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, 2023

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, 2023 was 143,326,208.

IONIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

TRADEMARKS

"Ionis," the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this report are the property of Ionis Pharmaceuticals, Inc. "Akcea," the Akcea logo, and other trademarks or service marks 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, 2023 (unaudited)	December 31, 2022
ASSETS		
Current assets:		
Cash and cash equivalents	$ 424,790	$ 276,472
Short-term investments	1,960,598	1,710,397
Contracts receivable	27,956	25,538
Inventories	25,538	22,033
Other current assets	177,872	168,254
Total current assets	2,616,754	2,202,694
Property, plant and equipment, net	91,634	74,294
Right-of-use assets	176,718	181,544
Deposits and other assets	86,025	75,344
Total assets	$ 2,971,131	$ 2,533,876
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 24,021	$ 17,921
Accrued compensation	29,322	49,178
Accrued liabilities	104,745	140,101
Income taxes payable	24,732	6,249
Current portion of deferred contract revenue	96,252	90,577
Other current liabilities	8,903	7,535
Total current liabilities	287,975	311,561
Long-term deferred contract revenue	254,398	287,768
1.75 percent convertible senior notes, net	560,937	—
0 percent convertible senior notes, net	623,809	622,242
0.125 percent convertible senior notes, net	114,081	544,504
Liability related to sale of future royalties, net	510,174	—
Long-term lease liabilities	175,020	178,941
Long-term obligations	16,436	15,973
Total liabilities	2,542,830	1,960,989
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 143,167,414 and 142,057,736 shares issued and outstanding at June 30, 2023 (unaudited) and December 31, 2022, respectively	143	142
Additional paid-in capital	2,118,309	2,059,850
Accumulated other comprehensive loss	(50,913)	(57,480)
Accumulated deficit	(1,639,238)	(1,429,625)
Total stockholders' equity	428,301	572,887
Total liabilities and stockholders' equity	$ 2,971,131	$ 2,533,876

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,	
	2023	**2022**	**2023**	**2022**
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 61,012	$ 59,627	$ 111,258	$ 113,444
Other commercial revenue	16,885	18,557	34,406	37,024
Total commercial revenue	77,897	78,184	145,664	150,468
Research and development revenue:				
Collaborative agreement revenue	91,013	38,247	129,347	88,032
Eplontersen joint development revenue	19,501	17,360	43,924	37,210
Total research and development revenue	110,514	55,607	173,271	125,242
Total revenue	188,411	133,791	318,935	275,710
Expenses:				
Cost of sales	2,537	4,745	3,880	8,914
Research, development and patent	229,927	180,758	427,740	341,884
Selling, general and administrative	46,142	33,802	91,658	67,929
Total operating expenses	278,606	219,305	523,278	418,727
Loss from operations	(90,195)	(85,514)	(204,343)	(143,017)
Other income (expense):				
Investment income	20,792	3,403	39,419	5,396
Interest expense	(2,291)	(2,130)	(3,899)	(4,252)
Interest expense related to sale of future royalties	(17,655)	—	(33,170)	—
Gain (loss) on investments	718	(6,337)	189	(12,963)
Other income (expense)	11,183	(12,297)	11,414	(12,110)
Loss before income tax expense	(77,448)	(102,875)	(190,390)	(166,946)
Income tax expense	(7,842)	(2,260)	(19,223)	(3,354)
Net loss	$ (85,290)	$ (105,135)	$ (209,613)	$ (170,300)
Basic and diluted net loss per share	$ (0.60)	$ (0.74)	$ (1.47)	$ (1.20)
Shares used in computing basic and diluted net loss per share	143,098	141,794	142,918	141,697

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,	
	2023	2022	2023	2022
Net loss	$ (85,290)	$ (105,135)	$ (209,613)	$ (170,300)
Unrealized gains (losses) on debt securities, net of tax	(2,000)	(5,018)	6,393	(20,774)
Currency translation adjustment	70	(411)	174	(565)
Comprehensive loss	$ (87,220)	$ (110,564)	$ (203,046)	$ (191,639)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(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, 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
Balance at March 31, 2023	143,023	$ 143	$ 2,089,358	$ (48,983)	$ (1,553,948)	$ 486,570
Net loss	—	—	—	—	(85,290)	(85,290)
Change in unrealized losses, net of tax	—	—	—	(2,000)	—	(2,000)
Foreign currency translation	—	—	—	70	—	70
Issuance of common stock in connection with employee stock plans	144	—	2,390	—	—	2,390
Stock-based compensation expense	—	—	26,561	—	—	26,561
Balance at June 30, 2023	143,167	$ 143	$ 2,118,309	$ (50,913)	$ (1,639,238)	$ 428,301

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 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
Balance at December 31, 2022	142,058	$ 142	$ 2,059,850	$ (57,480)	$ (1,429,625)	$ 572,887
Net loss	—	—	—	—	(209,613)	(209,613)
Change in unrealized gains, net of tax	—	—	—	6,393	—	6,393
Foreign currency translation	—	—	—	174	—	174
Issuance of common stock in connection with employee stock plans	1,109	1	4,949	—	—	4,950
Stock-based compensation expense	—	—	53,510	—	—	53,510
Balance at June 30, 2023	143,167	$ 143	$ 2,118,309	$ (50,913)	$ (1,639,238)	$ 428,301

See accompanying notes.

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

	Six Months Ended June 30,	
	2023	**2022**
Operating activities:		
Net loss	$ (209,613)	$ (170,300)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	5,225	7,484
Amortization of right-of-use operating lease assets	4,826	1,300
Amortization of other assets	1,244	1,197
Amortization of premium (discount) on investments, net	(12,481)	7,867
Amortization of debt issuance costs	2,966	2,688
Non-cash royalty revenue related to sale of royalties	(12,562)	—
Non-cash interest related to sale of future royalties	32,915	—
Stock-based compensation expense	53,510	50,738
Loss (gain) on investments	(301)	54
Gain on early retirement of debt	(11,292)	—
Non-cash losses related to disposal of property, plant and equipment	205	527
Non-cash losses related to other assets	570	951
Changes in operating assets and liabilities:		
Contracts receivable	(2,254)	55,145
Inventories	(3,505)	4,995
Other current and long-term assets	(19,696)	(39)
Income taxes payable	18,483	(22)
Accounts payable	5,517	(2,672)
Accrued compensation	(19,856)	(13,825)
Accrued liabilities and other current liabilities	(37,562)	45,170
Deferred contract revenue	(27,695)	(41,004)
Net cash used in operating activities	(231,356)	(49,746)
Investing activities:		
Purchases of short-term investments	(932,362)	(663,195)
Proceeds from sale of short-term investments	701,034	380,375
Purchases of property, plant and equipment	(22,483)	(6,040)
Acquisition of licenses and other assets, net	(2,314)	(1,993)
Net cash used in investing activities	(256,125)	(290,853)
Financing activities:		
Proceeds from equity, net	4,950	3,462
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	—	(9,572)
Proceeds from issuance of 1.75 percent convertible senior notes	575,000	—
1.75 percent convertible senior notes issuance costs	(13,658)	—
Repurchase of $434.1 million principal amount of 0.125 percent convertible senior notes	(420,158)	—
Proceeds from sale of future royalties	500,000	—
Payments of transaction costs related to sale of future royalties	(10,434)	—
Principal payments on mortgage debt	(75)	—
Net cash provided by (used in) financing activities	635,625	(6,110)
Effects of exchange rates on cash	174	(565)
Net increase (decrease) in cash and cash equivalents	148,318	(347,274)
Cash and cash equivalents at beginning of period	276,472	869,191
Cash and cash equivalents at end of period	$ 424,790	$ 521,917
Supplemental disclosures of cash flow information:		
Interest paid	$ 529	$ 1,544
Income taxes paid	$ 510	$ 2
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 251	$ 1,121

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2023
(Unaudited)

1. Organization and Basis of Presentation

Organization and Business Activity

We incorporated in California on January 10, 1989. In conjunction with our initial public offering, we reorganized as a Delaware corporation in April 1991. We are a leader in the discovery and development of RNA-targeted therapeutics.

Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and six months ended June 30, 2023 and 2022 on the same basis as the audited financial statements for the year ended December 31, 2022. 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, 2022 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In our condensed consolidated financial statements, we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our wholly owned subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries (“we”, “us” or “our”).

We 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.

Use of Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States, or 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.

2. Significant Accounting Policies

Our significant accounting policies have not changed substantially from those included in our Annual Report on Form 10-K for the year ended December 31, 2022, other than as discussed below.

Liability Related to Sale of Future Royalties

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma Investments, or Royalty Pharma, to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our arrangements with Biogen and Novartis, respectively. Refer to Note 11, *Liability Related to Sale of Future Royalties*, for further details on the agreement.

Under our agreement with Royalty Pharma, we record upfront payments and milestone payments we receive from the sale of future royalties as a liability, net of transaction costs. We record royalty payments made to Royalty Pharma as a reduction of the liability and amortize the transaction costs over the estimated life of the royalty stream. We account for the associated interest expense under the effective interest rate method, while continuing to recognize the full amount of royalty revenue in the period in which the counterparty sells the related product and recognizes the related revenue.

We calculate the liability related to the sale of future royalties, effective interest rate and the related interest expense using our current estimate of anticipated future royalty payments under the arrangement, which we periodically reassess based on internal projections and information from our partners who are responsible for commercializing the medicines. If there is a material change in our estimate, we will prospectively adjust the liability related to the sale of future royalties, effective interest rate and the related interest expense.

Recently Adopted Accounting Standards

We do not expect any recently issued accounting standards to have a material impact to our financial results.

3. Supplemental Financial Data

Inventories

Our inventory consisted of the following (in thousands):

	June 30, 2023	December 31, 2022
Raw materials:		
Raw materials - clinical	$ 17,665	$ 17,061
Raw materials - commercial	5,585	2,699
Total raw materials	23,250	19,760
Work in process	2,092	2,109
Finished goods	196	164
Total inventory	$ 25,538	$ 22,033

Accrued Liabilities

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

	June 30, 2023	December 31, 2022
Clinical development expenses	$ 83,524	$ 116,460
In-licensing expenses	7,179	7,945
Commercial expenses	3,151	3,498
Other miscellaneous expenses	10,891	12,198
Total accrued liabilities	$ 104,745	$ 140,101

4. Revenues

During the three and six months ended June 30, 2023 and 2022, our revenues were comprised of the following (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 61,012	$ 59,627	$ 111,258	$ 113,444
Other commercial revenue:				
TEGSEDI and WAYLIVRA revenue, net	10,655	10,386	17,133	16,547
Licensing and other royalty revenue	6,230	8,171	17,273	20,477
Total other commercial revenue	16,885	18,557	34,406	37,024
Total commercial revenue	77,897	78,184	145,664	150,468
Research and development revenue:				
Collaborative agreement revenue	91,013	38,247	129,347	88,032
Eplontersen joint development revenue	19,501	17,360	43,924	37,210
Total research and development revenue	110,514	55,607	173,271	125,242
Total revenue	$ 188,411	$ 133,791	$ 318,935	$ 275,710

Refer to Note 5, *Collaborative Arrangements and Licensing Agreements*, for further details on our collaborative agreement revenue.

5. Collaborative Arrangements and Licensing Agreements

Below, we have included our AstraZeneca, Biogen and GSK collaborations, which are our only collaborations with substantive changes during 2023 from those included in Part IV, Item 15, Note 7, *Collaborative Arrangements and Licensing Agreements*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022.

AstraZeneca

We have two collaborations with AstraZeneca, one focused on the joint development and commercialization of eplontersen for the treatment of transthyretin amyloidosis, or ATTR, and one focused on the treatment of cardiovascular, renal and metabolic diseases. From inception through June 30, 2023, we have received nearly $610 million from these collaborations.

We are jointly developing and preparing to commercialize eplontersen with AstraZeneca in the U.S. In addition, we granted AstraZeneca exclusive rights to commercialize eplontersen outside the U.S. In the second quarter of 2023, we earned a $20 million license fee payment when we licensed rights to Latin America for eplontersen to AstraZeneca. We recognized the upfront payment in full in the second quarter of 2023 because AstraZeneca had full use of the license without any continuing involvement from us. We will achieve the next payment of up to $50 million upon the first regulatory approval under this collaboration.

Under our collaboration for cardiovascular, renal and metabolic diseases, AstraZeneca has licensed multiple medicines from us. AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for each of the medicines it has licensed from us. In the second quarter of 2023, we achieved a $20 million milestone payment when AstraZeneca initiated a Phase 2b study for ION839, an investigational ligand-conjugated antisense, or LICA, medicine designed to inhibit the production of patatin-like phospholipase domain-containing 3, or PNPLA3, protein. We recognized these milestone payments as R&D revenue in full in the second quarter of 2023 because we did not have any remaining performance obligations related to the milestone payments. We will achieve the next payment of up to $30 million if AstraZeneca licenses a medicine under this collaboration.

During the three and six months ended June 30, 2023 and 2022, we earned the following revenue from our relationship with AstraZeneca (in thousands, except percentages):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Revenue from our relationship with AstraZeneca	$ 59,501	$ 17,768	$ 83,926	$ 37,611
Percentage of total revenue	32%	13%	26%	14%

We did not have any deferred revenue from our relationship with AstraZeneca at June 30, 2023 or December 31, 2022.

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. Under our 2013 strategic neurology collaboration, Biogen developed QALSODY (tofersen), our recently approved medicine to treat people with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. Under our collaborations, we and Biogen are currently developing numerous investigational medicines to treat neurodegenerative diseases in addition to SMA and SOD1-ALS, including medicines in development to treat people with amyotrophic lateral sclerosis, or ALS, 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, 2023, we have received more than $3.6 billion in payments from our Biogen collaborations.

In the second quarter of 2023, we earned a $16 million milestone payment from Biogen when the FDA approved Biogen's New Drug Application, or NDA, for QALSODY. We recognized this milestone payment as R&D revenue in full in the second quarter of 2023 because we did not have any remaining performance obligations related to the milestone payment. Under our collaboration agreement with Biogen, we are eligible to receive tiered royalties ranging from 11 percent to 15 percent on sales of QALSODY. Following the NDA approval in April 2023, we began earning royalties from QALSODY sales, which we recognize as other commercial revenue in our condensed consolidated statements of operations. We will achieve the next milestone payment for QALSODY of $20 million if the European Medicines Agency approves Biogen's Marketing Authorization Application filing of QALSODY.

During the three and six months ended June 30, 2023 and 2022, we earned the following revenue from our relationship with Biogen (in thousands, except percentages):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Revenue from our relationship with Biogen	$ 97,402	$ 76,887	$ 167,903	$ 170,754
Percentage of total revenue	52%	58%	53%	62%

Our condensed consolidated balance sheets at June 30, 2023 and December 31, 2022 included deferred revenue of $323.1 million and $351.2 million, respectively, from our relationship with Biogen.

GSK

In March 2010, we entered into a collaboration with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases and some conditions causing blindness. Our collaboration with GSK currently includes bepirovirsen, our medicine in development targeting hepatitis B virus, or HBV. We designed this medicine to reduce the production of viral proteins associated with HBV infection. In the third quarter of 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program. From inception through June 30, 2023, we have received more than $105 million in an upfront payment and payments related to the HBV program.

In the first quarter of 2023, we earned a $15 million milestone payment when GSK initiated a Phase 3 program of bepirovirsen. We recognized this milestone payment as R&D revenue in full in the first quarter of 2023 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of $15 million if the FDA accepts an NDA filing of bepirovirsen for review.

During the three and six months ended June 30, 2023 and 2022, we earned the following revenue from our relationship with GSK (in thousands, except percentages):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Revenue from our relationship with GSK	$ —	$ —	$ 15,000	$ —
Percentage of total revenue	0%	0%	5%	0%

We did not have any deferred revenue from our relationship with GSK at June 30, 2023 or December 31, 2022.

6. 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, 2023 and 2022 by dividing our net loss by our weighted-average number of common shares outstanding during the period.

Diluted net loss per share

For the three and six months ended June 30, 2023 and 2022, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 1.75 percent convertible senior notes, or 1.75% Notes;
- 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.

Additionally, as of June 30, 2023, 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.

7. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of June 30, 2023:

One year or less	77%
After one year but within two years	16%
After two years but within three and a half years	7%
Total	100%

As illustrated above, at June 30, 2023, 93 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 debt securities with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Standard & Poor's, Moody's or Fitch, respectively.

At June 30, 2023, we had an equity ownership interest of less than 20 percent in seven private companies and three public companies with which we conduct business.

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

June 30, 2023	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 605,532	$ 25	$ (4,763)	$ 600,794
Debt securities issued by U.S. government agencies	281,703	4	(1,314)	280,393
Debt securities issued by the U.S. Treasury (1)	622,829	6	(5,031)	617,804
Debt securities issued by states of the U.S. and political subdivisions of the states	42,230	—	(269)	41,961
Total debt securities with a maturity of one year or less	1,552,294	35	(11,377)	1,540,952
Corporate debt securities	220,569	133	(5,135)	215,567
Debt securities issued by U.S. government agencies	39,443	—	(870)	38,573
Debt securities issued by the U.S. Treasury	194,967	—	(3,659)	191,308
Debt securities issued by states of the U.S. and political subdivisions of the states	12,000	66	(235)	11,831
Total debt securities with a maturity of more than one year	466,979	199	(9,899)	457,279
Total available-for-sale debt securities	$ 2,019,273	$ 234	$ (21,276)	$ 1,998,231
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 253	$ (3,928)	$ 8,222
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(5,125)	42,991
Total equity securities	35,012	25,254	(9,053)	51,213
Total available-for-sale debt and equity securities	$ 2,054,285	$ 25,488	$ (30,329)	$ 2,049,444

December 31, 2022	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 513,790	$ 23	$ (4,365)	$ 509,448
Debt securities issued by U.S. government agencies	133,585	—	(1,829)	131,756
Debt securities issued by the U.S. Treasury (1)	512,655	23	(5,124)	507,554
Debt securities issued by states of the U.S. and political subdivisions of the states	57,484	18	(686)	56,816
Other municipal debt securities	6,008	—	(14)	5,994
Total debt securities with a maturity of one year or less	1,223,522	64	(12,018)	1,211,568
Corporate debt securities	227,631	14	(10,143)	217,502
Debt securities issued by U.S. government agencies	34,339	—	(1,040)	33,299
Debt securities issued by the U.S. Treasury	245,030	—	(4,109)	240,921
Debt securities issued by states of the U.S. and political subdivisions of the states	18,314	116	(329)	18,101
Total debt securities with a maturity of more than one year	525,314	130	(15,621)	509,823
Total available-for-sale debt securities	$ 1,748,836	$ 194	$ (27,639)	$ 1,721,391
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ —	$ (1,358)	$ 10,539
Privately held equity securities included in deposits and other assets (3)	23,115	17,257	—	40,372
Total equity securities	35,012	17,257	(1,358)	50,911
Total available-for-sale debt and equity securities	$ 1,783,848	$ 17,451	$ (28,997)	$ 1,772,302

(1) Includes investments classified as cash equivalents in our condensed consolidated balance sheets.

(2) Our publicly traded equity securities are included in other current assets. We recognize publicly traded equity securities at fair value. In the six months ended June 30, 2023, we recognized a $2.3 million unrealized loss in our condensed consolidated statements of operations related to a decrease in the fair value of our investments in publicly traded companies.

(3) Our privately held equity securities are included in deposits and other assets. We recognize our privately held 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, which are Level 3 inputs. In the six months ended June 30, 2023, we recorded a net gain of $2.6 million in our condensed consolidated statements of operations related to changes in the fair value of our investments in privately held companies.

The following is a summary of our investments we consider to be temporarily impaired at June 30, 2023 (in thousands, except for number of investments):

		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	406	$ 512,975	$ (2,381)	$ 238,238	$ (7,517)	$ 751,213	$ (9,898)
Debt securities issued by U.S. government agencies	86	265,446	(1,208)	36,037	(976)	301,483	(2,184)
Debt securities issued by the U.S. Treasury	70	674,046	(6,202)	103,565	(2,488)	777,611	(8,690)
Debt securities issued by states of the U.S. and political subdivisions of the states	130	25,394	(183)	22,593	(321)	47,987	(504)
Total temporarily impaired securities	692	$ 1,477,861	$ (9,974)	$ 400,433	$ (11,302)	$ 1,878,294	$ (21,276)

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 rather than underlying credit deterioration for any of the issuers. We believe it is more likely than not that we will be able to hold our debt securities with declines in value to maturity. Therefore, we intend to hold these securities to maturity and anticipate full recovery of our debt securities' amortized cost basis at maturity.

8. Fair Value Measurements

The following tables present the major security types we held at June 30, 2023 and December 31, 2022 that we regularly measure and carry at fair value. 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 security's fair value (in thousands):

	At June 30, 2023	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 316,359	$ 316,359	$ —
Corporate debt securities (2)	816,361	—	816,361
Debt securities issued by U.S. government agencies (3)	318,966	—	318,966
Debt securities issued by the U.S. Treasury (4)	809,112	809,112	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	53,792	—	53,792
Publicly traded equity securities included in other current assets (5)	8,222	8,222	—
Total	$ 2,322,812	$ 1,133,693	$ 1,189,119

	At December 31, 2022	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 211,655	$ 211,655	$ —
Corporate debt securities (6)	726,950	—	726,950
Debt securities issued by U.S. government agencies (4)	165,055	—	165,055
Debt securities issued by the U.S. Treasury (4)	748,475	748,475	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	74,917	—	74,917
Other municipal debt securities (4)	5,994	—	5,994
Publicly traded equity securities included in other current assets (5)	10,539	10,539	—
Total	$ 1,943,585	$ 970,669	$ 972,916

The following footnotes reference lines in our condensed consolidated balance sheets:

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

(2) $33.7 million was included in cash and cash equivalents, with the difference included in short-term investments, in our condensed consolidated balance sheets.

(3) $4.0 million was included in cash and cash equivalents, with the difference included in short-term investments, in our condensed consolidated balance sheets.

(4) Included in short-term investments in our condensed consolidated balance sheets.

(5) Included in other current assets in our condensed consolidated balance sheets.

(6) $11.0 million was included in cash and cash equivalents, with the difference included in short-term investments, in our condensed consolidated balance sheets.

Convertible Notes

Our 1.75% Notes, 0% Notes and 0.125% Notes had a fair value of $576.3 million, $599.8 million and $107.5 million at June 30, 2023, respectively. Our 0% Notes and 0.125% Notes had a fair value of $587.3 million and $498.9 million at December 31, 2022, respectively. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

9. 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, 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.

For the six months ended June 30, 2023 and 2022, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2023	**2022**
Risk-free interest rate	3.6%	1.8%
Dividend yield	0.0%	0.0%
Volatility	47.3%	55.1%
Expected life	6.3 years	6.3 years

ESPP:

	Six Months Ended June 30,	
	2023	**2022**
Risk-free interest rate	5.2%	0.6%
Dividend yield	0.0%	0.0%
Volatility	36.7%	50.2%
Expected life	6 months	6 months

RSUs:

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. The RSUs we 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, 2023 and 2022 was $39.50 and $34.38 per share, respectively.

PRSUs:

Beginning in 2020, we added PRSU awards to the compensation for our Chief Executive Officer, Dr. Brett Monia. In 2022, we added PRSU awards to the compensation for our other Section 16 officers. Beginning in 2023, we added PRSU awards to the compensation for all executive officers.

Under the terms of the PRSUs we granted in 2020 through 2022, 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.

Under the terms of the PRSUs we granted in 2023, 100 percent of the PRSUs may vest at the end of the three-year performance period based on our relative TSR as compared to a peer group of companies and as measured at the end of the 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 to 200 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. The weighted-average grant date fair value of PRSUs granted to our executive officers for the six months ended June 30, 2023 and 2022 were $58.99 and $42.28 per share, respectively.

The following table summarizes stock-based compensation expense for the three and six months ended June 30, 2023 and 2022 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Cost of sales	$ 118	$ 53	$ 237	$ 213
Research, development and patent expense	19,249	18,500	38,816	37,582
Selling, general and administrative expense	7,194	5,949	14,457	12,943
Total stock-based compensation expense	$ 26,561	$ 24,502	$ 53,510	$ 50,738

As of June 30, 2023, total unrecognized estimated stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $50.5 million, $70.7 million and $8.4 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized stock-based compensation expense for future forfeitures, including any PRSUs that do not vest. 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 1.9 years, respectively.

10. 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. Additionally, we expect to reflect the royalty purchase agreement with Royalty Pharma as a taxable sale, requiring us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023. The resulting tax liability is partially offset by the utilization of our R&D tax credits.

We recorded income tax expense of $7.8 million and $19.2 million for the three and six months ended June 30, 2023, respectively, compared to $2.3 million and $3.4 million for the same periods in 2022, respectively. The increase in income tax expense for the three months and six months ended June 30, 2023, compared to the same periods in 2022, relates primarily to the impact of the Royalty Pharma transaction.

We continue to maintain a full valuation allowance on all our net deferred tax assets.

11. Liability Related to Sale of Future Royalties

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our arrangements with Biogen and Novartis, respectively. As a result, we received an upfront payment of $500 million and we are eligible to receive up to $625 million in additional milestone payments. Under the terms of the agreement, Royalty Pharma will receive 25 percent of our SPINRAZA royalty payments from 2023 through 2027, increasing to 45 percent of royalty payments in 2028, on up to $1.5 billion in annual sales. In addition, Royalty Pharma will receive 25 percent of any future royalty payments on pelacarsen, our medicine in development to treat patients with elevated lipoprotein(a), or Lp(a), and cardiovascular disease. Royalty Pharma's royalty interest in SPINRAZA will revert to us after total SPINRAZA royalty payments to Royalty Pharma reach either $475 million or $550 million, depending on the timing and occurrence of FDA approval of pelacarsen.

We recorded the upfront payment of $500 million as a liability related to the sale of future royalties, net of transaction costs of $10.4 million, which we are amortizing over the estimated life of the arrangement using the effective interest rate method. We recognize royalty revenue in the period in which the counterparty sells the related product and recognizes the related revenue. We record royalty payments made to Royalty Pharma as a reduction of the liability.

We determine the effective interest rate used to record interest expense under this agreement based on an estimate of future royalty payments to Royalty Pharma. As of June 30, 2023, the estimated effective interest rate under the agreement was 13.5 percent.

The following is a summary of our liability related to sale of future royalties for the six months ended June 30, 2023 (in thousands):

Proceeds from sale of future royalties	$	500,000
Royalty payments to Royalty Pharma		(12,562)
Interest expense related to sale of future royalties		32,915
Liability related to sale of future royalties as of June 30, 2023		520,353
Issuance costs related to sale of future royalties		(10,434)
Amortization of issuance costs related to sale of future royalties as of June 30, 2023		255
Net liability related to sale of future royalties as of June 30, 2023	$	510,174

There are numerous factors, most of which are not within our control, that could materially impact the amount and timing of royalty payments from Biogen and Novartis, and result in changes to our estimate of future royalty payments to Royalty Pharma. Such factors include, but are not limited to, the commercial sales of SPINRAZA, the regulatory approval and commercial sales of pelacarsen, competing products or other significant events.

12. Convertible Debt

1.75 Percent Convertible Senior Notes

In June 2023, we completed a $575.0 million offering of convertible senior notes. We used $420.4 million of the net proceeds from the issuance of the 1.75% Notes to repurchase $434.1 million in principal of our 0.125% Notes. We expect to use the residual net proceeds to settle the 0.125% Notes that remain outstanding.

At June 30, 2023, we had the following 1.75% Notes outstanding (in millions except interest rate and price per share data):

		1.75% Notes
Outstanding principal balance	$	575.0
Unamortized debt issuance costs	$	14.1
Maturity date		June 2028
Interest rate		1.75 percent
Effective interest rate		2.3 percent
Conversion price per share	$	53.73
Total shares of common stock subject to conversion		10.7

0 Percent Convertible Senior Notes and Call Spread

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

At June 30, 2023, we had the following 0% Notes outstanding (in millions except interest rate and price per share data):

	0% Notes
Outstanding principal balance	$ 632.5
Unamortized debt issuance costs	$ 8.7
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 sheets. Refer to Part IV, Item 15, 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, 2022 for our Call Spread accounting policy. 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

As discussed above, in June 2023, we repurchased $434.1 million of our 0.125% Notes. As a result, the remaining principal balance of our 0.125% Notes was $114.8 million as of June 30, 2023. Additionally, we recorded a $11.3 million gain on the early retirement of debt, which we recorded as other income in our condensed consolidated statements of operations. The gain on the early retirement of our debt is the difference between the amount paid to repurchase our 0.125% Notes and the net carrying balance of the liability at the time that we completed the repurchase.

At June 30, 2023, we had the following 0.125% Notes outstanding with interest payable semi-annually (in millions except interest rate and price per share data):

	0.125% Notes
Outstanding principal balance	$ 114.8
Unamortized debt issuance costs	$ 0.7
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	1.4

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. Following the repurchase of $434.1 million of our 0.125% Notes in June 2023, the note hedges and warrants remain outstanding.

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 sheets. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Other Terms of Convertible Senior Notes

The 1.75%, 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.

13. 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 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 Ionis' board of directors, or 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 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.

On July 18, 2022, Ionis filed a Form 8-K disclosing the pending settlement and attaching the Notice of Pendency of Settlement of Action. On September 21, 2022, the Court held a hearing to consider whether the terms of the settlement should be approved, at which hearing the Cohen Action plaintiff objected to the settlement. At the conclusion of the hearing, the Court declined to approve the settlement and directed the parties to meet and confer on the issue of the scope of the release. On February 7, 2023, the parties entered into an Amended Stipulation and Agreement of Compromise, Settlement and Release, which folded the Cohen Action into the settlement, or the Revised Settlement. The settlement did not have a material impact on our condensed consolidated financial statements. On April 24, 2023, the Court issued an Order and Final Judgment approving the Revised Settlement and dismissing the Shumacher and Cohen Actions, and all claims contained therein, with prejudice. The Order does not contain any admission of wrongdoing by any defendant.

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 QALSODY (tofersen), SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen), eplontersen, olezarsen, donidalorsen, ulefnersen (ION363), pelacarsen, bepirovirsen, IONIS-FB-L_{Rx}, our technologies and our other 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 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, 2022, 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 were founded over 30 years ago to deliver innovative medicines for diseases with great medical need. Today, we are building on our advancements in RNA-targeted therapeutics to move us closer to achieving our vision to be the leader in genetic medicines. 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 four marketed medicines: QALSODY, SPINRAZA, TEGSEDI and WAYLIVRA. On April 25, 2023, the U.S. Food and Drug Administration, or FDA, granted Biogen accelerated approval of QALSODY for the treatment of superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. Additionally, the FDA accepted our New Drug Application, or NDA, of eplontersen for polyneuropathy caused by hereditary TTR amyloidosis, or ATTRv-PN. Eplontersen's Prescription Drug User Fee Act, or PDUFA, date is December 22, 2023. We also have a rich innovative late- and mid-stage pipeline primarily focused on our leading cardiovascular and neurology franchises. For the second consecutive quarter, we expanded our late-stage pipeline with the start of Roche's Phase 3 study of IONIS-FB-L_{Rx} in patients with immunoglobulin A nephropathy, or IgAN, in the second quarter of 2023. Prior to this, GSK initiated a Phase 3 program of bepirovirsen in the first quarter of 2023.

We believe our substantial and sustainable revenue and strong balance sheet enable us to continue investing in our commercial readiness efforts for multiple late-stage programs and our innovative pipeline. 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 with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Our partner, Biogen, is responsible for commercializing SPINRAZA worldwide. From inception through June 30, 2023, we have earned more than $1.9 billion in revenues from our SPINRAZA collaboration, including more than $1.5 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, a debilitating, progressive, and fatal disease. We launched TEGSEDI in the United States, or U.S., and the European Union, or EU, in late 2018. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi, and in the second quarter of 2021, Sobi began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC Therapeutics International Limited, or PTC, is commercializing TEGSEDI in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine that received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. In Latin America, PTC is commercializing WAYLIVRA in Brazil for two indications, FCS and familial partial lipodystrophy, or FPL, and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

QALSODY is an antisense medicine that received accelerated approval in April 2023 from the FDA for the treatment of adult patients with SOD1-ALS, a rare, neurodegenerative disorder that causes progressive loss of motor neurons leading to death. Our partner, Biogen, is responsible for commercializing QALSODY worldwide. The European Medicines Agency, or EMA, is currently reviewing QALSODY for approval in the EU.

Medicines in Registration and Phase 3 Studies

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

- Eplontersen: our medicine in development for transthyretin amyloidosis, or ATTR
  - We are currently conducting the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN, the Phase 3 CARDIO-TTRansform study in patients with ATTR cardiomyopathy, or ATTR-CM, and additional studies supporting our ATTR development program
    - In March 2023, the FDA accepted the NDA for eplontersen in the U.S. for patients with ATTRv-PN with a PDUFA date of December 22, 2023
    - In July 2023, we reported positive results from the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN showing eplontersen continued to halt neuropathy disease progression and improve quality of life through 85 weeks
    - In July 2023, we completed enrollment of the Phase 3 CARDIO-TTRansform study of eplontersen in patients with ATTR-CM

- Olezarsen: our medicine in development for FCS and severe hypertriglyceridemia, or SHTG
  - We are currently conducting a broad Phase 3 development program for olezarsen that includes the Phase 3 BALANCE study in patients with FCS and three Phase 3 studies supporting development for the treatment of SHTG: CORE, CORE2 and ESSENCE
    - We remain on track for data from the Phase 3 BALANCE FCS study in the second half of 2023
    - In January 2023, the FDA granted olezarsen fast track designation for the treatment of patients with FCS

- Donidalorsen: our medicine in development for hereditary angioedema, or HAE
  - We are currently conducting the Phase 3 OASIS-HAE study in patients with HAE and the Phase 3 OASIS-Plus supportive study for HAE patients previously treated with other prophylactic therapies
    - In June 2023, we completed enrollment of the Phase 3 OASIS-HAE study of donidalorsen in patients with hereditary angioedema; we remain on track for data in the first half of 2024
    - We reported positive data from the Phase 2 study and Phase 2 open-label extension, or OLE, study throughout 2022 and early 2023, including new topline two-year OLE data in June 2023

- Ulefnersen (ION363): our medicine in development for amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or FUS
  - We are currently conducting a Phase 3 study of ulefnersen in juvenile and adult patients with FUS-ALS

- QALSODY: our medicine to treat patients with SOD1-ALS that is approved in the U.S., under regulatory review in the EU and in development for presymptomatic patients
  - In April 2023, the FDA granted Biogen accelerated approval of QALSODY for patients with SOD1-ALS
  - The EMA is currently reviewing QALSODY’s Marketing Authorization Application, or MAA, in the EU

- Pelacarsen: our medicine in development to treat patients with elevated lipoprotein(a), or Lp(a) and cardiovascular disease
  - Novartis is developing pelacarsen, including conducting the ongoing Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with established cardiovascular disease and elevated Lp(a)
    - In July 2022, Novartis achieved full enrollment in the Lp(a) HORIZON study

- Bepirovirsen: our medicine in development for hepatitis B virus, or HBV
  - GSK is developing bepirovirsen, including conducting the ongoing B-Well Phase 3 program in patients with HBV
    - GSK presented durable response data from the Phase 2 B-Sure long-term follow-up study of bepirovirsen in complete responder patients from the Phase 2b B-Clear study of patients with HBV

- IONIS-FB-L_{Rx}: our medicine in development for IgAN and geographic atrophy, or GA
  - In the second quarter of 2023, Roche advanced IONIS-FB-L_{Rx} into Phase 3 development in patients with IgAN
  - In November 2022, we presented positive data from a Phase 2 study of IONIS-FB-L_{Rx} in patients with IgAN
  - In June 2023, we completed enrollment in the Phase 2 GOLDEN study of IONIS-FB-L_{Rx} in patients with GA

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 Part II, 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, 2022.

Results of Operations

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Total revenue	$ 188.4	$ 133.8	$ 318.9	$ 275.7
Total operating expenses	$ 278.6	$ 219.3	$ 523.3	$ 418.7
Loss from operations	$ (90.2)	$ (85.5)	$ (204.3)	$ (143.0)
Net loss	$ (85.3)	$ (105.1)	$ (209.6)	$ (170.3)

Revenue

Total revenues for the three and six months ended June 30, 2023 were $188.4 million and $318.9 million, respectively, compared to $133.8 million and $275.7 million for the same periods in 2022 and were comprised of the following (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 61.0	$ 59.6	$ 111.3	$ 113.4
Other commercial revenue:				
TEGSEDI and WAYLIVRA revenue, net	10.7	10.4	17.1	16.6
Licensing and other royalty revenue	6.2	8.2	17.3	20.5
Total other commercial revenue	16.9	18.6	34.4	37.1
Total commercial revenue	77.9	78.2	145.7	150.5
R&D revenue:				
Amortization from upfront payments	15.1	18.4	28.8	35.8
Milestone payments	51.1	17.7	73.6	44.9
License fees	20.0	—	20.0	2.0
Other services	4.8	2.1	6.9	5.3
Collaborative agreement revenue	91.0	38.2	129.3	88.0
Eplontersen joint development revenue	19.5	17.4	43.9	37.2
Total R&D revenue	110.5	55.6	173.2	125.2
Total revenue	$ 188.4	$ 133.8	$ 318.9	$ 275.7

Our revenue increased in the second quarter and first half of 2023 compared to the same periods in 2022 because of increased payments from partnered programs. We believe our substantial and sustainable revenue is an important source of funding that supports our investments to bring potentially transformational medicines to the market.

Commercial revenue for the second quarter and first half of 2023 included $61 million and $111 million from SPINRAZA royalties, respectively. Global SPINRAZA product sales of $437 million and $880 million were essentially flat for the second quarter and first half of 2023, respectively, compared to the same periods in 2022, reflecting SPINRAZA's resilience against emerging competition. Our commercial revenue in the second quarter and first half of 2023 also included royalties from the U.S. launch of QALSODY.

R&D revenue essentially doubled for the second quarter of 2023 and increased more than 35% for the first half of 2023 compared to the same periods in 2022 as numerous partnered programs advanced.

Eplontersen Collaboration with AstraZeneca

Our financial results for the three and six months ended June 30, 2023 and 2022 reflected the cost-sharing provisions related to our collaboration with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. Under the terms of the collaboration agreement, AstraZeneca is currently paying 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading and conducting 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.

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 selling, general and administrative, or SG&A expenses, respectively. We expect our medical affairs and commercialization expenses to increase as eplontersen advances toward the market under our collaboration with AstraZeneca.

Our revenue and expenses under this collaboration were as follows (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Eplontersen joint development revenue	$ 19.5	$ 17.4	$ 43.9	$ 37.2
Research and development expenses related to Phase 3 development expenses for eplontersen	38.3	35.0	85.4	71.1
Medical affairs expenses for eplontersen	1.1	0.5	1.8	0.8
Commercialization expenses for eplontersen	2.5	0.5	3.8	0.7

Operating Expenses

Our operating expenses were as follows (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 252.1	$ 194.8	$ 469.8	$ 367.9
Non-cash compensation expense related to equity awards	26.5	24.5	53.5	50.8
Total operating expenses	$ 278.6	$ 219.3	$ 523.3	$ 418.7

Operating expenses, excluding non-cash compensation expense related to equity awards, for the three and six months ended June 30, 2023 increased compared to the same periods in 2022. Our R&D expenses increased as we advanced our pipeline, which included an increase in the costs associated with our clinical studies as most of our Phase 3 studies were either fully enrolled or approaching full enrollment at the end of June 2023. Our SG&A expenses increased due to expenses related to our go-to-market activities for eplontersen, olezarsen and donidalorsen. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the remainder of 2023 as we continue to advance our late-stage medicines in development and prepare for commercialization.

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

Cost of Sales

Our cost of sales is comprised of costs related to our commercial revenue, which 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,	
	2023	2022	2023	2022
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 2.4	$ 4.6	$ 3.7	$ 8.6
Non-cash compensation expense related to equity awards	0.1	0.1	0.2	0.3
Total cost of sales	$ 2.5	$ 4.7	$ 3.9	$ 8.9

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for drug discovery, 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,	
	2023	2022	2023	2022
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 210.7	$ 162.3	$ 388.9	$ 304.3
Non-cash compensation expense related to equity awards	19.2	18.5	38.8	37.6
Total research, development and patent expenses	$ 229.9	$ 180.8	$ 427.7	$ 341.9

Drug Discovery

We use our proprietary technologies 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 drug discovery research, and that of our partners. Drug discovery is also the function that is responsible for advancing our core technology. This function is also responsible for making investments in complementary technologies to expand the reach of our technologies.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 27.6	$ 24.5	$ 52.2	$ 43.6
Non-cash compensation expense related to equity awards	4.0	4.5	7.9	8.6
Total drug discovery expenses	$ 31.6	$ 29.0	$ 60.1	$ 52.2

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended June 30, 2023 compared to the same periods in 2022 as we continued to advance our research programs.

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,	
	2023	2022	2023	2022
TEGSEDI and WAYLIVRA	$ 2.6	$ 3.4	$ 2.6	$ 5.5
Eplontersen	28.7	24.3	65.7	51.3
Olezarsen	31.3	12.7	58.1	21.4
Donidalorsen	7.2	1.9	12.5	3.6
Ulefnersen (ION363)	2.9	1.8	5.2	3.5
Other development projects	34.1	30.6	53.2	60.1
Development overhead expenses	30.4	21.5	55.5	40.8
Total drug development, excluding non-cash compensation expense related to equity awards	137.2	96.2	252.8	186.2
Non-cash compensation expense related to equity awards	8.3	7.0	17.1	15.6
Total drug development expenses	$ 145.5	$ 103.2	$ 269.9	$ 201.8

Our development expenses, excluding non-cash compensation expense related to equity awards, increased for the three and six months ended June 30, 2023 compared to the same periods in 2022 primarily due to our advancing late-stage pipeline and full or nearly full enrollment of multiple Phase 3 studies.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials, we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our medicines are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we may adjust the development strategy for each medicine. Although we may characterize a medicine as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous medicines based on each medicine's particular needs at that time. This means we are constantly shifting resources among medicines. Therefore, what we spend on each medicine during a particular period is usually a function of what is required to keep the medicines progressing in clinical development, not what medicines we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one medicine to another and cannot be used to accurately predict future costs for each medicine. Because we always have numerous medicines in preclinical and varying stages of 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 funding and coordinating investigator-sponsored trials, communicating scientific and clinical information to healthcare providers, medical professionals and patients, and managing publications.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 4.5	$ 4.8	$ 8.8	$ 7.6
Non-cash compensation expense related to equity awards	0.9	0.4	1.9	0.7
Total medical affairs expenses	$ 5.4	$ 5.2	$ 10.7	$ 8.3

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, was relatively consistent in the three and six months ended June 30, 2023 compared to the same periods in 2022. We expect medical affairs expenses, excluding non-cash compensation expense related to equity awards, to increase in the remainder of 2023 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, validation batches to support regulatory approvals, laboratory supplies and outside services. Our manufacturing and development chemistry function is responsible for providing drug supplies to 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,	
	2023	2022	2023	2022
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 22.2	$ 23.1	$ 36.9	$ 39.4
Non-cash compensation expense related to equity awards	2.2	2.6	4.3	5.3
Total manufacturing and development chemistry expenses	$ 24.4	$ 25.7	$ 41.2	$ 44.7

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, information technology 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,	
	2023	2022	2023	2022
Personnel costs	$ 6.7	$ 5.0	$ 13.2	$ 10.1
Occupancy	6.9	4.2	14.2	8.2
Patent expenses	0.8	1.5	1.9	2.2
Insurance	0.9	0.9	1.8	1.8
Computer software and licenses	0.6	0.4	1.2	1.0
Other	3.3	1.7	5.9	4.2
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	19.2	13.7	38.2	27.5
Non-cash compensation expense related to equity awards	3.8	4.0	7.6	7.4
Total R&D support expenses	$ 23.0	$ 17.7	$ 45.8	$ 34.9

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended June 30, 2023 compared to the same periods in 2022. The increase was primarily related to increased occupancy and personnel costs to support advancing our pipeline and our technology. In October 2022, we executed a sale and leaseback transaction for our headquarters in Carlsbad, California. As a result, beginning in the fourth quarter of 2022, our occupancy costs increased because we began incurring rent expense for these facilities.

Selling, General and Administrative Expenses

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,	
	2023	2022	2023	2022
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 38.9	$ 27.9	$ 77.2	$ 55.0
Non-cash compensation expense related to equity awards	7.2	5.9	14.5	12.9
Total selling, general and administrative expenses	$ 46.1	$ 33.8	$ 91.7	$ 67.9

SG&A expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended June 30, 2023 compared to the same periods in 2022 due to increased expenses related to our go-to-market activities for eplontersen, olezarsen and donidalorsen.

Investment Income

The following table sets forth information on investment income (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Investment income	$ 20.8	$ 3.4	$ 39.4	$ 5.4

Our investment income increased primarily due to an increase in interest rates associated with our investments in debt securities and an increase in our cash available for investment during the three and six months ended June 30, 2023 compared to the same periods in 2022. Our cash balance increased due to the $500 million upfront payment we received in January 2023 from our royalty purchase agreement with Royalty Pharma Investments, or Royalty Pharma, and net proceeds we received from the debt offering in June 2023.

Interest Expense

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Convertible notes:				
Non-cash amortization of debt issuance costs	$ 1.4	$ 1.3	$ 2.7	$ 2.7
Interest expense payable in cash	0.8	0.2	1.0	0.3
Interest on mortgage for primary R&D and manufacturing facilities	0.1	0.6	0.2	1.3
Total interest expense	$ 2.3	$ 2.1	$ 3.9	$ 4.3

In June 2023, we completed a $575.0 million offering of our 1.75% Notes and repurchased $434.1 million in principal of our 0.125% Notes. As a result, beginning in the second quarter of 2023, our interest expense related to our convertible notes increased because we began incurring interest expense for our 1.75% Notes.

Interest Expense Related to Sale of Future Royalties

We recorded $17.7 million and $33.2 million of interest expense related to the sale of future royalties in the three and six months ended June 30, 2023, respectively, as a result of the Royalty Pharma transaction, in which we sold a minority interest in our future royalties to Royalty Pharma for a $500 million upfront payment and $625 million of potential future payments. Refer to Part I, Item 1, Note 11, *Liability Related to Sale of Future Royalties*, in the Notes to our condensed consolidated financial statements for further details.

Gain (Loss) on Investments

The following table sets forth information on gain (loss) on investments (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2023	2022	2023	2022
Gain (loss) on investments	$ 0.7	$ (6.3)	$ 0.2	$ (13.0)

The period-over-period fluctuations in our gain (loss) on investments were driven by changes in the fair value of our investments in privately held and publicly traded biotechnology companies. The loss on investments in the three and six months ended June 30, 2022 was primarily driven by losses on our investments in publicly traded biotechnology companies.

Other Expense

In the three months ended June 30, 2023, we completed a $575.0 million offering of our 1.75% Notes and used $420.4 million of the net proceeds to repurchase $434.1 million in principal of our 0.125% Notes. As a result, we recorded an $11.3 million gain on early retirement of debt, which reflects the difference between the amount we paid to repurchase a portion of our 0.125% Notes and the net carrying balance of the liability at the time that we repurchased the debt. Refer to Part I, Item 1, Note 12, *Convertible Debt*, in the Notes to our condensed consolidated financial statements for further details regarding our convertible debt.

In the second quarter of 2022, we recorded a non-operating expense of $12.5 million related to a settlement agreement for a litigation claim that we determined to be probable and estimable as of June 30, 2022. Refer to Part IV, Item 15, Note 9, *Legal Proceedings*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022 for further details regarding the litigation.

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 Internal Revenue Code, or IRC, Section 174. Additionally, we expect to reflect the royalty purchase agreement with Royalty Pharma as a taxable sale, requiring us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023. The resulting tax liability is partially offset by the utilization of our R&D tax credits.

We recorded income tax expense of $7.8 million and $19.2 million for the three and six months ended June 30, 2023, respectively, compared to $2.3 million and $3.4 million for the same periods in 2022, respectively. The increase in income tax expense for the three months and six months ended June 30, 2023, compared to the same periods in 2022, relates primarily to the impact of the Royalty Pharma transaction.

We continue to maintain a full valuation allowance on all our net deferred tax assets.

Net Loss and Net Loss per Share

We had a net loss of $85.3 million and $209.6 million for the three and six months ended June 30, 2023, respectively. We had a net loss of $105.1 million and $170.3 million for the same periods in 2022. The period-over-period fluctuations in our net loss were driven by factors discussed in the sections above. Basic and diluted net loss per share for the three and six months ended June 30, 2023 were $0.60 and $1.47, respectively, compared to $0.74 and $1.20 for the same periods in 2022.

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 royalties, most notably from SPINRAZA, and TEGSEDI and WAYLIVRA commercial revenue. From our inception through June 30, 2023, we have earned approximately $6.7 billion in revenue. We have also financed our operations through the sale of our equity securities, the issuance of long-term debt and the sale of future royalties. From the time we were founded through June 30, 2023, we have raised net proceeds of approximately $2.1 billion from the sale of our equity securities. Additionally, from our inception through June 30, 2023, we have borrowed approximately $2.7 billion under long-term debt arrangements and received proceeds of $0.5 billion from the sale of future royalties to finance a portion of our operations.

Our cash, cash equivalents and short-term investments, working capital and long-term obligations increased from December 31, 2022 to June 30, 2023. As discussed above, in the second quarter of 2023, we issued $575.0 million of 1.75% Notes (due in June 2028) and repurchased $434.1 million of the $548.8 million principal of our 0.125% Notes. In the first quarter of 2023, we received an upfront payment of $500.0 million when we entered into a royalty purchase agreement with Royalty Pharma and recorded a corresponding long-term liability related to the sale of future royalties.

The following table summarizes our contractual obligations, excluding our liability related to the sale of future royalties, as of June 30, 2023. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

Contractual Obligations

(selected balances described below)	Payments Due by Period (in millions) Total	Less than 1 year	More than 1 year
1.75% Notes (principal and interest payable)	$ 625.4	$ 10.1	$ 615.3
0% Notes (principal payable)	632.5	—	632.5
0.125% Notes (principal and interest payable)	114.9	0.1	114.8
Operating leases	289.6	20.2	269.4
Building mortgage payments (principal and interest payable)	10.5	0.5	10.0
Other obligations (principal and interest payable)	0.8	0.1	0.7
Total	$ 1,673.7	$ 31.0	$ 1,642.7

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility leases, a facility mortgage, equipment financing arrangements and other obligations. 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 Part I, Item 1, Note 12, *Convertible Debt*, in the Notes to our condensed consolidated financial statements for the significant terms of each convertible debt instrument.

Operating 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 manufacturing facility mortgage, which has an interest rate of 4.20 percent, matures in August 2027.

In October 2022, we concurrently entered into two purchase and sale agreements with a real estate investor. Under the agreements, we sold and leased back the facilities at our headquarters location in Carlsbad, California and will sell, subject to meeting certain closing conditions, two lots of undeveloped land adjacent to our headquarters. We sold the facilities at our headquarters, which includes our primary R&D facility, for a total purchase price of $263.4 million and we expect to receive total proceeds of $33.0 million upon the close of the sale of the two lots. We used a portion of the sale proceeds to extinguish our mortgage debt on our primary R&D facility of $51.3 million.

In October 2022, we entered into a build-to-suit lease agreement to lease a development chemistry and manufacturing facility in Oceanside, California. The lessor will develop and construct a 217,000-square-foot building, composed of manufacturing space, office space, research and development space and warehouse space. We will design and construct tenant improvements to customize the facility's interior space. We will lease the facility for an initial term of 20 years and 3 months with options to extend the lease for two additional terms of 10 years each. The lease will commence when the lessor's construction is complete and we are able to begin constructing tenant improvements. Under the lease, the lessor was to commence grading of the land upon which our building is to be constructed on or before July 31, 2023. Because the lessor did not commence grading of the land on or before July 31, 2023, we sent a notice of termination to the lessor on August 1, 2023. If the lessor does not commence grading of the land by August 31, 2023, the lease will terminate. We do not believe the potential termination of the lease will impact our ability to successfully commercialize our medicines.

Operating Leases

Refer to our Leases accounting policy in Part IV, Item 15, Note 4, *Long-Term Obligations and Commitments*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022 for further details on our operating leases.

Liability Related to Sale of Future Royalties

Refer to Part I, Item 1, Note 11, *Liability Related to Sale of Future Royalties*, in the Notes to our condensed consolidated financial statements for further details on our royalty purchase agreement with Royalty Pharma.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2023 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, 2023. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2023.

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

For details of legal proceedings, refer to Part I, Item 1, Note 13, *Legal Proceedings*, in the Notes to our condensed consolidated financial statements.

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, 2022.

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:

- Our ability to generate substantial revenue from the sale of our medicines;
- The availability of adequate coverage and payment rates for our medicines;
- Our and our partners' ability to compete effectively;
- 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;
- The impacts of the COVID-19 pandemic and ongoing war between Russia and Ukraine; and
- The other factors set forth below.

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 our 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 currently rely on third parties for the commercialization of our marketed medicines, have limited experience as a company in commercializing medicines and 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 continue to 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and our other 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, 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, 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 in the past disclosed that SPINRAZA revenue 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, 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 of the medicines that we may develop.

For example, TEGSEDI requires periodic blood and urine monitoring and is available in the U.S. only through a risk evaluation and mitigation strategy ("REMS") program. In addition, the product label for TEGSEDI 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 COVID-19 pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, 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, QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, 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. In addition, third-party payers may never consider our future products as cost-effective and 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, or ACA, 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 ACA, as well as efforts to repeal or replace certain aspects of the ACA. It is unclear how future litigation and healthcare reform measures will impact the ACA 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, increase competition (including by enhancing support for generic and biosimilar drugs), lower out-of-pocket drug costs for patients, curtail spread pricing practices by pharmacy benefit managers, and foster scientific innovation to promote better health care and improved health. In addition, the Inflation Reduction Act of 2022, or the IRA, among other things, allows the U.S. Department of Health and Human Services, or HHS, to negotiate the price of certain single-source drugs covered under Medicare and imposes rebates under Medicare Part B and Medicare Part D. In an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation requires manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. Furthermore, any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. Our future product sales may be subject to additional discounts from list price in the form of rebates and discounts provided to covered entities under the Public Health Service Act 340B drug pricing program. Changes to the 340B program or to Medicare or Medicaid programs at the federal or state level, including outcomes of ongoing litigation in our industry, may impact our product prices and rebate liability. Further, in February 2023, in response to President Biden's executive order released in October 2022, the Secretary of the U.S. Department of HHS selected three new models for testing by the Centers for Medicare & Medicaid Services Innovation Center to help lower the high cost of drugs, promote accessibility to life-changing drug therapies and improve quality of care. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future.

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, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If we or our partners fail to compete effectively, our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA, and eplontersen, 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. In addition, other companies are engaged in developing RNA-targeted 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, 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 some of 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA, and eplontersen, and our other medicines in development.

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 or more successfully commercialize their products.

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 and pegozafermin could compete with WAYLIVRA and olezarsen;
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, and NTLA-2002 could compete with donidalorsen;
- Olpasiran and SLN360 could compete with pelacarsen; and
- NI-204 could compete with QALSODY.

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 in the past disclosed that SPINRAZA revenue decreased 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, 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 indication(s) 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 authorities 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.

We depend on our collaborations with Biogen for the development and commercialization of SPINRAZA and QALSODY.*

We have entered into separate collaborative arrangements with Biogen to develop and commercialize SPINRAZA and QALSODY. We entered into these collaborations primarily to:

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

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA and QALSODY, generate additional clinical data for SPINRAZA and QALSODY, manufacture SPINRAZA and QALSODY, successfully launch QALSODY and continue to successfully commercialize SPINRAZA. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaborations. If Biogen fails to further develop SPINRAZA or QALSODY, obtain additional regulatory approvals for SPINRAZA or QALSODY, manufacture SPINRAZA or QALSODY, successfully launch QALSODY or continue to successfully commercialize SPINRAZA, or if Biogen's efforts in any of these respects are ineffective, revenues for SPINRAZA or QALSODY would be negatively affected.

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

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, we 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.

If we are not successful in expanding our manufacturing capabilities or 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 need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. As our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. To that end, in 2022 we entered into a lease agreement ("Lease") with a lessor to construct a new manufacturing facility in Oceanside, California to expand our manufacturing infrastructure. However, because the lessor missed a key milestone under the Lease, we sent a notice of termination to the lessor on August 1, 2023. If the lessor does not achieve the key milestone by August 31, 2023, the Lease will terminate. While it remains important to expand our manufacturing infrastructure in the future, we believe our current capabilities and those we obtain through third-party manufacturers will support our manufacturing needs while we secure a suitable alternative for our manufacturing facility. When we do secure a suitable alternative, we will incur substantial expenditures to build the new manufacturing facility and, following its completion, will likely need to hire and train additional staff to operate the facility. 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 and we will not realize the value of our investment in the expansion.

In addition, 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.

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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development, or could result in enforcement action after authorization that might limit the commercial success of our medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, and our medicines in development.

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 COVID-19 pandemic or the ongoing war between Russia and Ukraine, could limit the commercial success of our medicines.

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 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 adversely affect our business, prospects, financial condition and results of operations.

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 QALSODY, 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 QALSODY, 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 QALSODY, 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 QALSODY, SPINRAZA, TEGSEDI and WAYLIVRA, or our medicines in development, the agency will not approve the specific medicine or will require additional studies, which could be time consuming and expensive and 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 QALSODY, SPINRAZA, TEGSEDI or WAYLIVRA, or delays in these authorizations, could prevent or delay commercial introduction of the medicine, and, as a result, could negatively impact our ability to generate revenue from product sales.

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

Drug discovery and drug development have 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(s), 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 QALSODY, bepirovirsen, donidalorsen, eplontersen, IONIS-FB-L_{Rx}, olezarsen, pelacarsen and ulefnersen (ION363), do not show sufficient efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

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 QALSODY did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring QALSODY 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 QALSODY, bepirovirsen, donidalorsen, eplontersen, IONIS-FB-L_{Rx}, olezarsen, pelacarsen and ulefnersen.

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;
- 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 COVID-19 pandemic could make some of these factors more likely to occur.

In addition, our current medicines, including QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen 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, 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 QALSODY, bepirovirsen, donidalorsen, eplontersen, IONIS-FB-L_{Rx}, olezarsen, pelacarsen and ulefnersen, could reduce the commercial potential or viability of our medicines.

We depend on third parties to conduct 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, Medpace, Inc., Parexel International Corporation, Syneos Health, Inc. and Thermo Fisher Scientific Inc. for the clinical studies for our medicines, including donidalorsen, eplontersen, olezarsen and ulefnersen. 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, but we are responsible for ensuring that such investigators 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 disruptions caused by the COVID-19 pandemic, or a termination of our relationship with such 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 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 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 some 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 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;
- GSK for development and funding of bepirovirsen; and
- Roche for development and funding of IONIS-FB-L_{Rx}.

If any of these pharmaceutical companies stops developing and 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, in 2022, Pfizer and Bayer decided to discontinue the clinical development programs for vupanorsen and fesomersen, respectively.

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

For example, a collaborator such as AstraZeneca, 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 to 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 QALSODY, SPINRAZA, bepirovirsen, eplontersen, IONIS-FB-L_{Rx} and pelacarsen.

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.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

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 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. In addition, as we commercialize more medicines on our own, we will need to invest significant financial resources to continue developing the infrastructure required to successfully commercialize our medicines, including the build-out of a new manufacturing facility. All of these activities will require significant cash. As of June 30, 2023, we had cash, cash equivalents and short-term investments equal to $2.4 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including QALSODY, 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:

- successful commercialization of QALSODY, SPINRAZA, TEGSEDI and WAYLIVRA;
- the profile and launch timing of our medicines, including bepirovirsen, donidalorsen, eplontersen, IONIS-FB-L_{Rx}, olezarsen, pelacarsen and ulefnersen;
- 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 on acceptable terms or at all. 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.

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

Because drug discovery and development require 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, 2023, we had an accumulated deficit of approximately $1.6 billion and stockholders' equity of approximately $0.4 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has historically come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. We will now and continuing into the foreseeable future need to invest significant financial resources to develop capabilities to commercialize medicines on our own and expect that our income in the future will be driven primarily by commercial sales. If we do not earn substantial revenue from commercial sales, we may incur additional operating losses in the future, which could restrict our ability to successfully develop additional medicines or sustain future profitability.

We may not be entitled to obtain additional milestone payments under our royalty monetization agreement with Royalty Pharma.

In January 2023, we entered into a Royalty Purchase Agreement with Royalty Pharma Investments. In addition to the $500 million we received at closing, this agreement makes available to us up to an additional $625 million in milestone payments. However, these additional milestone payments are subject to satisfaction of certain conditions related to the regulatory approval or commercial sales of pelacarsen, in certain cases by specific deadlines. Should we not satisfy such conditions by the applicable deadlines, or if we fail to meet our obligations or default under this agreement, the actual amount of additional payments to us could be substantially less than the maximum amounts available thereunder.

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, any of 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA and eplontersen, 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 QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA or eplontersen, or any of our 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 product liability

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 QALSODY, 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.

Risks related to our personnel

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, and as we move towards commercializing medicines on our own, we will become increasingly dependent on the principal members of our commercial team. We do not have employment agreements with any of our employees that would prevent them from leaving us. The loss of our management, key scientific or commercial employees might slow the achievement of important research and development or commercial goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work and that we recruit and retain qualified marketing, sales, market access, distribution, and related personnel to commercialize our medicines. We may not be able to attract and retain skilled and experienced personnel on acceptable terms because of intense competition for experienced personnel 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 personnel.

Risks related to the COVID-19 pandemic and other events

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

Our business could be 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 disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, some physician and hospital policies that were put in place as a result of the COVID-19 pandemic restricted in-person access by third parties, which in some cases impacted our commercialization efforts for TEGSEDI and WAYLIVRA. In addition, in December 2021, Novartis announced that enrollment for the Phase 3 HORIZON study had been delayed due to the COVID-19 pandemic. The COVID-19 pandemic continues to evolve, and while we believe we have not 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.

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 currently 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 and QALSODY. 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, 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.

Risks related to cybersecurity

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 us) 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.

Risks related to our securities and the global credit markets

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 impacts of the COVID-19 pandemic. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to QALSODY, SPINRAZA, TEGSEDI, WAYLIVRA, bepirovirsen, donidalorsen, eplontersen, IONIS-FB-$L_{Rx,}$ olezarsen, pelacarsen and ulefnersen, the price of our securities could decrease.

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, 2023, the market price of our common stock ranged from $48.82 to $32.69 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 COVID-19 pandemic, the ongoing war between Russia and Ukraine and measures taken in response thereto and the recent failure of Silicon Valley Bank caused significant disruptions of global financial markets and resulted in increased volatility in the trading price of our common stock. 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, chairperson 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 June 2023, we completed a $575 million offering of 1.75% Notes and used a portion of the net proceeds from the issuance of the 1.75% Notes to repurchase $434.1 million of our 0.125% Notes for $420.4 million. 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 23.0 million shares of our common stock upon conversion of our 1.75% Notes, 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.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business, financial condition or stock price.*

The global credit and financial markets have experienced extreme volatility and disruptions recently, including as a result of the ongoing COVID-19 pandemic and war between Russia and Ukraine and measures taken in response thereto, and more recently, the failure of Silicon Valley Bank. These disruptions can result in severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our operations, growth plans, financial performance or stock price. In addition, 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. Furthermore, due to the rapidly rising inflation rate, we may experience significantly 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 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.

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.

Risks related to compliance with laws

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. 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.

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 for pollution liability in amounts and types that we consider commercially reasonable, 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 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 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. In July 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted, and in August 2022, the SEC adopted additional rules and regulations under the Dodd-Frank Act related to "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 has and may in the future lead to additional compliance costs and impact the manner in which we operate our business.

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 carry forward 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 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.

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

Trading Plans

During the quarter ended June 30, 2023, our Section 16 officers and directors adopted or terminated contracts, instructions or written plans for the purchase or sale of our securities as noted in the table below.

			Trading Arrangement			
	Action	Date	Rule 10b5-1*	Non-Rule 10b5-1**	Total Shares to Be Sold	Expiration Date
Allene Diaz, Board Member	Adoption	May 3, 2023	X		1,866	Upon the execution of all instructions provided in the plan
C. Frank Bennett, EVP, Chief Scientific Officer	Adoption	June 29, 2023	X		49,685	Upon the execution of all instructions provided in the plan
Eric Swayze, EVP, Research	Termination	June 28, 2023	X		49,730	Upon the execution of all instructions provided in the plan

* Contract, instruction or written plan intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) under the Exchange Act.
** "Non-Rule 10b5-1 trading arrangement" as defined in item 408(c) of Regulation S-K under the Exchange Act.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
4.1	Indenture, dated as of June 12, 2023, by and between the Registrant and U.S. Bank Trust Company, National Association, as Trustee. Filed as an exhibit to the Registrant's Current Report on Form 8-K filed June 12, 2023 and incorporated herein by reference.
4.2	Form of Global Note, representing the Registrant's 1.75% Convertible Senior Notes due 2028 (included as Exhibit A to the Indenture). Filed as an exhibit to the Registrant's Current Report on Form 8-K filed June 12, 2023 and incorporated herein by reference.
10.1	Amendment No. 3 dated April 27, 2023 to the Collaboration and License Agreement by and between the Registrant and BicycleTx Limited dated July 9, 2021. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.2	First Amendment dated June 15, 2023 to the Purchase and Sale Agreement by and between the Registrant and Oxford I Asset Management USA Inc. dated as of October 20, 2022.
10.3	Letter Agreement dated June 29, 2023 in reference to the Collaboration and License Agreement dated December 6, 2021 by and between Akcea Therapeutics, Inc. and AstraZeneca AB. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
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, 2023, 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, 2023
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	August 9, 2023

Certain portions of this exhibit, marked by [***], have been excluded because they are both not material and are the type that the registrant treats as private or confidential.

AMENDMENT NO. 3 TO COLLABORATION AND LICENSE AGREEMENT

This Amendment No. 3 to Collaboration and License Agreement ("**Third Amendment**") is made and entered into effective as of 27th April 2023 ("**Third Amendment Effective Date**") by and between **BicycleTx Limited**, a company incorporated in England and Wales with a place of business at Blocks A & B, Portway Building Granta Park, Great Abington, Cambridge, United Kingdom, CB21 6GS ("**BicycleTx**"), and Ionis Pharmaceuticals, Inc., a Delaware corporation with a principal place of business at 2855 Gazelle Court, Carlsbad, California 92010, USA ("**Ionis**").

BicycleTx and Ionis are referred to herein individually as a "**Party**" and collectively as the "**Parties**".

BACKGROUND

WHEREAS, BicycleTx and Ionis entered into that certain Collaboration and License Agreement dated as of July 9, 2021, as amended (the "**Agreement**"), pursuant to which the Parties agreed to collaborate in the research and development of products incorporating TfR1 Bicycles directed against certain Targets;

WHEREAS, the Agreement provides for BicycleTx to perform the Research Activities, subject to certain terms and conditions, including [***] at BicycleTx's cost, with the allocation of costs for any additional BicycleTx work requested by Ionis over and above [***] to be discussed in good faith and mutually agreed by the Parties;

WHEREAS, the Parties amended the Agreement by the First Amendment effective as of 17 December 2021, to enable the Parties to conduct certain Additional Research Activities during the Additional Research Period to evaluate the potential for TfR1 Bicycles [***];

WHEREAS, the Parties further amended the Agreement by the Second Amendment effective as of 28 July 2022 to extend the Additional Research Term and the Initial Period;

WHEREAS, the Parties now seek to conduct certain further additional activities to [***], and the Parties thus desire to amend the Agreement to provide for BicycleTx to perform such further additional activities [***], as further set forth in this Third Amendment; and

WHEREAS, Section 12.3 of the Agreement provides that the Agreement may only be modified by a written instrument duly executed by authorized representatives of each Party.

NOW, THEREFORE, the Parties desire, for good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, to amend the Agreement as set forth in this Third Amendment.

ARTICLE 1
DEFINITIONS

1.1 **Capitalized Terms.** Capitalized terms used in this Third Amendment shall have the meanings set forth in the Agreement, unless otherwise defined in this Third Amendment. Section references set forth in this Third Amendment shall refer to section references in this Third Amendment, unless expressly stated to refer to sections of the Agreement.

ARTICLE 2
AMENDMENT

2.1 **Further Additional Activities**. BicycleTx will perform the research activities assigned to it in Schedule 1 attached hereto (the "**Further Additional Activities**") during the period beginning on [***] and continuing until the [***] anniversary of such date (the "**Further Additional Research Period**") in accordance with Section 4.5.1(a) of the Agreement. The Further Additional Activities shall be deemed Research Activities requested by Ionis pursuant to Section 4.2.2 of the Agreement, subject to the terms and conditions of this Third Amendment. Ionis shall use Commercially Reasonable Efforts to perform the Further Additional Activities allocated to it at its sole cost and expense.

2.2 **Amendment of the Research Plan**. Notwithstanding Section 4.2.3 of the Agreement, the Parties hereby agree that the Research Plan shall be deemed amended as of the Third Amendment Effective Date to incorporate the Further Additional Activities, without the requirement for a separate written agreement by the JSC.

2.3 **Level of Effort; Payment**. BicycleTx shall allocate [***] to perform the Further Additional Activities. BicycleTx's FTE rate for such additional FTEs shall be [***]. Within [***] after the Third Amendment Effective Date, Ionis shall pay to BicycleTx the sum of [***] in consideration of the performance by BicycleTx of the Further Additional Activities for the duration of the Further Additional Research Period.

ARTICLE 3
MISCELLANEOUS

3.1 **No Waiver**. Nothing in this Third Amendment is intended to operate as a waiver of any claims either Party may have against the other Party arising prior to the date of this Third Amendment under the Agreement. Any term or condition of this Third Amendment may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver shall be effective unless it is in writing and signed by the Party waiving such term or condition. The waiver by either Party hereto of any right hereunder or of a breach by the other Party shall not be deemed a waiver of any other right hereunder or of any other breach by such other Party whether of a similar nature or otherwise.

3.2 **Miscellaneous.** This Third Amendment and the performance, enforcement, breach, and termination thereof shall be interpreted, governed by, and construed in accordance with the laws of the State of New York, United States excluding any conflicts or choice of law rule or principle that might otherwise refer construction or interpretation of this Third Amendment to the substantive law of another jurisdiction. Any dispute arising from or relating to this Third Amendment will be subject to resolution in accordance with Section 12.2 of the Agreement. Except as specifically amended by the First Amendment, Second Amendment and this Third Amendment, the terms and conditions of the Agreement shall remain in full force and effect. Except to the extent expressly provided herein, the Agreement, including all appendices, exhibits and schedules to each of the foregoing, sets forth the entire agreement and understanding between the Parties with respect to the subject matter of the Agreement and all prior agreements, understandings, promises, and representations, whether written or oral, with respect thereto are superseded hereby. This Third Amendment may be executed in two or more counterparts in original, PDF, or other electronic format, each of which shall be an original, and all of which together shall constitute one instrument.

[Remainder of Page Intentionally Left Blank]

THIS AMENDMENT NO. 3 TO COLLABORATION AND LICENSE AGREEMENT is executed by the authorized representatives of the Parties as of the Third Amendment Effective Date.

BICYCLETX LIMITED	**IONIS PHARMACEUTICALS, INC.**
By: /s/ Michael Skinner	By: /s/ Brett Monia
Name: Michael Skinner	Name: Brett Monia
Title: CTO	Title: CEO

Schedule 1
Further Additional Activities

[***]

EXHIBIT 10.2

FIRST AMENDMENT
TO PURCHASE AND SALE AGREEMENT

THIS FIRST AMENDMENT TO PURCHASE AND SALE AGREEMENT (this "**Amendment**") is entered into as of June 15, 2023, by and between **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation ("**Seller**") and **OXFORD I ASSET MANAGEMENT USA INC.**, a Delaware corporation ("**Buyer**").

RECITALS:

A. Seller and Buyer are parties to that certain Purchase and Sale Agreement dated as of October 20, 2022 (the "**Purchase Agreement**") for the purchase and sale of certain real property located in Carlsbad, California, as more particularly set forth in the Purchase Agreement. Capitalized terms used but not otherwise defined herein shall have the meanings ascribed to such terms in the Purchase Agreement.

B. Seller and Buyer desire to amend the Purchase Agreement as set forth herein.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto agree, and the Purchase Agreement is amended, as follows:

1. **Closing Date**. Notwithstanding anything to the contrary contained in the Purchase Agreement, the "**Closing Date**" shall be the date that is thirty (30) days following written agreement by Buyer and Seller that (a) the Development Conditions have been satisfied; and (b) the Buyer-Seller Lease (including all schedules and/or exhibits contemplated to be attached thereto) has been agreed upon and finalized in a manner satisfactory to Buyer and Seller. If the Development Conditions have not been satisfied or the Buyer-Seller Lease (including all schedules and/or exhibits contemplated to be attached thereto) has not been agreed upon between Buyer and Seller and finalized on or before June 30, 2023 (the "**Outside Approval Date**"), then Buyer may, by delivering written notice to Seller within five (5) business days thereafter, (i) waive such condition and proceed with the Closing on a date designated by Buyer not later than thirty (30) days after such Outside Approval Date; (ii) terminate the Purchase Agreement whereupon Escrow Holder shall promptly return the Deposit to Buyer and neither Buyer nor Seller shall have any further rights or obligations under the Purchase Agreement, except for the Surviving Obligations, including without limitation the rights of Buyer pursuant to Section 3.4 of the Purchase Agreement; or (iii) extend the Outside Approval Date one (1) or more times to provide additional time for any such outstanding condition to be satisfied (such extension not to exceed sixty (60) days in the aggregate) whereupon Buyer shall continue to have the right to exercise its options pursuant to romanettes (i), (ii), and (iii) (if applicable) prior to the extended Outside Approval Date in accordance with the terms and conditions herein. In furtherance of the foregoing, and notwithstanding anything in the Purchase Agreement to the contrary, Seller and Buyer agree to work diligently and in good faith to finalize the Buyer-Seller Lease as contemplated herein and (1) prior to the Outside Approval Date (as may be extended herein), Seller and Buyer shall respond to any submissions and/or requests for information in connection with finalizing the Pre-Closing Funding Agreement and the Buyer-Seller Lease (including all schedules and/or exhibits contemplated to be attached thereto) within two (2) business days of receipt of request therefor, and (2) except where a different period is expressly provided in the Work Letter to the extent incorporated herein by reference, commencing on the Outside Approval Date (as may be extended herein) and continuing thereafter, Seller and Buyer shall respond to any submissions and/or requests for information within five (5) days of receipt of request therefor.

2. **Outside Satisfaction Date**. From and after the date hereof, (i) all references to the term "**Outside Satisfaction Date**" in the Purchase Agreement shall be replaced with the term Outside Approval Date (as defined herein and as may be extended pursuant to the terms hereof), and (ii) Section 3.3(d) is hereby deleted in its entirety and of no further force or effect.

3. **Conflicts**. In the event of any conflict between the terms and provisions of this Amendment and the terms and provisions of the Purchase Agreement, the terms and provisions of this Amendment shall control.

4. **Ratification**. Except as specifically modified by this Amendment, the Purchase Agreement remains in full force and effect without modification, and the Purchase Agreement is hereby ratified and confirmed.

5. **Counterparts**. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, but all of which when taken together will constitute one and the same instrument. Each party has the right to rely upon a facsimile or emailed counterpart of this Amendment signed by the other party to the same extent as if such party received an original counterpart.

6. **Governing Law**. This Amendment shall be construed and the rights and obligations of Seller and Buyer hereunder determined in accordance with the internal laws of the State of California without regard to the principles of conflicts of law.

[*Remainder of page intentionally blank; signature page(s) follow*]

IN WITNESS WHEREOF, this Amendment has been executed as of the date and year first above written.

SELLER:

IONIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: /s/ Elizabeth L. Hougen
Name: Elizabeth. Hougen
Title: CFO

BUYER:

OXFORD I ASSET MANAGEMENT USA INC.,
a Delaware corporation

By: /s/ Tycho Suter
Name: Tycho Suter
Title: Vice President

By: /s/ Kristen Binck
Name: Kristen Binck
Title: Vice President

2850 Gazelle Ct
Carlsbad, CA 92010

Exhibit 10.3

Certain portions of this exhibit, marked by [***], have been excluded because they are both not material and are the type that the registrant treats as private or confidential.

CONFIDENTIAL

June 29, 2023

AstraZeneca AB
SE-431 83 Mölndal
Gothenburg, Sweden
Attention: Kajsa Lundqvist

Re: Collaboration and License Agreement dated December 6, 2021, by and between Akcea Therapeutics, Inc. ("***Akcea***") and AstraZeneca AB ("***AstraZeneca***")

Dear Kajsa:

This letter ("***Letter Agreement***") is in reference to the Collaboration and License Agreement dated December 6, 2021, as amended and supplemented to date (the "***Agreement***"), for the co-development, manufacture, and co-commercialization of eplontersen. All capitalized terms used but not otherwise defined herein will have the meaning set forth in the Agreement.

Akcea hereby notifies AstraZeneca that pursuant to Sections 7.1 and 7.2 of the PTC Agreement, Akcea and its Affiliates have the right, as of [***], to grant an exclusive license under the Licensed Technology to AstraZeneca to Exploit the Licensed Compounds and the Licensed Products in the PTC Territory. Subject to the terms and conditions of the Agreement and this Letter Agreement and effective as of the date of the last signature hereto (the "***PTC Territory License Date***"), Akcea hereby grants to AstraZeneca, and AstraZeneca accepts, an exclusive (even as to Akcea and its Affiliates), royalty-bearing, non-transferable (except in accordance with Section 17.3), sublicensable (through multiple tiers, but subject to Section 8.3) license under the Licensed Technology to Exploit the Licensed Compounds and the Licensed Products in the Field in the PTC Territory.

In partial consideration for the rights and licenses granted to AstraZeneca hereunder with respect to the PTC Territory, within 30 days after receipt of an invoice from Akcea, AstraZeneca will pay Akcea a one-time upfront fee of $20,000,000.

In partial consideration for the rights and licenses granted to AstraZeneca hereunder, and subject to the terms of the Agreement and this Letter Agreement, in accordance with Section 11.4 of the Agreement, AstraZeneca will pay Akcea the one-time milestone payments, as set forth in TABLE 1 below, when a Development or regulatory milestone event listed in TABLE 1 is first achieved by or on behalf of AstraZeneca or its Affiliates or its or their Sublicensees during the Term:

TABLE 1

No.	Milestone Event	Milestone Payment
1.	[***]	$[***]
2.	[***]	$[***]

AstraZeneca shall be entitled to credit any Eligible Development Expenses that have been, or will in the future be, allocated to AstraZeneca for the Development of the Licensed Product, in accordance with Section 2.4.1 of the Agreement, against the milestone payments in TABLE 1 above, to the extent any such milestone payment becomes due. [***].

In addition, in further consideration for the rights and licenses granted to AstraZeneca hereunder, during the Royalty Term, subject to the terms of the Agreement and this Letter Agreement, AstraZeneca will pay to Akcea royalties at the royalty rates set forth below on the aggregate Net Sales resulting from the sale of each Licensed Product in the ROW Territory, which will now include the PTC Territory, as set forth in TABLE 2 below:

TABLE 2

Royalty Tier	**ROW Net Sales of Licensed Products in a Calendar Year**	**ROW Royalty Rate**
1.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year less than $[***]	[***]%
2.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***] but less than $[***]	[***]%
3.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***] but less than $[***]	[***]%
4.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***] but less than $[***]	[***]%
5.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***]	[***]%

ROW Net Sales in a Calendar Year will be calculated by [***] during the Royalty Term. Each ROW Royalty Rate set forth above in TABLE 2 shall apply only to that portion of the Net Sales of all Licensed Products in the ROW Territory during a given Calendar Year that falls within the indicated royalty tier. No ROW Royalties are due on Net Sales of Licensed Products arising from named patient, compassionate use and other programs providing for the delivery of Licensed Product at no cost. The sales of Licensed Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Royalty Term. ROW Royalties will be payable on a Licensed Product-by-Licensed Product and country-by-country basis during the Royalty Term for such Licensed Product in such country until the expiration of the Royalty Term for such Licensed Product in such country. [***]. AstraZeneca will provide reports and payments to Akcea consistent with Section 11.7.

The terms of Section 17.14 (Headings; Construction; Interpretation) of the Agreement will govern the terms of this Letter Agreement. Except as otherwise expressly set forth herein, the provisions of the Agreement will remain in full force and effect and each Party reserves its rights thereunder. In the event of any express conflict or inconsistency between any of this Letter Agreement and the Agreement, the terms of this Letter Agreement will apply.

This Letter Agreement may be executed in counterparts, each of which will be deemed an original notwithstanding variations in format or file designation that may result from electronic transmission, storage and printing of copies of this Letter Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

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

Sincerely,

/s/ Brett Monia

Brett Monia
President
Akcea Therapeutics, Inc.

AGREED TO AND CONFIRMED BY ASTRAZENECA AB (publ):

By: /s/ Kajsa Lundqvist
Name: Kajsa Lundqvist
Title: Head of Business Planning and Operations
Date: June 30, 2023

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, 2023

/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, 2023

/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, 2023, 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, 2023

/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.