UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 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 August 3, 2022 was 141,941,338.

IONIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

PART I	**FINANCIAL INFORMATION**	
ITEM 1:	Financial Statements:	
	Condensed Consolidated Balance Sheets as of June 30, 2022 (unaudited) and December 31, 2021	3
	Condensed Consolidated Statements of Operations for the three and six months ended June 30, 2022 and 2021 (unaudited)	4
	Condensed Consolidated Statements of Comprehensive Loss for the three and six months ended June 30, 2022 and 2021 (unaudited)	5
	Condensed Consolidated Statements of Stockholders' Equity for the three and six months ended June 30, 2022 and 2021 (unaudited)	6
	Condensed Consolidated Statements of Cash Flows for the six months ended June 30, 2022 and 2021 (unaudited)	8
	Notes to Condensed Consolidated Financial Statements (unaudited)	9
ITEM 2:	Management's Discussion and Analysis of Financial Condition and Results of Operations:	
	Overview	28
	Results of Operations	32
	Liquidity and Capital Resources	37
ITEM 3:	Quantitative and Qualitative Disclosures about Market Risk	39
ITEM 4:	Controls and Procedures	39
PART II	OTHER INFORMATION	39
ITEM 1:	Legal Proceedings	39
ITEM 1A:	Risk Factors	40
ITEM 2:	Unregistered Sales of Equity Securities and Use of Proceeds	58
ITEM 3:	Default upon Senior Securities	58
ITEM 4:	Mine Safety Disclosures	58
ITEM 5:	Other Information	58
ITEM 6:	Exhibits	59
SIGNATURES		60

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)

	June 30, 2022 (unaudited)	December 31, 2021
ASSETS		
Current assets:		
Cash and cash equivalents	$ 521,917	$ 869,191
Short-term investments	1,499,910	1,245,782
Contracts receivable	6,751	61,896
Inventories	19,811	24,806
Other current assets	142,759	143,374
Total current assets	2,191,148	2,345,049
Property, plant and equipment, net	177,015	178,069
Patents, net	29,054	29,005
Deposits and other assets	58,916	59,567
Total assets	$ 2,456,133	$ 2,611,690
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 10,351	$ 11,904
Accrued compensation	24,985	38,810
Accrued liabilities	134,336	88,560
Income taxes payable	14	36
Current portion of long-term obligations	4,732	3,526
Current portion of deferred contract revenue	93,393	97,714
Total current liabilities	267,811	240,550
Long-term deferred contract revenue	315,196	351,879
0 percent convertible senior notes, net	620,678	619,119
0.125 percent convertible senior notes, net	543,407	542,314
Long-term obligations, less current portion	25,093	26,378
Long-term mortgage debt	59,222	59,713
Total liabilities	1,831,407	1,839,953
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 141,830,659 and 141,210,015 shares issued and outstanding at June 30, 2022 (unaudited) and December 31, 2021, respectively	142	141
Additional paid-in capital	2,008,794	1,964,167
Accumulated other comprehensive loss	(54,007)	(32,668)
Accumulated deficit	(1,330,203)	(1,159,903)
Total stockholders' equity	624,726	771,737
Total liabilities and stockholders' equity	$ 2,456,133	$ 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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 59,627	$ 72,168	$ 113,444	$ 132,154
TEGSEDI and WAYLIVRA revenue, net	10,386	11,544	16,547	31,382
Licensing and other royalty revenue	8,171	2,149	20,477	6,773
Total commercial revenue	78,184	85,861	150,468	170,309
Research and development revenue:				
Collaborative agreement revenue	38,247	39,889	88,032	67,048
Eplontersen joint development revenue	17,360	—	37,210	—
Total research and development revenue	55,607	39,889	125,242	67,048
Total revenue	133,791	125,750	275,710	237,357
Expenses:				
Cost of sales	4,745	2,958	8,914	5,537
Research, development and patent	180,758	139,306	341,884	279,107
Selling, general and administrative	33,802	56,455	67,929	117,653
Total operating expenses	219,305	198,719	418,727	402,297
Loss from operations	(85,514)	(72,969)	(143,017)	(164,940)
Other income (expense):				
Investment income, net	3,403	2,734	5,396	7,364
Interest expense	(2,130)	(2,357)	(4,252)	(4,771)
Gain (loss) on investments	(6,337)	860	(12,963)	873
Other expense	(12,297)	(8,816)	(12,110)	(8,813)
Loss before income tax expense	(102,875)	(80,548)	(166,946)	(170,287)
Income tax expense	(2,260)	(327)	(3,354)	(457)
Net loss	$ (105,135)	$ (80,875)	$ (170,300)	$ (170,744)
Basic and diluted net loss per share	$ (0.74)	$ (0.57)	$ (1.20)	$ (1.21)
Shares used in computing basic and diluted net loss per share	141,794	140,962	141,697	140,866

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Net loss	$ (105,135)	$ (80,875)	$ (170,300)	$ (170,744)
Unrealized losses on debt securities, net of tax	(5,018)	(1,697)	(20,774)	(4,703)
Currency translation adjustment	(411)	104	(565)	(22)
Comprehensive loss	$ (110,564)	$ (82,468)	$ (191,639)	$ (175,469)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Three Months Ended June 30, 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 March 31, 2021	140,924	$ 141	$ 1,925,801	$ (24,203)	$ (1,221,175)	$ 680,564
Net loss	—	—	—	—	(80,875)	(80,875)
Change in unrealized losses, net of tax	—	—	—	(1,697)	—	(1,697)
Foreign currency translation	—	—	—	104	—	104
Issuance of common stock in connection with employee stock plans	108	—	1,882	—	—	1,882
Issuance of warrants	—	—	89,752	—	—	89,752
Purchase of note hedges	—	—	(136,620)	—	—	(136,620)
Stock-based compensation expense	—	—	30,022	—	—	30,022
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(10)	—	(458)	—	—	(458)
Balance at June 30, 2021	141,022	$ 141	$ 1,910,379	$ (25,796)	$ (1,302,050)	$ 582,674
Balance at March 31, 2022	141,753	$ 142	$ 1,983,078	$ (48,578)	$ (1,225,068)	$ 709,574
Net loss	—	—	—	—	(105,135)	(105,135)
Change in unrealized losses, net of tax	—	—	—	(5,018)	—	(5,018)
Foreign currency translation	—	—	—	(411)	—	(411)
Issuance of common stock in connection with employee stock plans	87	—	1,614	—	—	1,614
Stock-based compensation expense	—	—	24,502	—	—	24,502
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(9)	—	(400)	—	—	(400)
Balance at June 30, 2022	141,831	$ 142	$ 2,008,794	$ (54,007)	$ (1,330,203)	$ 624,726

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Six Months Ended June 30, 2021 and 2022
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity
Balance at December 31, 2020	140,366	$ 140	$ 1,895,519	$ (21,071)	$ (1,131,306)	$ 743,282
Net loss	—	—	—	—	(170,744)	(170,744)
Change in unrealized losses, net of tax	—	—	—	(4,703)	—	(4,703)
Foreign currency translation	—	—	—	(22)	—	(22)
Issuance of common stock in connection with employee stock plans	917	1	9,641	—	—	9,642
Issuance of warrants	—	—	89,752	—	—	89,752
Purchase of note hedges	—	—	(136,620)	—	—	(136,620)
Stock-based compensation expense	—	—	67,882	—	—	67,882
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(261)	—	(15,795)	—	—	(15,795)
Balance at June 30, 2021	141,022	$ 141	$ 1,910,379	$ (25,796)	$ (1,302,050)	$ 582,674
Balance at December 31, 2021	141,210	$ 141	$ 1,964,167	$ (32,668)	$ (1,159,903)	$ 771,737
Net loss	—	—	—	—	(170,300)	(170,300)
Change in unrealized losses, net of tax	—	—	—	(20,774)	—	(20,774)
Foreign currency translation	—	—	—	(565)	—	(565)
Issuance of common stock in connection with employee stock plans	935	1	3,461	—	—	3,462
Stock-based compensation expense	—	—	50,738	—	—	50,738
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(314)	—	(9,572)	—	—	(9,572)
Balance at June 30, 2022	141,831	$ 142	$ 2,008,794	$ (54,007)	$ (1,330,203)	$ 624,726

See accompanying notes.

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

	Six Months Ended June 30,	
	2022	**2021**
Operating activities:		
Net loss	$ (170,300)	$ (170,744)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	7,484	7,951
Amortization of right-of-use operating lease assets	1,300	781
Amortization of patents	1,197	1,137
Amortization of premium on investments, net	7,867	8,824
Amortization of debt issuance costs	2,688	2,193
Stock-based compensation expense	50,738	67,882
Loss (gain) on investments	54	(873)
Loss on early retirement of debt	—	8,627
Non-cash losses related to disposal of property, plant and equipment	527	—
Non-cash losses related to patents	951	827
Changes in operating assets and liabilities:		
Contracts receivable	55,145	52,200
Inventories	4,995	(2,134)
Other current and long-term assets	(39)	9,179
Income taxes payable	(22)	551
Accounts payable	(2,672)	(2,819)
Accrued compensation	(13,825)	(35,506)
Accrued liabilities and other current liabilities	45,170	(14,914)
Deferred contract revenue	(41,004)	(50,476)
Net cash used in operating activities	(49,746)	(117,314)
Investing activities:		
Purchases of short-term investments	(663,195)	(740,721)
Proceeds from sale of short-term investments	380,375	727,859
Purchases of property, plant and equipment	(6,040)	(6,130)
Acquisition of licenses and other assets, net	(1,993)	(3,182)
Net cash used in investing activities	(290,853)	(22,174)
Financing activities:		
Proceeds from equity, net	3,462	9,642
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(9,572)	(15,795)
Proceeds from the issuance of 0 percent convertible notes	—	632,500
0 percent convertible senior notes issuance costs	—	(15,551)
Repurchase of $247.9 million principal amount of the 1 percent convertible senior notes	—	(256,963)
Proceeds from issuance of warrants	—	89,752
Purchase of note hedges	—	(136,620)
Net cash (used in) provided by financing activities	(6,110)	306,965
Effects of exchange rates on cash	(565)	(22)
Net (decrease) increase in cash and cash equivalents	(347,274)	167,455
Cash and cash equivalents at beginning of period	869,191	397,664
Cash and cash equivalents at end of period	$ 521,917	$ 565,119
Supplemental disclosures of cash flow information:		
Interest paid	$ 1,544	$ 2,866
Income taxes paid	$ 2	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,121	$ 278

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2022
(Unaudited)

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and six months ended June 30, 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. 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, 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 second quarter of 2022, we achieved a $20 million milestone payment from Roche when we advanced the Phase 2 study in patients with dry age-related macular degeneration, or AMD, under our collaboration agreement with Roche to develop IONIS-FB-L_{Rx}. We added this payment to the transaction price and allocated it to our R&D services performance obligation for IONIS-FB-L_{Rx}. We are recognizing revenue related to this milestone payment over our estimated period of performance. As a result, we recorded a cumulative catch-up adjustment of $13.8 million to increase revenue as of June 30, 2022 for this payment. We estimate we will satisfy our performance obligation in the fourth quarter of 2023.

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. Because we are leading the Phase 3 development program, we made an accounting policy election to recognize as non-customer revenue the cost-share funding from AstraZeneca, net of our share of AstraZeneca's development expenses, 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 June 30, 2022, approximately 69.9 percent of our contracts receivables were from three 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 June 30, 2022 and 2021, we recognized $22.6 million and $26.8 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. During the six months ended June 30, 2022 and 2021, we recognized $48.4 million and $51.4 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.

Accrued Liabilities

Our accrued liabilities consisted of the following (in thousands):

	June 30, 2022	December 31, 2021
Clinical expenses	$ 89,007	$ 65,730
In-licensing expenses	7,332	8,044
Commercial expenses	5,066	2,471
Other miscellaneous expenses	32,931	12,315
Total accrued liabilities	$ 134,336	$ 88,560

Estimated Liability for Clinical Development Costs

We have numerous medicines in preclinical studies and/or clinical trials at clinical sites throughout the world. On at least a quarterly basis, we estimate our liability for preclinical and clinical development costs we have incurred and services that we have received but for which we have not yet been billed and maintain an accrual to cover these costs. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We estimate our liability using assumptions about study and patient activities and the related expected expenses for those activities determined based on the contracted fees with our service providers. The assumptions we use represent our best estimates of the activity and expenses at the time of our accrual and involve inherent uncertainties and the application of our judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

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 June 30, 2022, we held equity investments in three publicly held companies and eight privately held companies.

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 publicly held companies based on observable inputs such as quoted prices in active markets for identical assets. 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. We recorded an immaterial amount of fair value adjustments related to our equity investments for the six months ended June 30, 2022 and 2021.

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.

Our inventory consisted of the following (in thousands):

	June 30, 2022	December 31, 2021
Raw materials:		
Raw materials- clinical	$ 14,686	$ 14,507
Raw materials- commercial	889	4,139
Total raw materials	15,575	18,646
Work in process	3,927	5,770
Finished goods	309	390
Total inventory	$ 19,811	$ 24,806

Leases

We determine if an arrangement contains a lease at inception of the arrangement. As of June 30, 2022, we only had 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, right-of-use assets 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 and six months ended June 30, 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 June 30, 2022 and 2021 were $0.74 and $0.57, respectively. Our basic net loss per share for the six months ended June 30, 2022 and 2021 were $1.20 and $1.21, respectively.

Diluted net loss per share

For the three and six months ended June 30, 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 percent convertible senior notes, or 0% Notes;
- Note hedges related to the 0% Notes;
- 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 and six months ended June 30, 2021, common stock that we could have issued from our 1 percent convertible senior notes, or 1% Notes, would also have had an anti-dilutive effect on net loss per share.

Additionally as of June 30, 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, *Derivatives and Hedging*, or ASC 815, 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 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 six months ended June 30, 2022 and 2021, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2022	**2021**
Risk-free interest rate	1.8%	0.5%
Dividend yield	0.0%	0.0%
Volatility	55.1%	54.8%
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 six months ended June 30, 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:

	Six Months Ended June 30,	
	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 six months ended June 30, 2022 was $34.38 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 Section 16 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 Section 16 officers for the six months ended June 30, 2022 and 2021 were $42.28 and $77.17 per share, respectively.

The following table summarizes stock-based compensation expense for the three and six months ended June 30, 2022 and 2021 (in thousands).

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Cost of sales	$ 53	$ —	$ 213	$ 182
Research, development and patent expense	18,500	22,748	37,582	48,647
Selling, general and administrative expense	5,949	7,274	12,943	19,053
Total stock-based compensation expense	$ 24,502	$ 30,022	$ 50,738	$ 67,882

As of June 30, 2022, total unrecognized estimated stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $54.3 million, $61.6 million and $4.4 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized stock-based compensation expense for future forfeitures. We expect to recognize the cost of stock-based compensation expense related to our non-vested stock options, RSUs and PRSUs over a weighted average amortization period of 1.3 years, 1.6 years and 1.4 years, respectively. Our stock-based compensation expense related to equity awards decreased in the first half of 2022 compared to the same period in 2021 due to decreased headcount as a result of the Akcea Merger and restructuring our commercial operations for TEGSEDI and WAYLIVRA.

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 June 30, 2022:

One year or less	68%
After one year but within two years	26%
After two years but within three and a half years	6%
Total	100%

As illustrated above, at June 30, 2022, 94 percent of our available-for-sale securities had a maturity of less than two years.

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

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

At June 30, 2022, we had an equity ownership interest of less than 20 percent in eight private companies and three public companies with which we conduct business.

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

June 30, 2022	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (1)	$ 481,866	$ 4	$ (3,749)	$ 478,121
Debt securities issued by U.S. government agencies	55,207	—	(927)	54,280
Debt securities issued by the U.S. Treasury (1)	340,480	34	(1,829)	338,685
Debt securities issued by states of the U.S. and political subdivisions of the states	148,750	1	(493)	148,258
Other municipal debt securities	6,384	—	(90)	6,294
Total securities with a maturity of one year or less	1,032,687	39	(7,088)	1,025,638
Corporate debt securities	294,276	1	(11,542)	282,735
Debt securities issued by U.S. government agencies	35,545	—	(1,451)	34,094
Debt securities issued by the U.S. Treasury	158,476	61	(3,100)	155,437
Debt securities issued by states of the U.S. and political subdivisions of the states	26,109	2	(748)	25,363
Total securities with a maturity of more than one year	514,406	64	(16,841)	497,629
Total available-for-sale securities	$ 1,547,093	$ 103	$ (23,929)	$ 1,523,267
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ —	$ (7,159)	$ 4,738
Privately held equity securities included in deposits and other assets (3)	23,115	17,257	—	40,372
Total equity securities	35,012	17,257	(7,159)	45,110
Total available-for-sale and equity securities	$ 1,582,105	$ 17,360	$ (31,088)	$ 1,568,377

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:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 7,145	$ (837)	$ 18,205
Privately held 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 publicly traded companies. We recognize publicly traded equity securities at fair value. In the six months ended June 30, 2022, we recognized a $13.5 million unrealized loss in our condensed consolidated statement of operations related to a decrease in the fair value of our investments in publicly traded companies.

(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 June 30, 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	380	$ 703,643	$ (14,199)	$ 42,106	$ (1,092)	$ 745,749	$ (15,291)
Debt securities issued by U.S. government agencies	11	65,974	(1,781)	14,400	(597)	80,374	(2,378)
Debt securities issued by the U.S. Treasury	48	420,076	(4,767)	4,837	(162)	424,913	(4,929)
Debt securities issued by states of the U.S. and political subdivisions of the states	403	119,174	(975)	10,617	(266)	129,791	(1,241)
Other municipal debt securities	3	1,308	(14)	4,986	(76)	6,294	(90)
Total temporarily impaired securities	845	$1,310,175	$ (21,736)	$ 76,946	$ (2,193)	$1,387,121	$ (23,929)

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, which includes our investments in equity securities in privately held biotechnology companies. We classify most of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

The following tables present the major security types we held at June 30, 2022 and December 31, 2021 that we regularly measure and carry at fair value. As of June 30, 2022 and December 31, 2021, one of our investments in publicly held biotechnology companies 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 June 30, 2022	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 409,877	$ 409,877	$ —	$ —
Corporate debt securities (2)	760,856	—	760,856	—
Debt securities issued by U.S. government agencies (2)	88,374	—	88,374	—
Debt securities issued by the U.S. Treasury (2)	494,122	494,122	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	173,621	—	173,621	—
Other municipal debt securities (2)	6,294	—	6,294	—
Publicly traded equity securities included in other current assets	4,738	376	—	4,362
Privately held equity securities included in deposits and other assets	40,372	—	—	40,372
Total	$ 1,978,254	$ 904,375	$ 1,029,145	$ 44,734

	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 (2)	764,059	—	764,059	—
Debt securities issued by U.S. government agencies (2)	120,868	—	120,868	—
Debt securities issued by the U.S. Treasury (2)	182,634	182,634	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	174,464	—	174,464	—
Other municipal debt securities (2)	6,099	—	6,099	—
Publicly traded equity securities included in other current assets	18,205	3,875	—	14,330
Privately held equity securities included in deposits and other assets	32,322	—	—	32,322
Total	$ 1,839,850	$ 727,708	$ 1,065,490	$ 46,652

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) Included in short-term investments.

(3) $23.4 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.

(4) $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 $485.2 million and $577.0 million at June 30, 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 income tax expense of $2.3 million and $0.3 million for the three months ended June 30, 2022 and 2021, respectively, and income tax expense of $3.4 million and $0.5 million for the six months ended June 30, 2022 and 2021, respectively.

6. Collaborative Arrangements and Licensing Agreements

Below, we have included our Biogen and Roche collaborations, which are our only collaborations 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 June 30, 2022, we have received $3.3 billion from our Biogen collaborations.

During the three and six months ended June 30, 2022 and 2021, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
SPINRAZA royalties (commercial revenue)	$ 59.6	$ 72.2	$ 113.4	$ 132.2
R&D revenue	17.3	27.8	57.4	45.9
Total revenue from our relationship with Biogen	$ 76.9	$ 100.0	$ 170.8	$ 178.1
Percentage of total revenue	58%	80%	62%	75%

Our condensed consolidated balance sheet at June 30, 2022 and December 31, 2021 included deferred revenue of $368.3 million and $407.5 million, respectively, related to our relationship with Biogen.

During the first six months 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.

In July 2022, we earned a $9 million milestone payment from Biogen when the U.S. Food and Drug Administration, or FDA, accepted Biogen's New Drug Application, or NDA, filing of tofersen, an investigational antisense medicine for the treatment of superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. We will achieve the next payment of up to $10 million if Biogen advances another medicine under our 2013 strategic neurology collaboration.

Roche

We have two collaborations with Roche, one to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases, and one to develop treatments for Huntington's disease, or HD.

In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx}. We are currently conducting Phase 2 studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with geographic atrophy, or GA, the advanced stage of dry AMD, and a second for the treatment of patients with immunoglobulin A nephropathy, or IgAN. After positive data from a Phase 2 clinical study, Roche licensed IONIS-FB-L_{Rx} in July 2022 and plans to advance IONIS-FB-L_{Rx} into Phase 3 development for patients with IgAN. As a result, Roche is responsible for global development, regulatory and commercialization activities and costs for the Phase 3 IgAN study of IONIS-FB-L_{Rx}. We will continue to lead and conduct the open label Phase 2 study in patients with IgAN and the Phase 2 study in patients with GA. In July 2022, we amended our IONIS-FB-L_{Rx} collaboration agreement with Roche. Under our amended collaboration agreement, we are eligible to receive up to $145 million in development milestones, $279 million in regulatory milestones and $280 million in sales-related milestone payments. In addition, we are also eligible to receive tiered royalties from the high teens to 20 percent on net sales.

Under the collaboration agreement with Roche to develop treatments for HD, we discovered and developed tominersen, an investigational medicine targeting huntingtin, or HTT, protein, through completion of our Phase 1/2 clinical study in people with early stage HD. In the fourth quarter of 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen. In March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest HD based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded iDMC. In January 2022, Roche announced it is actively preparing to initiate a new Phase 2 study of tominersen in patients with HD. Post-hoc analyses from the GENERATION HD1 study suggested tominersen may benefit younger adult patients with lower disease burden. From inception through June 30, 2022, we have received over $245 million from our Roche collaborations.

During the three and six months ended June 30, 2022 and 2021, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
R&D revenue	$ 19.5	$ 3.6	$ 23.9	$ 7.5
Percentage of total revenue	15%	3%	9%	3%

Our condensed consolidated balance sheet at June 30, 2022 and December 31, 2021 included deferred revenue of $29.7 million and $31.6 million, respectively, related to our relationship with Roche.

In the second quarter of 2022, we achieved a $20 million milestone payment from Roche when we advanced the Phase 2 study in patients with dry AMD under our IONIS-FB-L_{Rx} collaboration. We added this payment to the transaction price and allocated it to our R&D services performance obligation for IONIS-FB-L_{Rx}. We are recognizing revenue for our R&D services performance obligation over our estimated period of performance.

In July 2022, we earned a $35 million payment from Roche when Roche licensed IONIS-FB-L_{Rx}. We will achieve the next payment of up to $90 million if Roche advances a medicine under our IONIS-FB-L_{Rx} 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 June 30, 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	$ 11.8
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 June 30, 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	$ 5.4
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 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 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.

8. 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 we consider the potential loss from any legal proceeding to be probable and we can reasonably estimate the amount, we accrue a liability for the estimated loss. The outcome of any proceeding is not determinable in advance. Therefore, we are required to use significant judgment to determine the probability of a loss and whether the amount of the loss is reasonably estimable. Our assessment of a potential liability and the amount of accruals we 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 Ionis and Akcea entered into, in which Akcea became a wholly-owned subsidiary of Ionis. Ionis believes this lawsuit is without merit. However, the outcome of this lawsuit or any other lawsuit that may be filed challenging the October 2020 take-private transaction is uncertain. Accordingly, on June 3, 2022, the parties reached an agreement in principle to settle the Delaware Action for $12.5 million, subject to the approval of the Delaware Court of Chancery. A Stipulation and Agreement of Compromise, Settlement and Release relating to this matter (the "Stipulation and Settlement Agreement") has been executed and filed with the Delaware Court of Chancery, where it awaits Court approval. The terms of the Stipulation and Settlement Agreement include no finding of wrongdoing on the part of any of the Defendants. A hearing on the Stipulation and Settlement Agreement is scheduled for October 11, 2022. We recorded a legal reserve of $12.5 million as of June 30, 2022 for the proposed litigation settlement. We recorded the corresponding litigation settlement expense within other expense in the accompanying condensed consolidated statements of operations for the three and six months ended June 30, 2022. In July 2022, we entered into a settlement agreement with our insurance carrier wherein the insurance carrier agreed to contribute toward the settlement in the amount of $4.5 million. We will record the insurance contribution in the third quarter of 2022.

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 subsidiary, 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 recently reported positive Phase 3 interim analysis data from the NEURO-TTRansform study of eplontersen in patients with hereditary transthyretin amyloidosis polyneuropathy, or ATTRv-PN. As a result, we plan to file a New Drug Application, or NDA, with the U.S. Food and Drug Administration, or FDA, in the second half of 2022. Additionally, the FDA recently accepted Biogen's NDA filing of tofersen for the treatment of superoxide dismutase 1 ALS, or SOD1-ALS, and granted tofersen priority review. Tofersen's Prescription Drug User Fee Act, or PDUFA, date is January 25, 2023. These achievements put us on track to potentially add two new marketed products to our commercial portfolio, if these medicines are approved. We also have a rich late-stage pipeline of medicines, primarily focused on our cardiovascular and neurology franchises. Based on recent positive data from bepirovirsen for patients with chronic hepatitis B virus, or HBV and IONIS-FB-L_{Rx} for patients with immunoglobulin A nephropathy, or IgAN, our partners plan to advance these medicines into Phase 3 development, which could expand our late-stage pipeline to eight medicines in Phase 3 development for ten 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 is our partner responsible for commercializing SPINRAZA worldwide. Through June 30, 2022, we have earned more than $1.7 billion in revenues from our SPINRAZA collaboration, including more than $1.3 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 ATTRv-PN. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or 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 beginning with Brazil. In the first half of 2022, we continued to expand into new markets in Europe and Latin America through Sobi and PTC, respectively.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. 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 transthyretin amyloidosis, or ATTR
  - We reported eplontersen met the co-primary and secondary endpoints in the interim analysis of the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN
  - 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
  - The FDA granted orphan drug designation to eplontersen for the treatment of patients with ATTR
- Tofersen: our medicine in development for SOD1-ALS
  - The FDA accepted the NDA filing for tofersen and granted priority review for tofersen with a PDUFA action date of January 2023
  - Biogen presented new data from the ongoing VALOR open-label extension, or OLE, study at the European Network to Cure ALS meeting
  - Biogen announced FDA acceptance of NDA filing for tofersen
- Olezarsen: our medicine in development for familial chylomicronemia syndrome, or FCS, and severe hypertriglyceridemia, or SHTG
  - We achieved full enrollment in the BALANCE Phase 3 study in patients with FCS
  - 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*
  - Enrollment is ongoing in the Phase 3 study in patients with hypertriglyceridemia
- Pelacarsen: our medicine in development for lipoprotein(a), or Lp(a), driven cardiovascular disease
  - Novartis achieved full enrollment in the Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with established cardiovascular disease and elevated lipoprotein(a), or Lp(a)
- Donidalorsen: our medicine in development for hereditary angioedema, or HAE
  - 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

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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Total revenue	$ 133.8	$ 125.8	$ 275.7	$ 237.4
Total operating expenses	$ 219.3	$ 198.7	$ 418.7	$ 402.3
Loss from operations	$ (85.5)	$ (73.0)	$ (143.0)	$ (164.9)
Net loss	$ (105.1)	$ (80.9)	$ (170.3)	$ (170.7)

Our revenue in the first half of 2022 increased more than 15 percent compared to the same period last year. The increase was driven by significant partner payments we earned across multiple partnered programs, including $57 million from Biogen for advancing several neurology disease programs, $37 million from AstraZeneca for its share of the global Phase 3 development costs for eplontersen and $22 million from Roche for advancing IONIS-FB-L_{Rx}. Already in the third quarter of 2022, we earned $44 million in a license fee and milestone payment from Roche and Biogen, respectively.

Our commercial revenue in the first half of 2022 decreased 12 percent compared to the same period last year. SPINRAZA royalties decreased in the first half of 2022 primarily due to competition outside of the U.S. In the U.S., SPINRAZA sales stabilized in the first half of 2022 compared to the same period last year, increasing 2 percent. 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 half 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. These decreases were partially offset by increasing licensing and royalty revenue.

Our operating expenses, excluding non-cash compensation expense related to equity awards, increased in the first half 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 decreased due to savings we realized from integrating Akcea and restructuring our commercial operations for TEGSEDI and WAYLIVRA. We are redeploying these savings to advance our pipeline and go-to-market activities for eplontersen, donidalorsen and olezarsen. 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 wholly owned pipeline, invest in expanding and diversifying our technology and advance our go-to-market activities.

As of June 30, 2022, we had $2.0 billion in cash and short-term investments and remain well capitalized with the resources we need to continue investing to drive future growth.

Eplontersen Collaboration with AstraZeneca

Our financial results for the six months ended June 30, 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. Because 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, net of our share of AstraZeneca's development expenses, in the same period we incur the related development expenses. From inception through June 2022, we have earned $37 million in joint development revenue under this collaboration.

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 six months ended June 30, 2022, we recognized $0.8 million and $0.7 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 for the six months ended June 30, 2022 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)	$37M	55% of Ionis' Phase 3 development expenses, including internal+external costs & CMC costs, net of our share of AstraZeneca's Phase 3 development expenses
	Development Expenses (R&D expenses)	$71M	100% of Ionis' Phase 3 development expenses

Recent Business Updates

Second Quarter 2022 Marketed Products Highlights

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

- $431 million in worldwide SPINRAZA sales in the second quarter
- Biogen reported new results from the RESPOND study of SPINRAZA, stating the results indicate there are residual unmet clinical needs in infants and toddlers with SMA who were previously treated with gene therapy
- Biogen reported final data from Part A of the ongoing, three-part DEVOTE study demonstrating that a higher dosing regimen of SPINRAZA leads to higher levels of the drug in the cerebrospinal fluid and is generally well-tolerated

TEGSEDI® and WAYLIVRA®: important medicines approved for the treatment of patients with ATTRv-PN and FCS, respectively

- Continued to expand into new markets in Europe and Latin America through Sobi and PTC, respectively

Second Quarter 2022 and Recent Events

Advancing our next two potential marketed products to the market

- Reported eplontersen met the co-primary and key secondary endpoints in the interim analysis of the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN; on-track to file the NDA with the FDA in the second half of this year
- Biogen reported longer-term data from the Phase 3 VALOR study and ongoing open-label extension study of tofersen showing clinical benefit in patients with SOD1-ALS at the European Network to Cure ALS meeting
- Biogen reported that an NDA for tofersen was accepted and granted priority review by the FDA with a PDUFA action date of January 25, 2023

Advancing our late-stage pipeline

- Novartis achieved full enrollment in the Phase 3 Lp(a)HORIZON cardiovascular outcomes study of pelacarsen in patients with established cardiovascular disease and elevated Lp(a) with data expected in 2025
- Achieved full enrollment in the Phase 3 BALANCE study of olezarsen in patients with FCS with data expected in 2023

Advancing our mid-stage pipeline

- GSK presented positive data from the Phase 2b B-Clear study of bepirovirsen in patients with chronic hepatitis B at the European Association for the Study of the Liver's International Liver Congress™. Based on these results, GSK plans to advance bepirovirsen into a Phase 3 monotherapy study in the first half of 2023
- Roche reported positive data from the Phase 2 study of IONIS-FB-L_{Rx} in patients with IgAN. Based on these results, Roche licensed IONIS-FB-L_{Rx} and plans to advance the medicine into a Phase 3 study
- Bayer reported fesomersen met the primary endpoint in Phase 2b RE-THINc ESRD study in patients with end-stage renal disease. Fesomersen also demonstrated substantial and statistically significant reductions in Factor XI activity levels
- Achieved full enrollment in the Phase 2b study of IONIS-AGT-L_{Rx} in patients with treatment-resistant hypertension, with data expected in the second half of 2022
- Initiated a Phase 2 study of ION904, a follow-on medicine to IONIS-AGT-L_{Rx} in patients with treatment-resistant hypertension targeting AGT
- Granted orphan drug designation and rare pediatric disease designation by the FDA for ION582 for the treatment of patients with Angelman syndrome

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 revenues for the three and six months ended June 30, 2022 were $133.8 million and $275.7 million, respectively, compared to $125.8 million and $237.4 million for the same periods in 2021 and were comprised of the following (amounts in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 59.6	$ 72.2	$ 113.4	$ 132.2
TEGSEDI and WAYLIVRA revenue, net	10.4	11.5	16.6	31.4
Licensing and other royalty revenue	8.2	2.2	20.5	6.7
Total commercial revenue	78.2	85.9	150.5	170.3
R&D revenue:				
Amortization from upfront payments	18.4	20.0	35.8	40.1
Milestone payments	17.7	14.9	44.9	20.1
License fees	—	—	2.0	—
Other services	2.1	5.0	5.3	6.9
Collaborative agreement revenue	38.2	39.9	88.0	67.1
Eplontersen joint development revenue	17.4	—	37.2	—
Total R&D revenue	55.6	39.9	125.2	67.1
Total revenue	$ 133.8	$ 125.8	$ 275.7	$ 237.4

Our revenue in the first half of 2022 increased more than 15 percent compared to the same period last year. The increase was driven by significant partner payments we earned across multiple partnered programs, including $57 million from Biogen for advancing several neurology disease programs, $37 million from AstraZeneca for its share of the global Phase 3 development costs for eplontersen and $22 million from Roche for advancing IONIS-FB-L_{Rx}. Already in the third quarter of 2022, we earned $44 million in a license fee and milestone payment from Roche and Biogen, respectively.

Our commercial revenue in the first half of 2022 decreased compared to the same period last year. SPINRAZA royalties decreased in the first half of 2022 primarily due to competition outside of the U.S. In the U.S., SPINRAZA sales stabilized in the first half of 2022 compared to the same period last year, increasing 2 percent. 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 half 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. These decreases were partially offset by increasing licensing and royalty revenue.

Operating Expenses

Our operating expenses were as follows (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 194.8	$ 153.7	$ 367.9	$ 312.6
Restructuring expenses	—	15.0	—	21.8
Total operating expenses, excluding non-cash compensation expense related to equity awards	194.8	168.7	367.9	334.4
Non-cash compensation expense related to equity awards	24.5	30.0	50.8	67.9
Total operating expenses	$ 219.3	$ 198.7	$ 418.7	$ 402.3

Our operating expenses, excluding non-cash compensation expense related to equity awards, increased in the first half 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 decreased due to savings we realized from integrating Akcea and restructuring our commercial operations for TEGSEDI and WAYLIVRA. We are redeploying these savings to advance our pipeline and go-to-market activities for eplontersen, donidalorsen and olezarsen. 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 wholly owned pipeline, invest in expanding and diversifying our technology and advance our go-to-market activities.

Our non-cash compensation expense related to equity awards decreased in the first half of 2022 compared to the same period in 2021 due to decreased headcount as a result of the Akcea Merger and restructuring our commercial operations for TEGSEDI and WAYLIVRA.

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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 4.6	$ 3.0	$ 8.6	$ 5.3
Non-cash compensation expense related to equity awards	0.1	—	0.3	0.2
Total cost of sales	$ 4.7	$ 3.0	$ 8.9	$ 5.5

Our cost of sales, excluding non-cash compensation expense related to equity awards, increased insignificantly during the six months ended June 30, 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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 162.3	$ 112.9	$ 304.3	$ 224.2
Restructuring expenses	—	3.7	—	6.3
Total research, development and patent expenses, excluding non-cash compensation expense related to equity awards	162.3	116.6	304.3	230.5
Non-cash compensation expense related to equity awards	18.5	22.7	37.6	48.6
Total research, development and patent expenses	$ 180.8	$ 139.3	$ 341.9	$ 279.1

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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 24.5	$ 23.2	$ 43.6	$ 49.8
Non-cash compensation expense related to equity awards	4.5	5.3	8.6	11.6
Total antisense drug discovery expenses	$ 29.0	$ 28.5	$ 52.2	$ 61.4

Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards, decreased in the six months ended June 30, 2022 compared to the same period in 2021. In the first quarter of 2021, we incurred a certain non-recurring in-licensing expense, which resulted in higher antisense drug discovery expenses in the six months ended June 30, 2021. We expect antisense drug discovery expenses to increase in the second half 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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
TEGSEDI and WAYLIVRA	$ 3.4	$ —	$ 5.5	$ 1.4
Eplontersen	24.3	15.9	51.3	29.2
Olezarsen	12.7	4.1	21.4	5.5
Donidalorsen	1.9	0.8	3.6	2.6
ION363	1.8	1.6	3.5	3.7
Other antisense development projects	30.6	25.0	60.1	45.8
Development overhead expenses	21.5	18.2	40.8	36.5
Restructuring expenses	—	3.4	—	5.7
Total antisense drug development, excluding non-cash compensation expense related to equity awards	96.2	69.0	186.2	130.4
Non-cash compensation expense related to equity awards	7.0	9.5	15.6	21.6
Total antisense drug development expenses	$ 103.2	$ 78.5	$ 201.8	$ 152.0

Our development expenses, excluding non-cash compensation expense related to equity awards, increased for the six months ended June 30, 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. 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.

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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 4.8	$ 3.5	$ 7.6	$ 6.4
Non-cash compensation expense related to equity awards	0.4	0.3	0.7	0.6
Total medical affairs expenses	$ 5.2	$ 3.8	$ 8.3	$ 7.0

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, increased slightly in the six months ended June 30, 2022 compared to the same period in 2021. We expect medical affairs expenses to continue increasing 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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 23.1	$ 8.6	$ 39.4	$ 20.4
Restructuring expenses	—	0.3	—	0.6
Total manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	23.1	8.9	39.4	21.0
Non-cash compensation expense related to equity awards	2.6	3.1	5.3	6.2
Total manufacturing and development chemistry expenses	$ 25.7	$ 12.0	$ 44.7	$ 27.2

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, increased in the six months ended June 30, 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, olezarsen 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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Personnel costs	$ 5.0	$ 4.2	$ 10.1	$ 8.5
Occupancy	4.2	3.2	8.2	6.4
Patent expenses	1.5	1.3	2.2	2.1
Insurance	0.9	0.8	1.8	1.6
Computer software and licenses	0.4	0.6	1.0	1.1
Other	1.7	1.9	4.2	3.2
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	13.7	12.0	27.5	22.9
Non-cash compensation expense related to equity awards	4.0	4.5	7.4	8.6
Total R&D support expenses	$ 17.7	$ 16.5	$ 34.9	$ 31.5

R&D support expenses, excluding non-cash compensation expense related to equity awards, for the six months ended June 30, 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 June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 27.9	$ 37.8	$ 55.0	$ 83.1
Restructuring expenses	—	11.4	—	15.5
Total selling, general and administrative expenses, excluding non-cash compensation related to equity awards	27.9	49.2	55.0	98.6
Non-cash compensation expense related to equity awards	5.9	7.3	12.9	19.1
Total selling, general and administrative expenses	$ 33.8	$ 56.5	$ 67.9	$ 117.7

SG&A expenses, excluding non-cash compensation expense related to equity awards, for the six months ended June 30, 2022 decreased compared to the same period in 2021 due to operating efficiencies achieved from the Akcea Merger and restructuring our commercial operations for TEGSEDI and WAYLIVRA, partially offset by increased expenses for 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 and six months ended June 30, 2022 were $3.4 million and $5.4 million, respectively, compared to $2.7 million and $7.4 million for the same periods in 2021. Our investment income decreased for the six months ended June 30, 2022 because we earned a lower average return on our investments due to market conditions during the six months ended June 30, 2022 compared to the same period in 2021.

Interest Expense

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Convertible notes:				
Non-cash amortization of debt issuance costs	$ 1.3	$ 1.4	$ 2.7	$ 2.2
Interest expense payable in cash	0.2	0.4	0.3	1.4
Interest on mortgages for primary R&D and manufacturing facilities	0.6	0.6	1.3	1.2
Total interest expense	$ 2.1	$ 2.4	$ 4.3	$ 4.8

Gain (Loss) on Investments

We recorded a loss on investments of $13.0 million for the six months ended June 30, 2022 compared to a gain on investments of $0.9 million for the same period in 2021. During the six months ended June 30, 2022, we revalued our investments in publicly held biotechnology companies and recognized losses of $13.5 million on our investments. During the six months ended June 30, 2021, we revalued our investments in publicly held biotechnology companies and recognized a gain of $1.2 million, partially offset by losses recognized on our debt securities investments.

Other Expense

In July 2022, we entered into a settlement agreement for a litigation claim that we determined to be probable and estimable as of June 30, 2022. As a result, we recorded a non-operating expense of $12.5 million in the three and six months ended June 30, 2022. In July 2022, we entered into a settlement agreement with our insurance carrier wherein the insurance carrier agreed to contribute to the litigation settlement in the amount of $4.5 million. We will record the insurance contribution in the third quarter of 2022. Refer to Note 8, *Legal Proceedings*, for further details regarding the litigation.

In April 2021, as a result of a debt offering and debt repurchase, we recorded an $8.6 million loss on early retirement of debt, reflecting the early retirement of a portion of our 1% Notes, in the three and six months ended June 30, 2021. The loss on the early retirement of our debt is the difference between the amount we paid to retire our 1% Notes and the net carrying balance of the liability at the time that we retired the debt.

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 income tax expense of $2.3 million and $3.4 million for the three and six months ended June 30, 2022, respectively, compared to income tax expense of $0.3 million and $0.5 million for the same periods in 2021.

Net Loss and Net Loss per Share

We had a net loss of $105.1 million and $170.3 million for the three and six months ended June 30, 2022, respectively. We had a net loss of $80.9 million and $170.7 million for the same periods in 2021. Our net loss increased for the six months ended June 30, 2022 compared to the same period in 2021 primarily due to increased revenue, partially offset by increased expenses year-over-year, as discussed in the revenue and expense sections, respectively. Basic and diluted net loss per share for the three and six months ended June 30, 2022 were $0.74 and $1.20, respectively, compared to $0.57 and $1.21 for the same periods in 2021.

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 June 30, 2022, we have earned approximately $6.1 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through June 30, 2022, we have raised net proceeds of approximately $2.0 billion from the sale of our equity securities. Additionally, from our inception through June 30, 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 June 30, 2022.

The following table summarizes our contractual obligations as of June 30, 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	**Payments Due by Period (in millions)**		
(selected balances described below)	**Total**	**Less than 1 year**	**More than 1 year**
0% Notes (principal payable)	$ 632.5	$ —	$ 632.5
0.125% Notes (principal and interest payable)	550.6	0.7	549.9
Building mortgage payments (principal and interest payable)	72.2	3.3	68.9
Operating leases	26.6	4.3	22.3
Other obligations (principal and interest payable)	0.8	0.1	0.7
Total	$ 1,282.7	$ 8.4	$ 1,274.3

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 June 30, 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 June 30, 2022. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 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 we consider the potential loss from any legal proceeding to be probable and we can reasonably estimate the amount, we accrue a liability for the estimated loss. The outcome of any proceeding is not determinable in advance. Therefore, we are required to use significant judgment to determine the probability of a loss and whether the amount of the loss is reasonably estimable. Our assessment of a potential liability and the amount of accruals we 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 Ionis and Akcea entered into, in which Akcea became a wholly-owned subsidiary of Ionis. Ionis believes this lawsuit is without merit. However, the outcome of this lawsuit or any other lawsuit that may be filed challenging the October 2020 take-private transaction is uncertain. Accordingly, on June 3, 2022, the parties reached an agreement in principle to settle the Delaware Action for $12.5 million, subject to the approval of the Delaware Court of Chancery. A Stipulation and Agreement of Compromise, Settlement and Release relating to this matter (the "Stipulation and Settlement Agreement") has been executed and filed with the Delaware Court of Chancery, where it awaits Court approval. The terms of the Stipulation and Settlement Agreement include no finding of wrongdoing on the part of any of the Defendants. A hearing on the Stipulation and Settlement Agreement is scheduled for October 11, 2022.

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 "Shumacher Action." The complaint names the Board as defendants and names Ionis as a nominal defendant. The Shumacher Action Plaintiff asserts a breach of fiduciary duty claim against the Board for awarding and receiving allegedly excessive compensation. The Shumacher Action Plaintiff also asserts an unjust enrichment claim against the non-executive 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. On March 18, 2022, Ionis and the Board moved to dismiss the complaint. On May 24, 2022, the parties entered into a Stipulation and Agreement of Compromise, Settlement and Release. On July 18, 2022, Ionis filed a Form 8-K disclosing the pending settlement and attaching the Notice of Pendency of Settlement of Action. The Court has scheduled a hearing for September 21, 2022, to consider whether the terms of the settlement should be approved. We and our Board have denied, and continue to deny, any and all allegations of wrongdoing or liability asserted in the Shumacher Action.

On May 25, 2022, another purported stockholder of Ionis filed a stockholder derivative complaint also in the Delaware Court of Chancery captioned Robert S. Cohen, et al. v. Joseph Loscalzo, et al., C.A. No. 2022-0453, or the "Cohen Action." The complaint names the Board as defendants and names Ionis as a nominal defendant. The Cohen Action Plaintiff asserts claims for breach of fiduciary duty, unjust enrichment, aiding and abetting breaches of fiduciary duty, and waste against the Board for awarding and receiving allegedly excessive non-executive director compensation for the years 2018, 2019, and 2020. On June 2, 2022, the Cohen Action Plaintiff filed a motion to consolidate the related Cohen Action and Shumacher Action. On July 5, 2022, the Court denied the motion to consolidate in favor of the settlement pending in the Shumacher Action. We and our Board have denied, and continue to deny, any and all allegations of wrongdoing or liability asserted in the Cohen Action.

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 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 believe 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 competitors in the U.S. market for TEGSEDI are patisiran and vutrisiran, both marketed by Alnylam Pharmaceuticals, Inc. Neither patisiran nor vutrisiran has a boxed warning nor does either require use of a REMS program. Additionally, the product label for WAYLIVRA in the European Union, or 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, tafamidis meglumine and vutrisiran compete with TEGSEDI and could compete with eplontersen;
- 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 and to ION582 for the treatment of patients with Angelman syndrome. 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 June 30, 2022, we had an accumulated deficit of approximately $1.3 billion and stockholders' equity of approximately $0.6 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 June 30, 2022, we had cash, cash equivalents and short-term investments equal to $2.0 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 us, providing strategic advice and continuing to participate in our 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 June 30, 2022, the market price of our common stock ranged from $44.42 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	First Amendment dated July 8, 2022 to Factor B Development, Collaboration, Option and License Agreement by and between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated October 9, 2018. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended June 30, 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)	August 9, 2022
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	August 9, 2022

CONFIDENTIAL

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

FIRST AMENDMENT TO FACTOR B DEVOLOPMENT, COLLABORATION, OPTION AND LICENSE AGREEMENT

This FIRST AMENDMENT TO FACTOR B DEVELOPMENT, COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Amendment***") is entered into as of the 8th day of July, 2022 (the "***Amendment Effective Date***") by and among **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("***Ionis***"), and **F. HOFFMANN-LA ROCHE LTD**, a Swiss corporation, having its principal place of business at Grenzacherstrasse 124, 4070 Basel, Switzerland ("***Roche Basel***") and **HOFFMANN-LA ROCHE INC.**, a New Jersey corporation, having its principal place of business at 150 Clove Road, Suite 8, Little Falls, New Jersey 07424 ("***Roche US***"; Roche Basel and Roche US are collectively referred to as "***Roche***"). Roche and Ionis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." All capitalized terms used in this Amendment but not otherwise defined herein will have the meaning set forth in the Agreement (as defined below).

RECITALS

WHEREAS, Ionis and Roche entered into the Factor B Development, Collaboration, Option and License Agreement on October 9, 2018 (the "***Agreement***");

WHEREAS, the Parties now wish to amend certain provisions of the Agreement as set forth herein;

NOW, THEREFORE, in consideration of the foregoing and the agreements set forth herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

1. **ARTICLE 2 is deleted in its entirety and replaced with new ARTICLE 2 as follows**:

"The intent of the Collaboration is for the Parties to develop IONIS-FB-L_{Rx} (i) for the treatment of immunoglobulin A nephropathy ("***IgA Nephropathy***"), and (ii) potentially for the treatment of geographic atrophy ("***GA***"). Ionis will Develop IONIS-FB-L_{Rx} through Completion of the Proposed Phase 2 Trials. Roche will have an Option to obtain an exclusive license to further Develop, Manufacture, and Commercialize IONIS-FB-L_{Rx}. Subject to Section 6.2, the Option will be deemed exercised on the Amendment Effective Date. From and after the Amendment Effective Date, Roche will be responsible for all further Development, Manufacturing and Commercializing activities related to the Products, except for the Phase 2 GA Trial and the Phase 2 IgA Nephropathy Trial being conducted by Ionis under the Development Plan. Ionis will remain responsible for conducting the Phase 2 GA Trial and the Phase 2 IgA Nephropathy Trial and will be responsible for the costs and risks associated therewith, until Completion of such Phase 2 GA Trial and the Phase 2 IgA Nephropathy Trial. The Parties will discuss in good faith and agree to the strategy and execution of the Phase 2 IgA Nephropathy Trial. The purpose of this ARTICLE 2 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the Development and Commercialization of the Products, and therefore this ARTICLE 2 is qualified in its entirety by the more detailed provisions of this Agreement set forth below."

2. **Section 3.1.7 is added as follows:**

"Until the Phase 2 IgA Nephropathy Trial is Completed or terminated, Roche will reimburse Ionis [***] for the [***]."

3. **Section 6.1 is deleted in its entirety and replaced with new Section 6.1 as follows:**

"**Option**. Ionis hereby grants Roche an exclusive option to obtain the license set forth in Section 7.1.1 (the "***Option***"), which Option is deemed exercised by Roche on the Amendment Effective Date."

4. **Section 6.2 is deleted in its entirety and replaced with new Section 6.2 as follows:**

"**Option Exercise; Option Expiration**. If, within [***] after Roche's receipt of an invoice from Ionis for the license fee set forth in Section 9.3 (the "***License Fee Payment Deadline***"), Roche pays Ionis the license fee set forth in Section 9.3, Ionis hereby grants to Roche the license set forth in Section 7.1.1. If by the License Fee Payment Deadline Roche fails to timely pay Ionis the license fee set forth in Section 9.3 and does not cure this failure within [***] after receiving notice of such failure from Ionis, then Roche's Option will be deemed expired. If Roche's Option expires, then the Agreement shall expire and Section 13.4.1 and Section 13.4.2 will apply."

5. **Section 8.1 (the first paragraph, i.e. excluding subsections 8.1.1 through 8.1.7) is deleted in its entirety and replaced with new Section 8.1 as follows**:

"**Roche Diligence**. After Option exercise, subject to the terms of this Agreement, Roche is solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of the Products, except with respect to any Phase 2 Trial being conducted by Ionis under the Development Plan that has not yet Completed by the time of Option exercise, which will remain the responsibility of Ionis until such Phase 2 Trial has Completed; *provided* that the Parties will discuss in good faith a possible strategy that utilizes [***]. Roche will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize Products in [***], including to meet the timelines and milestones set forth in the Development Plan, the IDCP and the Specific Performance Milestone Events. If IONIS-FB-L_{Rx} meets the primary efficacy endpoint in the Phase 2 GA Trial with no unexpected safety findings and [***], then the Parties will [***]."

6. **Section 8.1.3 is deleted in its entirety and replaced with new Section 8.1.3 as follows:**

"**Investigator's Brochure**. Ionis will provide updated versions of the investigator's brochure to Roche Annually and upon any substantive change to the safety or risk of the Products until the Completion or termination, as applicable, of the Proposed Phase 2 Trials. From and after the Completion or termination, as applicable, of the Proposed Phase 2 Trials, and in addition to the IDCP, Roche will keep Ionis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions of the investigator's brochure to Ionis Annually and upon any substantive change to the safety or risk of the Products."

7. **Section 9.3 is deleted in its entirety and replaced with new Section 9.3 as follows**:

"**License Fee**. Pursuant to Section 6.2, within thirty (30) days after receipt by Roche of an invoice therefor from Ionis, Roche will pay to Ionis a license fee of [***] within the timelines set forth in Section 6.2."

8. **Section 9.4 is deleted in its entirety and replaced with new Section 9.4 as follows**:

"**Milestone Payments for Achievement of Post-Licensing Milestone Events**. As further consideration for the licenses granted herein, Roche will pay to Ionis the applicable one-time milestone payments set forth in TABLE 1 below (each, a "***Post-Licensing Milestone Payment***") when the corresponding milestone event listed in TABLE 1 (each, a "***Post-Licensing Milestone Event***") is first achieved by a Product for the specified Indication:

TABLE 1

Post-Licensing Milestone Event	Post-Licensing Milestone Payment – GA*	Post-Licensing Milestone Payment – IgA Nephropathy	Post-Licensing Milestone Payment – First Additional Indication
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

* Post-Licensing Milestone Payments for GA in this TABLE 1 are payable for Post-Licensing Milestone Events with respect to GA; however, if [***], then Roche shall [***]. If, however, [***], then upon the [***] in GA, Roche shall pay to Ionis [***] for the [***] Post-Licensing Milestone Payment in GA, and, for clarity, in case such scenario occurs, Post-Licensing Milestone Payments are due only to the extent not previously paid for the second column of TABLE 1 (i.e. for GA). If [***], then such Indication shall be treated as an Additional Indication and the [***] will be payable as set forth in TABLE 1 to the extent not previously paid for a [***].

9. **Section 9.6.3 is deleted in its entirety and replaced with new Section 9.6.3 as follows:**

"If a particular Milestone Event is achieved contemporaneously with or in connection with another Milestone Event, then both Milestone Events will be deemed achieved and the milestone payments for both Milestone Events will be due. If [***] for GA is achieved before [***] for IgA Nephropathy has been achieved, then both the [***] for GA and the [***] Post-Licensing Milestone Payments will be due. If, however, [***] for IgA Nephropathy is achieved before [***] for GA is achieved, then the [***] Post-Licensing Milestone Payment will be due, and the [***] Post-Licensing Milestone Payment for GA will not be due until the [***] for GA is achieved."

10. **Section 13.1.3 is deleted in its entirety and replaced with new Section 13.1.3 as follows:**

"where Roche has not paid the license fee set forth in Section 9.3 by the License Fee Payment Deadline or the [***] cure period thereafter."

11. **Section 14.4.5 is deleted in its entirety and replaced with new Section 14.4.5 as follows:**

"**After Option Exercise**. After Option exercise, Ionis will have the right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding the Proposed Phase 2 Trials to the public; *provided*, that with respect to any proposed press release or other similar public communication by Ionis regarding the Proposed Phase 2 Trials, (i) Ionis will submit such proposed communication to Roche for review at least ten (10) Business Days in advance of such proposed public disclosure, unless such proposed public disclosure is with respect to a matter for which, in the opinion of Ionis' legal counsel, Ionis has a disclosure requirement under applicable law, regulations or rules, in which case Ionis will submit such proposed communication to Roche for review as soon as reasonably practicable, but in no event less than two (2) Business Days in advance of such proposed public disclosure, (ii) Roche will have the right to review and request changes to such communication, and (iii) Ionis will incorporate any reasonable changes that are timely requested by Roche. With respect to all other press releases, publications, presentations or other disclosures regarding the progress and results of IONIS-FB-L_{Rx} to the public, Roche will have the sole right after Option exercise, consistent with its practice with its other compounds and products, to issue such press releases, publications, presentations or other disclosures regarding the progress and results of IONIS-FB-L_{Rx}; *provided*, that with respect to any such proposed press release or other similar public communication by Roche disclosing regulatory discussions, the efficacy or safety data or results related to the Products or Roche's sales projections, (i) Roche will submit such proposed communication to Ionis for review at least two (2) Business Days in advance of such proposed public disclosure, (ii) Ionis will have the right to review and recommend changes to such communication, and (iii) Roche will in good faith consider any changes that are timely recommended by Ionis."

12. **Section 15.1.1 is deleted in its entirety and replaced with new Section 15.1.1 as follows:**

"**Escalation**. If any dispute occurs under this Agreement (other than a dispute regarding the construction, validity or enforcement of either Party's Patents, which disputes will be resolved pursuant to Section 15.2), either Party may request in writing that the dispute be referred for resolution to the Head of Roche Partnering of Roche and the Chief Business Officer of Ionis (the "***Executives***"), or their delegates. Within thirty (30) days after such a request, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of the dispute. Each Party's JSC representatives may participate in such meeting if desired. If the Executives fail to resolve the dispute within such thirty (30)-day period, then, except as set forth in Section 4.1.1(b)(ii), the dispute will be referred to binding arbitration under Section 15.1.2."

13. **In APPENDIX 1, the definition of "*Full Enrollment*" is added as follows:**

"'[***]' means [***]."

14. **In APPENDIX 1, the definition of "*Option Period*" is deleted in its entirety.**

15. **In APPENDIX 1, the definition of "*Option Deadline*" is deleted in its entirety.**

16. **In APPENDIX 1, the following definition is added:**

"'***License Fee Payment Deadline***' has the meaning set forth in Section 6.2."

17. **In APPENDIX 1, the definition of "*Second Indication*" is deleted in its entirety.**

18. **In APPENDIX 1, the definition of "*Successful Futility Analysis*" is added as follows:**

"'[***]' means [***]."

19. **In APPENDIX 1, the definition of "*Additional Indication*" is added as follows:**

"'***Additional Indication***' means (i) any Indication other than (y) GA or (z) IgA Nephropathy, or (ii) [***]."

20. **In APPENDIX 2, [***] are deleted.**

21. This Amendment and any dispute arising from the performance or breach hereof will be governed by and construed and enforced in accordance with the laws of the State of California, U.S., without reference to conflicts of laws principles.

22. The Parties agree that all terms of the Agreement not specifically modified by this Amendment will remain in full force and effect.

23. The Parties have agreed to Ionis issuing the press release attached to this Amendment.

24. This Amendment may be signed in counterparts, each and every one of which will be deemed an original, notwithstanding variations in format or file designation that may result from the electronic transmission, storage and printing of copies from separate computers or printers. Facsimile signatures and signatures transmitted via PDF will be treated as original signatures.

25. Headings in this Amendment are for reference only and do not affect the interpretation of this Amendment.

[*SIGNATURE PAGES FOLLOW*]

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their representatives thereunto duly authorized as of the Amendment Effective Date.

F. HOFFMANN-LA ROCHE LTD

By:/s/James Sabry

Name: James Sabry

Title: Global Head, Pharma Partnering

By:/s/Barbara Schroeder de Castro Lopes

Name: Barbara Schroeder de Castro Lopes

Title: Authorized Signatory

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their representatives thereunto duly authorized as of the Amendment Effective Date.

HOFFMANN-LA ROCHE INC.

By: /s/ John Parise

Name: John Parise

Title: Authorized Signatory

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their representatives thereunto duly authorized as of the Amendment Effective Date.

IONIS PHARMACEUTICALS, INC.

By:/s/Brett P. Monia

Name: Brett P. Monia

Title: Chief Executive Officer

Press Release

Ionis partner licenses rare kidney disease treatment and will advance into Phase 3 clinical study

- *Positive data from a Phase 2 study of IONIS-FB-L_{Rx} support further development for treatment of patients with IgA nephropathy*

CARLSBAD, Calif., July 11, 2022 – Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), today announced that its long-standing partner, Roche, will license and advance IONIS-FB-L_{Rx}, an investigational antisense medicine, into a Phase 3 clinical study in patients with immunoglobulin A nephropathy (IgAN). IgAN is a rare and serious condition that often leads to chronic kidney disease and renal failure. Roche's decision to advance the program comes after positive data from a Phase 2 clinical study in which IONIS-FB-L_{Rx} met its primary endpoint of change in 24-hour urinary protein at 29 weeks compared to baseline.

In the Phase 2 study, IONIS-FB-L_{Rx} (NCT04014335) demonstrated a favorable safety and tolerability profile. The study data are consistent with the clinical profile seen across Ionis' other LICA programs, further validating how advancements in the company's **LI**gand-**C**onjugated **A**ntisense technology platform position Ionis to deliver potentially transformative treatments for a range of unmet medical needs. Data from the Phase 2 study of IONIS-FB-L_{Rx} in patients with IgAN has been submitted for presentation at an upcoming medical meeting.

IgAN occurs when too much IgA protein accumulates in the kidneys, causing inflammation and tissue damage, which is the root cause of the disease. IONIS-FB-L_{Rx} was designed by Ionis to reduce the production of complement factor B (FB), which is associated with the development of several complement-mediated diseases, including IgAN.

"Roche's decision to advance the program reaffirms our shared confidence in the ability of Ionis' antisense medicines to effectively target the root cause of difficult to treat diseases like immunoglobulin A nephropathy," said Michael McCaleb, Ph.D., vice president, clinical development at Ionis. "The results of the Phase 2 study provide initial clinical evidence that IONIS-FB-L_{Rx} reduces complement and protein levels in the urine of patients with IgAN."

Roche will lead and be responsible for the Phase 3 study of IONIS-FB-L_{Rx} in patients with IgAN and for future global development, regulatory and commercialization activities.

IONIS-FB-L_{Rx} is also being evaluated in GOLDEN (NCT03815825), a Phase 2 clinical study to determine whether the medicine can slow or halt the progression of geographic atrophy due to age-related macular degeneration, or AMD. Ionis will receive $55 million from Roche for licensing IONIS-FB-L_{Rx} for IgAN and achieving a development milestone in the GOLDEN study.

About IgA Nephropathy (IgAN)

Immunoglobulin A nephropathy (IgAN) is an important cause of chronic kidney disease and renal failure. Also known as Berger's disease, IgAN is characterized by deposition of IgA and Complement 3 (C3) activation products in the glomerular mesangium of the kidneys, resulting in inflammation and tissue damage. Although IgAN may occur at any age, it generally presents in the second or third decade of life. The clinical presentation, disease progression and histologic findings are highly variable among affected individuals. Current therapies are aimed at reduction of protein levels in the urine with administration of angiotensin inhibitors and control of blood pressure. Sometimes immunosuppressive therapies are given; however, this practice is not universally accepted.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a premier late-stage pipeline highlighted by industry-leading cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming a leading, fully integrated biotechnology company.

To learn more about Ionis, visit www.ionispharma.com and follow us on Twitter @ionispharma.

Ionis' Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of Ionis' technologies, IONIS-FB-L_{Rx} and other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including but not limited to, those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements.

Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended Dec. 31, 2021, and the most recent Form 10-Q quarterly filing, which are on file with the Securities and Exchange Commission. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Ionis Pharmaceuticals® is a trademark of Ionis Pharmaceuticals, Inc.

Ionis Pharmaceuticals Investor Contact:
760-603-2331

Ionis Pharmaceuticals Media Contact:
760-603-4679

EXHIBIT 31.1

CERTIFICATION

I, Brett P. Monia, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 9, 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: August 9, 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 June 30, 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: August 9, 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.