participant by the Company (or any successor thereto) that are due in connection with the Participant's Qualifying Termination and that are in the same form as the benefits provided under the Plan (e.g., equity award vesting credit). Without limitation, this reduction includes a reduction for any benefits required pursuant to (i) any applicable legal requirement, including, without limitation, the Worker Adjustment and Retraining Notification Act of 1988 and any similar state or local laws (collectively, the "***WARN Act***"), (ii) a written employment, severance or equity award agreement with the Company, (iii) any Company policy or practice providing for the Participant to remain on the payroll for a limited period of time after being given notice of the termination of the Participant's employment, and (iv) any required salary continuation, notice pay, statutory severance payment, or other payments either required by local law, or owed pursuant to a collective labor agreement, as a result of the termination of the Participant's employment. The benefits provided under the Plan are intended to satisfy, to the greatest extent possible, and not to provide benefits duplicative of, any and all statutory, contractual and collective agreement obligations of the Company in respect of the form of benefits provided under the Plan that may arise out of a Qualifying Termination, and the Plan Administrator will so construe and implement the terms of the Plan. Reductions may be applied on a retroactive basis, with benefits previously provided being recharacterized as benefits pursuant to the Company's statutory or other contractual obligations. The payments pursuant to the Plan are in addition to, and not in lieu of, any unpaid salary, bonuses or employee welfare benefits to which a Participant may be entitled for the period ending with the Participant's Qualifying Termination.

(c) Indebtedness of Participants. If a Participant is indebted to the Company on the effective date of his or her Qualifying Termination, the Company reserves the right to offset the payment of any benefits under the Plan by the amount of such indebtedness. Such offset will be made in accordance with all applicable laws. The Participant's execution of the Participation Notice constitutes knowing written consent to the foregoing.

(d) Parachute Payments; No-Gross Ups.

(i) Except as otherwise expressly provided in an agreement between a Participant and the Company, if any payment or benefit the Participant would receive in connection with a Change in Control from the Company or otherwise (a "***Payment***") would (A) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (B) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "***Excise Tax***"), then such Payment will be equal to the Reduced Amount. The "***Reduced Amount***" will be either (1) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax, or (2) the largest portion, up to and including the total, of the Payment, whichever amount ((1) or (2)), after taking into account all applicable federal, state, provincial, foreign, and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in the Participant's receipt, on an after-tax basis, of the greatest economic benefit notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction in the payments and/or benefits will occur in the manner that results in the greatest economic benefit to the Participant, as determined in this paragraph; *provided*, that if more than one method of reduction will result in the same economic benefit, the portions of the Payment shall be reduced pro rata.

(ii) The professional firm engaged by the Company for general tax purposes as of the day prior to the effective date of the Change in Control shall make all determinations required to be made under this Section 6(d). If the professional firm so engaged by the Company is serving as an accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized independent registered public accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such professional firm required to be made hereunder. Any good faith determinations of the professional firm made hereunder shall be final, binding and conclusive upon the Company and the Participant.

(iii) Participants are not eligible to receive any tax gross-up payments under this Plan.

7. TAX MATTERS.

(a) Application of Section 409A of the Code. It is intended that all of the payments and benefits provided under the Plan satisfy, to the greatest extent possible, the exemptions from the application of Section 409A of the Code and the regulations and other guidance thereunder and any state law of similar effect (collectively, "***Section 409A***") provided under Treasury Regulations Sections 1.409A-1(b)(4), 1.409A-1(b)(5), and 1.409A-1(b)(9), and the Plan will be construed to the greatest extent possible as consistent with those provisions. To the extent not so exempt, the Plan (and any definitions in the Plan) will be construed in a manner that complies with Section 409A, and will incorporate by reference all required definitions and payment terms. Notwithstanding anything to the contrary herein, to the extent required to comply with Section 409A, a termination of employment shall not be deemed to have occurred for purposes of any provision of the Plan providing for the payments of amounts or benefits upon or following a termination of employment unless such termination is also a "separation from service" within the meaning of Section 409A and, for purposes of any such provision of the Plan, references to a "resignation," "termination, "termination of employment" or like terms shall mean separation from service. For purposes of Section 409A (including, without limitation, for purposes of Treasury Regulations Section 1.409A-2(b)(2)(iii)), a Participant's right to receive any installment payments under the Plan will be treated as a right to receive a series of separate payments and, accordingly, each installment payment under the Plan will at all times be considered a separate and distinct payment. If the Plan Administrator determines that any of the payments upon a Separation from Service provided under the Plan (or under any other arrangement with the Participant) constitute "deferred compensation" under Section 409A and if the Participant is a "specified employee" of the Company, as such term is defined in Section 409A(a)(2)(B)(i), at the time of his or her Separation from Service, then, solely to the extent necessary to avoid the incurrence of the adverse personal tax consequences under Section 409A, the timing of the payments upon a Separation from Service will be delayed as follows: on the earlier to occur of (i) the date that is six (6) months and one (1) day after the effective date of the Participant's Separation from Service, and (ii) the date of the Participant's death (such earlier date, the "***Delayed Initial Payment Date***"), the Company will (A) pay to the Participant a lump sum amount equal to the sum of the payments upon Separation from Service that the Participant would otherwise have received through the Delayed Initial Payment Date if the commencement of the payments had not been delayed pursuant to this Section 6(a), and (B) commence paying the balance of the payments in accordance with the applicable payment schedules set forth above. No interest will be due on any amounts so deferred.

(b) Withholding. All payments and benefits under the Plan will be subject to all applicable deductions and withholdings, including, without limitation, obligations to withhold for federal, state, provincial, foreign and local income and employment taxes.

(c) Tax Advice. By becoming a Participant in the Plan, the Participant agrees to review with Participant's own tax advisors the federal, state, provincial, local, and foreign tax consequences of participation in the Plan. The Participant will rely solely on such advisors and not on any statements or representations of the Company or any of its agents. The Participant understands that the Participant (and not the Company) will be responsible for the Participant's own tax liability that may arise as a result of becoming a Participant in the Plan.

8. Reemployment. In the event of a Participant's reemployment by the Company or one of its Affiliates during the CiC Severance Period or Non-CiC Severance Period, as applicable, the Company, in its sole and absolute discretion, may require such Participant to repay to the Company all or a portion of such severance benefits as a condition of reemployment.

9. Clawback; Recovery. All payments and severance benefits provided under the Plan will be subject to recoupment in accordance with any clawback policy that the Company is required to adopt pursuant to the listing standards of any national securities exchange or association on which the Company's securities are listed or as is otherwise required by the Dodd-Frank Wall Street Reform and Consumer Protection Act or other applicable law. In addition, the Board may impose such other clawback, recovery or recoupment provisions as the Board determines necessary or appropriate, including but not limited to a reacquisition right in respect of previously acquired shares of common stock of the Company or other cash or property upon the occurrence of a termination of employment for Cause.

10. Right to Interpret Plan; Amendment and Termination.

(a) Exclusive Discretion. The Plan Administrator (or the Representative, as applicable) will have the exclusive discretion and authority to establish rules, forms, and procedures for the administration of the Plan and to construe and interpret the Plan and to decide any and all questions of fact, interpretation, definition, computation or administration arising in connection with the operation of the Plan, including, without limitation, the eligibility to participate in the Plan, the amount of benefits paid under the Plan and any adjustments that need to be made in accordance with the laws applicable to a Participant. The rules, interpretations, computations and other actions of the Plan Administrator (or the Representative, as applicable) will be binding and conclusive on all persons.

(b) Amendment or Termination. This Plan and any Participation Notice executed hereunder cannot be amended, modified or terminated with respect to a Participant except by a written agreement signed by the Participant and the Company.

11. No Implied Employment Contract. The Plan will not be deemed (i) to give any employee or other service provider any right to be retained in the employ or services of the Company, or (ii) to interfere with the right of the Company to discharge any employee or other service provider at any time, with or without Cause, which right is hereby reserved.

12. Legal Construction. The Plan will be governed by and construed under the laws of the State of California (without regard to principles of conflict of laws), except to the extent preempted by ERISA.

13. CLAIMS, INQUIRIES AND APPEALS.

(A) Applications for Benefits and Inquiries. Any application for benefits, inquiries about the Plan or inquiries about present or future rights under the Plan must be submitted to the Plan Administrator in writing by an applicant (or his or her authorized representative). The Plan Administrator is set forth in Section 15(d).

(b) Denial of Claims. If any application for benefits is denied in whole or in part, the Plan Administrator must provide the applicant with written or electronic notice of the denial of the application, and of the applicant's right to review the denial. Any electronic notice will comply with the regulations of the U.S. Department of Labor. The notice of denial will be set forth in a manner designed to be understood by the applicant and will include the following:

(1) the specific reason or reasons for the denial;

(2) references to the specific Plan provision(s) upon which the denial is based;

(3) a description of any additional information or material that the Plan Administrator needs to complete the review and an explanation of why such information or material is necessary; and

(4) an explanation of the Plan's review procedures and the time limits applicable to such procedures, including a statement of the applicant's right to bring a civil action under Section 502(a) of ERISA following a denial on review of the claim, as described in Section 13(d).

The notice of denial will be given to the applicant within ninety (90) days after the Plan Administrator receives the application, unless special circumstances require an extension of time, in which case, the Plan Administrator has up to an additional ninety (90) days for processing the application. If an extension of time for processing is required, written notice of the extension will be furnished to the applicant before the end of the initial ninety (90) day period.

The notice of extension will describe the special circumstances necessitating the additional time and the date by which the Plan Administrator is to render its decision on the application.

(c) Request for a Review. Any person (or that person's authorized representative) for whom an application for benefits is denied, in whole or in part, may appeal the denial by submitting a request for a review to the Plan Administrator within sixty (60) days after the application is denied. A request for a review will be in writing and will be addressed to:

Ionis Pharmaceuticals, Inc.
Attn: Plan Administrator of the Severance Benefit Plan
2855 Gazelle
Carlsbad, California 92010

A request for review must set forth all of the grounds on which it is based, all facts in support of the request and any other matters that the applicant feels are pertinent. The applicant (or the applicant's representative) will have the opportunity to submit (or the Plan Administrator may require the applicant to submit) written comments, documents, records, and other information relating to his or her claim. The applicant (or his or her representative) will be provided, upon request and free of charge, reasonable access to, and copies of, all documents, records and other information relevant to his or her claim. The review will take into account all comments, documents, records and other information submitted by the applicant (or his or her representative) relating to the claim, without regard to whether such information was submitted or considered in the initial benefit determination.

(d) Decision on Review. The Plan Administrator will act on each request for review within sixty (60) days after receipt of the request, unless special circumstances require an extension of time (not to exceed an additional sixty (60) days), for processing the request for a review. If an extension for review is required, written notice of the extension will be furnished to the applicant within the initial sixty (60) day period. This notice of extension will describe the special circumstances necessitating the additional time and the date by which the Plan Administrator is to render its decision on the review. The Plan Administrator will give prompt, written or electronic notice of its decision to the applicant. Any electronic notice will comply with the regulations of the U.S. Department of Labor. If the Plan Administrator confirms the denial of the application for benefits, in whole or in part, the notice will set forth, in a manner designed to be understood by the applicant, the following:

(1) the specific reason or reasons for the denial;

(2) references to the specific Plan provision(s) upon which the denial is based;

(3) a statement that the applicant is entitled to receive, upon request and free of charge, reasonable access to, and copies of, all documents, records and other information relevant to the applicant's claim; and

(4) a statement of the applicant's right to bring a civil action under Section 502(a) of ERISA.

(e) Rules and Procedures. The Plan Administrator will establish rules and procedures, consistent with the Plan and with ERISA, as necessary and appropriate in carrying out its responsibilities in reviewing benefit claims. The Plan Administrator may require an applicant who wishes to submit additional information in connection with an appeal from the denial of benefits to do so at the applicant's own expense.

(f) Exhaustion of Remedies. No legal action for benefits under the Plan may be brought until the applicant (i) has submitted a written application for benefits in accordance with the procedures described by Section 13(a), (ii) has been notified by the Plan Administrator that the application is denied, (iii) has filed a written request for a review of the application in accordance with the appeal procedure described in Section 13(c), and (iv) has been notified that the Plan Administrator has denied the appeal. Notwithstanding the foregoing, if the Plan Administrator does not respond to an applicant's claim or appeal within the relevant time limits specified in this Section 13, the applicant may bring legal action for benefits under the Plan pursuant to Section 502(a) of ERISA.

14. Basis Of Payments To And From Plan. All benefits under the Plan will be paid by the Company. The Plan will be unfunded, and benefits hereunder will be paid only from the general assets of the Company.

15. Other Plan Information.

(a) Employer and Plan Identification Numbers. The Employer Identification Number assigned to the Company (which is the "Plan Sponsor" as that term is used in ERISA) by the Internal Revenue Service is 33-0336973. The Plan Number assigned to the Plan by the Plan Sponsor pursuant to the instructions of the Internal Revenue Service is 511.

(b) Ending Date for Plan's Fiscal Year. The date of the end of the fiscal year for the purpose of maintaining the Plan's records is December 31.

(c) Agent for the Service of Legal Process. The agent for the service of legal process with respect to the Plan is:

Ionis Pharmaceuticals, Inc.
Attn: General Counsel
2855 Gazelle
Carlsbad, California 92010

(d) Plan Sponsor and Administrator. The "Plan Sponsor" and the "Plan Administrator" of the Plan is:

Ionis Pharmaceuticals, Inc.
Attn: Plan Administrator of the Severance Benefit Plan
2855 Gazelle
Carlsbad, California 92010

The Plan Sponsor's and Plan Administrator's telephone number is (760) 603-3848. The Plan Administrator is the named fiduciary charged with the responsibility for administering the Plan.

16. Statement Of ERISA Rights.

Participants in the Plan (which is a welfare benefit plan sponsored by Ionis Pharmaceuticals, Inc.) are entitled to certain rights and protections under ERISA. For purposes of this Section 16 and, under ERISA, Participants are entitled to:

Receive Information About the Plan and Benefits

(a) Examine, without charge, at the Plan Administrator's office and at other specified locations, such worksites, all documents governing the Plan and a copy of the latest annual report (Form 5500 Series), if applicable, filed by the Plan with the U.S. Department of Labor and available at the Public Disclosure Room of the Employee Benefits Security Administration;

(b) Obtain, upon written request to the Plan Administrator, copies of documents governing the operation of the Plan and copies of the latest annual report (Form 5500 Series), if applicable, and an updated (as necessary) Summary Plan Description. The Plan Administrator may make a reasonable charge for the copies; and

(c) Receive a summary of the Plan's annual financial report, if applicable. The Plan Administrator is required by law to furnish each Participant with a copy of this summary annual report.

Prudent Actions by Plan Fiduciaries

In addition to creating rights for Participants, ERISA imposes duties upon the people who are responsible for the operation of the employee benefit plan. The people who operate the Plan, called "fiduciaries" of the Plan, have a duty to do so prudently and in the interest of Participants and beneficiaries. No one, including a Participant's employer, union (if applicable) or any other person, may fire a Participant or otherwise discriminate against a Participant in any way to prevent the Participant from obtaining a Plan benefit or exercising a Participant's rights under ERISA.

Enforcement of Participant Rights

If a claim for a Plan benefit is denied or ignored, in whole or in part, a Participant has a right to know why this was done, to obtain copies of documents relating to the decision without charge, and to appeal any denial, all within certain time schedules.

Under ERISA, there are steps a Participant can take to enforce the above rights. For instance, if a Participant requests a copy of Plan documents or the latest annual report from the Plan, if applicable, and does not receive them within thirty (30) days, the Participant may file suit in a federal court. In such a case, the court may require the Plan Administrator to provide the materials and pay the Participant up to $110 a day until the Participant receives the materials, unless the materials were not sent because of reasons beyond the control of the Plan Administrator.

If a Participant has a claim for benefits that is denied or ignored, in whole or in part, the Participant may file suit in a state or federal court.

If a Participant is discriminated against for asserting the Participant's rights, the Participant may seek assistance from the U.S. Department of Labor, or may file suit in a federal court. The court will decide who should pay court costs and legal fees. If a Participant is successful, the court may order the person the Participant has sued to pay these costs and fees. If the Participant loses, the court may order the Participant to pay these costs and fees, for example, if it finds the Participant's claim is frivolous.

Assistance with Questions

If a Participant has any questions about the Plan, the Participant should contact the Plan Administrator. If a Participant has any questions about this statement or about the Participant's rights under ERISA, or if the Participant needs assistance in obtaining documents from the Plan Administrator, the Participant should contact the nearest office of the Employee Benefits Security Administration, U.S. Department of Labor, listed in the Participant's telephone directory or the Division of Technical Assistance and Inquiries, Employee Benefits Security Administration, U.S. Department of Labor, 200 Constitution Avenue N.W., Washington, D.C. 20210. The Participant may also obtain certain publications about the Participant's rights and responsibilities under ERISA by calling the publications hotline of the Employee Benefits Security Administration.

17. General Provisions.

(a) Notices. Any notice, demand or request required or permitted to be given by either the Company or a Participant pursuant to the terms of the Plan will be in writing and will be deemed given when delivered personally, when received electronically (including email addressed to the Participant's Company email account and to the Company email account of the Company's head of legal affairs), or deposited in the U.S. Mail, First Class with postage prepaid, and addressed to the parties, in the case of the Company, at the address set forth in Section 15(d), in the case of a Participant, at the address as set forth in the Company's employment file maintained for the Participant as previously furnished by the Participant or such other address as a party may request by notifying the other in writing.

(b) Transfer and Assignment. The rights and obligations of a Participant under the Plan may not be transferred or assigned without the prior written consent of the Company. The Plan will be binding upon any surviving entity resulting from a Change in Control and upon any other person who is a successor by merger, acquisition, consolidation or otherwise to the business formerly carried on by the Company without regard to whether or not such person or entity actively assumes the obligations hereunder.

(c) Waiver. Any party's failure to enforce any provision or provisions of the Plan will not in any way be construed as a waiver of any such provision or provisions, nor prevent any party from thereafter enforcing each and every other provision of the Plan. The rights granted to the parties herein are cumulative and will not constitute a waiver of any party's right to assert all other legal remedies available to it under the circumstances.

(d) Severability. Should any provision of the Plan be declared or determined to be invalid, illegal or unenforceable, the validity, legality and enforceability of the remaining provisions will not in any way be affected or impaired.

(e) Section Headings. Section headings in the Plan are included only for convenience of reference and will not be considered part of the Plan for any other purpose.

18. Effective Date. The Plan shall become effective on the Effective Date.

EXHIBIT A

AMENDED AND RESTATED

IONIS PHARMACEUTICALS, INC.

SEVERANCE BENEFIT PLAN
PARTICIPATION NOTICE

To:_____

Date:_____

Ionis Pharmaceuticals, Inc. (the "***Company***") has adopted the Amended and Restated Ionis Pharmaceuticals, Inc. Severance Benefit Plan (the "***Plan***"). The Company is providing you this Participation Notice to inform you that you have been designated as a Participant in the Plan. A copy of the Plan document is attached to this Participation Notice. The terms and conditions of your participation in the Plan are as set forth in the Plan and this Participation Notice, which together constitute the Summary Plan Description for the Plan.

Your Non-CiC Severance Period is **[XX months][1].**

Your CiC Severance Period is **[XX months][2].**

Please return to the Company's head of Human Resources a copy of this Participation Notice signed by you and retain a copy of this Participation Notice, along with the Plan document, for your records.

IONIS PHARMACEUTICALS, INC.

_____
(Signature)

Name: _____

Title: _____

PARTICIPANT:

_____
(Signature)

Name: _____

Date: _____

[1] 18 months for CEO, 12 months for EVPs, 9 months for SVPs, and 6 months for VPs.
[2] 24 months for CEO, 18 months for EVPs, 12 months for SVPs, and 9 months for VPs.

EXHIBIT B

RELEASE AGREEMENT
[EMPLOYEES AGE 40 OR OVER; INDIVIDUAL TERMINATION]

I understand and agree completely to the terms set forth in the Amended and Restated Ionis Pharmaceuticals, Inc. Severance Benefit Plan (the "*Plan*").

I understand that this Release, together with the Plan, constitutes the complete, final and exclusive embodiment of the entire agreement between the Company, affiliates of the Company and me with regard to the subject matter hereof. I am not relying on any promise or representation by the Company or an affiliate of the Company that is not expressly stated therein. Certain capitalized terms used in this Release are defined in the Plan.

I hereby confirm my obligations under my Confidentiality Agreement.

I hereby resign all positions (if any) I hold on the Company's Board of Directors, including all committees.

Except as otherwise set forth in this Release, I hereby generally and completely release the Company and its affiliates, and their parents, subsidiaries, successors, predecessors and affiliates, and its and their partners, members, directors, officers, employees, stockholders, shareholders, agents, attorneys, predecessors, insurers, affiliates and assigns, from any and all claims, liabilities and obligations, both known and unknown, that arise out of or are in any way related to events, acts, conduct, or omissions occurring at any time prior to and including the date I sign this Release. This general release includes, but is not limited to: (a) all claims arising out of or in any way related to my employment with the Company and its affiliates, or their affiliates, or the termination of that employment; (b) all claims related to my compensation or benefits, including salary, bonuses, commissions, vacation pay, expense reimbursements, severance pay, fringe benefits, stock, stock options, or any other ownership interests in the Company and its affiliates, or their affiliates; (c) all claims for breach of contract, wrongful termination, and breach of the implied covenant of good faith and fair dealing; (d) all tort claims, including claims for fraud, defamation, emotional distress, and discharge in violation of public policy; and (e) all federal, state, provincial and local statutory claims, including claims for discrimination, harassment, retaliation, attorneys' fees, or other claims arising under [the Massachusetts Payment of Wages Law (Mass. Gen. Laws ch. 149 § 148),][3] the federal Civil Rights Act of 1964 (as amended), the federal Americans with Disabilities Act of 1990 (as amended), the federal Age Discrimination in Employment Act (as amended) ("***ADEA***"), and the federal Employee Retirement Income Security Act of 1974 (as amended).

Notwithstanding the foregoing, I understand that the following rights or claims are not included in my Release: (a) any rights or claims for indemnification I may have pursuant to any written indemnification agreement with the Company or its affiliate to which I am a party; the charter, bylaws, or operating agreements of the Company or its affiliate; or under applicable law; or (b) any rights which cannot be waived as a matter of law. In addition, I understand that nothing in this Release prevents me from filing, cooperating with, or participating in any proceeding before the Equal Employment Opportunity Commission or the Department of Labor, except that I hereby waive my right to any monetary benefits in connection with any such claim, charge or proceeding. I hereby represent and warrant that, other than the claims identified in this paragraph, I am not aware of any claims I have or might have that are not included in the Release.

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[3] For Massachusetts employees.

I acknowledge that I am knowingly and voluntarily waiving and releasing any rights I may have under the ADEA, and that the consideration given under the Plan for the waiver and release in the preceding paragraph hereof is in addition to anything of value to which I was already entitled. I further acknowledge that I have been advised by this writing, as required by the ADEA, that: (a) my waiver and release do not apply to any rights or claims that may arise after the date I sign this Release; (b) I should consult with an attorney prior to signing this Release (although I may choose voluntarily not to do so); (c) I have twenty-one (21) days to consider this Release (although I may choose voluntarily to sign this Release earlier); (d) I have seven (7) days following the date I sign this Release to revoke the Release by providing written notice to an officer of the Company; and (e) this Release will not be effective until the date upon which the revocation period has expired, which will be the eighth day after I sign this Release.

I hereby represent that I have been paid all compensation owed and for all hours worked; I have received all the leave and leave benefits and protections for which I am eligible pursuant to the Family and Medical Leave Act, or otherwise; and I have not suffered any on-the-job injury for which I have not already filed a workers' compensation claim.

I represent that I am not aware of any claim by me other than the claims that are released by this Release. I acknowledge that I may hereafter discover claims or facts in addition to or different than those which I now know or believe to exist with respect to the subject matter of this Release and which, if known or suspected at the time of entering into this Release, may have materially affected this Release and my decision to enter into it. Nevertheless, I hereby waive any right, claim or cause of action that might arise as a result of such different or additional claims or facts and I hereby expressly waive any and all rights and benefits confirmed upon me by the provisions of California Civil Code Section 1542, which provides as set forth below, as well as under any other statute or common law principles of similar effect:

"A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS THAT THE CREDITOR OR RELEASING PARTY DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE AND THAT, IF KNOWN BY HIM OR HER, WOULD HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR OR RELEASED PARTY."][4]

I agree not to disparage the Company and its affiliates, and the Company's and its affiliates' officers, directors, employees, shareholders, investors and agents, in any manner likely to be harmful to them or their business, business reputation or personal reputation; provided that I may respond accurately and fully to any question, inquiry or request for information when required by legal process or as part of a government investigation. Notwithstanding the foregoing, nothing in this Release shall limit my right to voluntarily communicate with the Equal Employment Opportunity Commission, United States Department of Labor, the National Labor Relations Board, the Securities and Exchange Commission, other federal government agency or similar state or local agency or to discuss the terms and conditions of my employment with others to the extent expressly permitted by Section 7 of the National Labor Relations Act.

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[4] For California employees.

I agree that for the one (1) year period after the date my employment ends, I will not, as an officer, director, employee, consultant, owner, partner, or in any other capacity, either directly or through others, solicit, induce, encourage, or participate in soliciting, inducing or encouraging any employee, consultant, or independent contractor of Company to terminate his, her or its relationship with Company or its Affiliates, even if I did not initiate the discussion or seek out the contact.

I acknowledge that to become effective, I must sign and return this Release to the Company so that it is received not later than twenty-one (21) days following the date it is provided to me.

PARTICIPANT:

(Signature)

Name:

Date:

EXHIBIT C

RELEASE AGREEMENT
[EMPLOYEES AGE 40 OR OVER; GROUP TERMINATION]

I understand and agree completely to the terms set forth in the Amended and Restated Ionis Pharmaceuticals, Inc. Severance Benefit Plan (the "*Plan*").

I understand that this Release, together with the Plan, constitutes the complete, final and exclusive embodiment of the entire agreement between the Company, affiliates of the Company and me with regard to the subject matter hereof. I am not relying on any promise or representation by the Company or an affiliate of the Company that is not expressly stated therein. Certain capitalized terms used in this Release are defined in the Plan.

I hereby confirm my obligations under my Confidentiality Agreement.

I hereby resign all positions (if any) I hold on the Company's Board of Directors, including all committees.

Except as otherwise set forth in this Release, I hereby generally and completely release the Company and its affiliates, and their parents, subsidiaries, successors, predecessors and affiliates, and its and their partners, members, directors, officers, employees, stockholders, shareholders, agents, attorneys, predecessors, insurers, affiliates and assigns, from any and all claims, liabilities and obligations, both known and unknown, that arise out of or are in any way related to events, acts, conduct, or omissions occurring at any time prior to and including the date I sign this Release. This general release includes, but is not limited to: (a) all claims arising out of or in any way related to my employment with the Company and its affiliates, or their affiliates, or the termination of that employment; (b) all claims related to my compensation or benefits, including salary, bonuses, commissions, vacation pay, expense reimbursements, severance pay, fringe benefits, stock, stock options, or any other ownership interests in the Company and its affiliates, or their affiliates; (c) all claims for breach of contract, wrongful termination, and breach of the implied covenant of good faith and fair dealing; (d) all tort claims, including claims for fraud, defamation, emotional distress, and discharge in violation of public policy; and (e) all federal, state, provincial and local statutory claims, including claims for discrimination, harassment, retaliation, attorneys' fees, or other claims arising under the [the Massachusetts Payment of Wages Law (Mass. Gen. Laws ch. 149 § 148),][5] federal Civil Rights Act of 1964 (as amended), the federal Americans with Disabilities Act of 1990 (as amended), the federal Age Discrimination in Employment Act (as amended) ("***ADEA***"), and the federal Employee Retirement Income Security Act of 1974 (as amended).

Notwithstanding the foregoing, I understand that the following rights or claims are not included in my Release: (a) any rights or claims for indemnification I may have pursuant to any written indemnification agreement with the Company or its affiliate to which I am a party; the charter, bylaws, or operating agreements of the Company or its affiliate; or under applicable law; or (b) any rights which cannot be waived as a matter of law. In addition, I understand that nothing in this Release prevents me from filing, cooperating with, or participating in any proceeding before the Equal Employment Opportunity Commission, or the Department of Labor, except that I hereby waive my right to any monetary benefits in connection with any such claim, charge or proceeding. I hereby represent and warrant that, other than the claims identified in this paragraph, I am not aware of any claims I have or might have that are not included in the Release.

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[5] For Massachusetts employees.

I acknowledge that I am knowingly and voluntarily waiving and releasing any rights I may have under the ADEA, and that the consideration given under the Plan for the waiver and release in the preceding paragraph hereof is in addition to anything of value to which I was already entitled. I further acknowledge that I have been advised by this writing, as required by the ADEA, that: (a) my waiver and release do not apply to any rights or claims that may arise after the date I sign this Release; (b) I should consult with an attorney prior to signing this Release (although I may choose voluntarily not to do so); (c) I have forty-five (45) days to consider this Release (although I may choose voluntarily to sign this Release earlier); (d) I have seven (7) days following the date I sign this Release to revoke the Release by providing written notice to an officer of the Company; (e) this Release will not be effective until the date upon which the revocation period has expired, which will be the eighth day after I sign this Release; and (f) I have received with this Release a detailed list of the job titles and ages of all employees who were terminated in this group termination and the ages of all employees of the Company in the same job classification or organizational unit who were not terminated.

I hereby represent that I have been paid all compensation owed and for all hours worked; I have received all the leave and leave benefits and protections for which I am eligible pursuant to the Family and Medical Leave Act, or otherwise; and I have not suffered any on-the-job injury for which I have not already filed a workers' compensation claim.

[I represent that I am not aware of any claim by me other than the claims that are released by this Release. I acknowledge that I may hereafter discover claims or facts in addition to or different than those which I now know or believe to exist with respect to the subject matter of this Release and which, if known or suspected at the time of entering into this Release, may have materially affected this Release and my decision to enter into it. Nevertheless, I hereby waive any right, claim or cause of action that might arise as a result of such different or additional claims or facts and I hereby expressly waive any and all rights and benefits confirmed upon me by the provisions of California Civil Code Section 1542, which provides as set forth below, as well as under any other statute or common law principles of similar effect:

"A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS THAT THE CREDITOR OR RELEASING PARTY DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE AND THAT, IF KNOWN BY HIM OR HER, WOULD HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR OR RELEASED PARTY."**][6]**

I agree not to disparage the Company and its affiliates, and the Company's and its affiliates' officers, directors, employees, shareholders, investors and agents, in any manner likely to be harmful to them or their business, business reputation or personal reputation; provided that I may respond accurately and fully to any question, inquiry or request for information when required by legal process or as part of a government investigation. Notwithstanding the foregoing, nothing in this Release shall limit my right to voluntarily communicate with the Equal Employment Opportunity Commission, United States Department of Labor, the National Labor Relations Board, the Securities and Exchange Commission, other federal government agency or similar state or local agency or to discuss the terms and conditions of my employment with others to the extent expressly permitted by Section 7 of the National Labor Relations Act.

I agree that for the one (1) year period after the date my employment ends, I will not, as an officer, director, employee, consultant, owner, partner, or in any other capacity, either directly or through others, solicit, induce, encourage, or participate in soliciting, inducing or encouraging any employee, consultant, or independent contractor of Company to terminate his, her or its relationship with Company or its Affiliates, even if I did not initiate the discussion or seek out the contact.

I acknowledge that to become effective, I must sign and return this Release to the Company so that it is received not later than forty-five (45) days following the date it is provided to me.

PARTICIPANT:

_____

(Signature)

Name: _____

Date: _____

6 For California employees.

EXHIBIT D

RELEASE AGREEMENT
[EMPLOYEES UNDER AGE 40]

I understand and agree completely to the terms set forth in the Amended and Restated Ionis Pharmaceuticals, Inc. Severance Benefit Plan (the "*Plan*").

I understand that this Release, together with the Plan, constitutes the complete, final and exclusive embodiment of the entire agreement between the Company, affiliates of the Company and me with regard to the subject matter hereof. I am not relying on any promise or representation by the Company or an affiliate of the Company that is not expressly stated therein. Certain capitalized terms used in this Release are defined in the Plan.

I hereby confirm my obligations under my Confidentiality Agreement.

I hereby resign all positions (if any) I hold on the Company's Board of Directors, including all committees.

Except as otherwise set forth in this Release, I hereby generally and completely release the Company and its affiliates, and their parents, subsidiaries, successors, predecessors and affiliates, and its and their partners, members, directors, officers, employees, stockholders, shareholders, agents, attorneys, predecessors, insurers, affiliates and assigns, from any and all claims, liabilities and obligations, both known and unknown, that arise out of or are in any way related to events, acts, conduct, or omissions occurring at any time prior to and including the date I sign this Release. This general release includes, but is not limited to: (a) all claims arising out of or in any way related to my employment with the Company and its affiliates, or their affiliates, or the termination of that employment; (b) all claims related to my compensation or benefits, including salary, bonuses, commissions, vacation pay, expense reimbursements, severance pay, fringe benefits, stock, stock options, or any other ownership interests in the Company and its affiliates, or their affiliates; (c) all claims for breach of contract, wrongful termination, and breach of the implied covenant of good faith and fair dealing; (d) all tort claims, including claims for fraud, defamation, emotional distress, and discharge in violation of public policy; and (e) all federal, state, provincial and local statutory claims, including claims for discrimination, harassment, retaliation, attorneys' fees, or other claims arising under the [the Massachusetts Payment of Wages Law (Mass. Gen. Laws ch. 149 § 148),][7] federal Civil Rights Act of 1964 (as amended), the federal Americans with Disabilities Act of 1990 (as amended), and the federal Employee Retirement Income Security Act of 1974 (as amended).

Notwithstanding the foregoing, I understand that the following rights or claims are not included in my Release: (a) any rights or claims for indemnification I may have pursuant to any written indemnification agreement with the Company or its affiliate to which I am a party; the charter, bylaws, or operating agreements of the Company or its affiliate; or under applicable law; or (b) any rights which cannot be waived as a matter of law. In addition, I understand that nothing in this Release prevents me from filing, cooperating with, or participating in any proceeding before the Equal Employment Opportunity Commission, or the Department of Labor, except that I hereby waive my right to any monetary benefits in connection with any such claim, charge or proceeding. I hereby represent and warrant that, other than the claims identified in this paragraph, I am not aware of any claims I have or might have that are not included in the Release.

---

[7] For Massachusetts employees.

I hereby represent that I have been paid all compensation owed and for all hours worked; I have received all the leave and leave benefits and protections for which I am eligible pursuant to the Family and Medical Leave Act, or otherwise; and I have not suffered any on-the-job injury for which I have not already filed a workers' compensation claim.

[I represent that I am not aware of any claim by me other than the claims that are released by this Release. I acknowledge that I may hereafter discover claims or facts in addition to or different than those which I now know or believe to exist with respect to the subject matter of this Release and which, if known or suspected at the time of entering into this Release, may have materially affected this Release and my decision to enter into it. Nevertheless, I hereby waive any right, claim or cause of action that might arise as a result of such different or additional claims or facts and I hereby expressly waive any and all rights and benefits confirmed upon me by the provisions of California Civil Code Section 1542, which provides as set forth below, as well as under any other statute or common law principles of similar effect:

"A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS THAT THE CREDITOR OR RELEASING PARTY DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE AND THAT, IF KNOWN BY HIM OR HER, WOULD HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR OR RELEASED PARTY."**]**[8]

I agree not to disparage the Company and its affiliates, and the Company's and its affiliates' officers, directors, employees, shareholders, investors and agents, in any manner likely to be harmful to them or their business, business reputation or personal reputation; provided that I may respond accurately and fully to any question, inquiry or request for information when required by legal process or as part of a government investigation. Notwithstanding the foregoing, nothing in this Release shall limit my right to voluntarily communicate with the Equal Employment Opportunity Commission, United States Department of Labor, the National Labor Relations Board, the Securities and Exchange Commission, other federal government agency or similar state or local agency or to discuss the terms and conditions of my employment with others to the extent expressly permitted by Section 7 of the National Labor Relations Act.

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8 For California employees.

I agree that for the one (1) year period after the date my employment ends, I will not, as an officer, director, employee, consultant, owner, partner, or in any other capacity, either directly or through others, solicit, induce, encourage, or participate in soliciting, inducing or encouraging any employee, consultant, or independent contractor of Company to terminate his, her or its relationship with Company or its Affiliates, even if I did not initiate the discussion or seek out the contact.

I acknowledge that to become effective, I must sign and return this Release to the Company so that it is received not later than fourteen (14) days following the date it is provided to me.

PARTICIPANT:

_____

(Signature)

Name:

_____

Date:

_____

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 4, 2022

/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 4, 2022

/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, 2022, 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 4, 2022

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

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

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