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 September 30, 2024

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 October 31, 2024 was 157,897,287.

IONIS PHARMACEUTICALS, INC.
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TRADEMARKS

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

PART I — FINANCIAL INFORMATION

ITEM 1. FINANCIAL STATEMENTS

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

	September 30, 2024 (unaudited)	December 31, 2023
ASSETS		
Current assets:		
Cash and cash equivalents	$ 334,605	$ 399,266
Short-term investments	2,148,671	1,931,935
Contracts receivable	17,928	97,778
Inventories	28,452	28,425
Other current assets	184,194	184,449
Total current assets	2,713,850	2,641,853
Property, plant and equipment, net	82,502	71,043
Right-of-use assets	164,424	171,896
Deposits and other assets	120,323	105,280
Total assets	$ 3,081,099	$ 2,990,072
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 9,052	$ 26,027
Accrued compensation	40,558	67,727
Accrued liabilities	124,396	147,894
Income taxes payable	41	2,151
0.125 percent convertible senior notes, net	44,467	44,332
Current portion of deferred contract revenue	76,018	151,128
Other current liabilities	10,034	8,831
Total current liabilities	304,566	448,090
Long-term deferred contract revenue	173,776	241,184
1.75 percent convertible senior notes, net	564,335	562,285
0 percent convertible senior notes, net	627,745	625,380
Liability related to sale of future royalties, net	538,102	513,736
Long-term lease liabilities	168,372	170,875
Long-term obligations	41,735	41,836
Total liabilities	2,418,631	2,603,386
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 157,813,136 and 144,340,526 shares issued and outstanding at September 30, 2024 (unaudited) and December 31, 2023, respectively	158	144
Additional paid-in capital	2,831,942	2,215,098
Accumulated other comprehensive loss	(24,173)	(32,645)
Accumulated deficit	(2,145,459)	(1,795,911)
Total stockholders' equity	662,468	386,686
Total liabilities and stockholders' equity	$ 3,081,099	$ 2,990,072

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 57,208	$ 67,253	$ 152,406	$ 178,511
WAINUA royalties	5,371	—	10,278	—
Other commercial revenue	13,152	16,828	44,676	51,235
Total commercial revenue	75,731	84,081	207,360	229,746
Research and development revenue:				
Collaborative agreement revenue	44,883	44,167	235,753	173,513
WAINUA joint development revenue	13,200	15,959	35,449	59,883
Total research and development revenue	58,083	60,126	271,202	233,396
Total revenue	133,814	144,207	478,562	463,142
Expenses:				
Cost of sales	1,071	2,191	7,385	6,071
Research, development and patent	219,761	215,330	656,040	643,070
Selling, general and administrative	61,638	69,951	179,395	161,608
Total operating expenses	282,470	287,472	842,820	810,749
Loss from operations	(148,656)	(143,265)	(364,258)	(347,607)
Other income (expense):				
Investment income	26,228	23,935	78,112	63,355
Interest expense	(4,161)	(4,203)	(12,803)	(8,102)
Interest expense related to sale of future royalties	(18,533)	(17,779)	(54,788)	(50,948)
Gain (loss) on investments	879	(1,943)	(321)	(1,753)
Other income	142	2,447	1,029	13,857
Loss before income tax benefit (expense)	(144,101)	(140,808)	(353,029)	(331,198)
Income tax benefit (expense)	3,621	(6,602)	3,481	(25,825)
Net loss	$ (140,480)	$ (147,410)	$ (349,548)	$ (357,023)
Basic and diluted net loss per share	$ (0.95)	$ (1.03)	$ (2.38)	$ (2.50)
Shares used in computing basic and diluted net loss per share	148,593	143,317	146,703	143,052

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Net loss	$ (140,480)	$ (147,410)	$ (349,548)	$ (357,023)
Unrealized gains on debt securities, net of tax	10,315	5,029	8,259	11,421
Currency translation adjustment	350	(153)	213	22
Comprehensive loss	$ (129,815)	$ (142,534)	$ (341,076)	$ (345,580)

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 June 30, 2023	143,167	$ 143	$ 2,118,309	$ (50,913)	$ (1,639,238)	$ 428,301
Net loss	—	—	—	—	(147,410)	(147,410)
Change in unrealized gains, net of tax	—	—	—	5,029	—	5,029
Foreign currency translation	—	—	—	(153)	—	(153)
Issuance of common stock in connection with employee stock plans, net	226	—	3,729	—	—	3,729
Stock-based compensation expense	—	—	25,964	—	—	25,964
Balance at September 30, 2023	143,393	$ 143	$ 2,148,002	$ (46,037)	$ (1,786,648)	$ 315,460
Balance at June 30, 2024	146,025	$ 146	$ 2,303,369	$ (34,838)	$ (2,004,979)	$ 263,698
Net loss	—	—	—	—	(140,480)	(140,480)
Change in unrealized gains, net of tax	—	—	—	10,315	—	10,315
Foreign currency translation	—	—	—	350	—	350
Issuance of common stock in connection with employee stock plans, net	288	—	7,002	—	—	7,002
Issuance of public common stock, net	11,500	12	489,081	—	—	489,093
Stock-based compensation expense	—	—	32,490	—	—	32,490
Balance at September 30, 2024	157,813	$ 158	$ 2,831,942	$ (24,173)	$ (2,145,459)	$ 662,468

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, 2022	142,058	$ 142	$ 2,059,850	$ (57,480)	$ (1,429,625)	$ 572,887
Net loss	—	—	—	—	(357,023)	(357,023)
Change in unrealized gains, net of tax	—	—	—	11,421	—	11,421
Foreign currency translation	—	—	—	22	—	22
Issuance of common stock in connection with employee stock plans, net	1,335	1	8,679	—	—	8,680
Stock-based compensation expense	—	—	79,473	—	—	79,473
Balance at September 30, 2023	143,393	$ 143	$ 2,148,002	$ (46,037)	$ (1,786,648)	$ 315,460
Balance at December 31, 2023	144,341	$ 144	$ 2,215,098	$ (32,645)	$ (1,795,911)	$ 386,686
Net loss	—	—	—	—	(349,548)	(349,548)
Change in unrealized gains, net of tax	—	—	—	8,259	—	8,259
Foreign currency translation	—	—	—	213	—	213
Issuance of common stock in connection with employee stock plans, net	1,972	2	33,205	—	—	33,207
Issuance of public common stock, net	11,500	12	489,081	—	—	489,093
Stock-based compensation expense	—	—	94,558	—	—	94,558
Balance at September 30, 2024	157,813	$ 158	$ 2,831,942	$ (24,173)	$ (2,145,459)	$ 662,468

See accompanying notes.

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

	Nine Months Ended September 30,	
	2024	**2023**
Operating activities:		
Net loss	$ (349,548)	$ (357,023)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	7,374	7,748
Amortization of right-of-use operating lease assets	7,472	7,234
Amortization of other assets	1,877	1,904
Amortization of discount on investments, net	(28,283)	(20,396)
Amortization of debt issuance costs	5,016	4,666
Non-cash royalty revenue related to sale of royalties	(30,422)	(27,814)
Non-cash interest related to sale of future royalties	54,330	50,541
Stock-based compensation expense	94,052	79,473
Loss on investments	320	1,429
Gain on early retirement of debt	—	(13,389)
Non-cash losses related to disposal of property, plant and equipment	114	14,646
Non-cash losses related to other assets	895	849
Changes in operating assets and liabilities:		
Contracts receivable	79,850	(116,814)
Inventories	(27)	(3,601)
Other current and long-term assets	(8,155)	(18,325)
Income taxes	(2,110)	24,821
Accounts payable	(19,215)	(12,462)
Accrued compensation	(27,169)	(15,397)
Accrued liabilities and other current liabilities	(28,661)	(24,219)
Deferred contract revenue	(142,518)	75,751
Net cash used in operating activities	(384,808)	(340,378)
Investing activities:		
Purchases of short-term investments	(1,519,227)	(1,353,100)
Proceeds from sale of short-term investments	1,339,284	1,193,724
Purchases of property, plant and equipment	(19,783)	(24,624)
Acquisition of licenses and other assets, net	(2,514)	(3,414)
Net cash used in investing activities	(202,240)	(187,414)
Financing activities:		
Proceeds from issuance of common stock through equity plans, net	33,207	8,680
Proceeds from issuance of common stock in public offering, net	489,093	—
Proceeds from issuance of 1.75 percent convertible senior notes	—	575,000
1.75 percent convertible senior notes issuance costs	—	(14,175)
Repurchase of $504.4 million principal amount of 0.125 percent convertible senior notes	—	(487,943)
Proceeds from sale of future royalties	—	500,000
Payments of transaction costs related to sale of future royalties	—	(10,434)
Proceeds from real estate transaction	—	32,352
Principal payments on mortgage debt	(126)	(122)
Net cash provided by financing activities	522,174	603,358
Effects of exchange rates on cash	213	22
Net increase (decrease) in cash and cash equivalents	(64,661)	75,588
Cash and cash equivalents at beginning of period	399,266	276,472
Cash and cash equivalents at end of period	$ 334,605	$ 352,060
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,714	$ 952
Income taxes paid	$ 2,072	$ 714
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 2,240	$ 341

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2024
(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 nine months ended September 30, 2024 and 2023 on the same basis as the audited financial statements for the year ended December 31, 2023. 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, 2023 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, 2023.

Recently Issued Accounting Standards

We do not expect any recently issued accounting standards other than those included in our Annual Report on Form 10-K for the year ended December 31, 2023 to have a material impact to our financial results.

3. Supplemental Financial Data

Inventories

Our inventory consisted of the following (in thousands):

	September 30, 2024	December 31, 2023
Raw materials:		
Raw materials - clinical	$ 20,773	$ 20,985
Raw materials - commercial	963	1,809
Total raw materials	21,736	22,794
Work in process	6,653	5,477
Finished goods	63	154
Total inventories	$ 28,452	$ 28,425

Accrued Liabilities

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

	September 30, 2024	December 31, 2023
Clinical development expenses	$ 90,239	$ 105,967
In-licensing expenses	7,082	7,454
Commercial expenses	5,016	4,875
Other miscellaneous expenses	22,059	29,598
Total accrued liabilities	$ 124,396	$ 147,894

4. Revenues

During the three and nine months ended September 30, 2024 and 2023, our revenues were comprised of the following (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 57,208	$ 67,253	$ 152,406	$ 178,511
WAINUA royalties	5,371	—	10,278	—
Other commercial revenue:				
TEGSEDI and WAYLIVRA revenue, net	8,924	8,286	25,744	25,420
Licensing and other royalty revenue	4,228	8,542	18,932	25,815
Total other commercial revenue	13,152	16,828	44,676	51,235
Total commercial revenue	75,731	84,081	207,360	229,746
Research and development revenue:				
Collaborative agreement revenue	44,883	44,167	235,753	173,513
WAINUA joint development revenue	13,200	15,959	35,449	59,883
Total research and development revenue	58,083	60,126	271,202	233,396
Total revenue	$ 133,814	$ 144,207	$ 478,562	$ 463,142

Revenue Sources

The following are sources of revenue and when we typically recognize revenue.

Commercial Revenue: SPINRAZA royalties and WAINUA royalties

We earn commercial revenue primarily in the form of royalty payments on net sales of SPINRAZA. In 2024, we began earning royalties on net sales of WAINUA.

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

We earn commercial revenue from TEGSEDI and WAYLIVRA sales under our distribution agreements with Sobi. In addition, we receive royalties from PTC Therapeutics International Limited, or PTC, for TEGSEDI and WAYLIVRA sales.

Commercial Revenue: Licensing and other royalty revenue

We also recognize as commercial revenue sales milestone payments and royalties we earn under our partnerships. For example, we earn royalty revenue on net sales of QALSODY, which is included in Licensing and other royalty revenue.

Research and development revenue under collaboration agreements

We enter into collaboration agreements to license and sell our technology on an exclusive or non-exclusive basis. Our collaboration agreements typically contain multiple elements, or performance obligations, including technology licenses or options to obtain technology licenses, research and development, or R&D, services and manufacturing services.

Upfront payments: When we enter into a collaboration agreement and receive an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services. If part or all of the upfront payment is a license fee, we recognize as revenue the portion related to the license when we deliver the license to our partner because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery.

Milestone payments: We include variable consideration in the transaction price when it is probable. We typically include milestone payments for R&D services in the transaction price when they are achieved. We include these milestone payments when they are achieved because typically there is considerable uncertainty in the R&D processes that trigger these payments. Similarly, we include approval milestone payments in the transaction price once the medicine is approved by the applicable regulatory agency. We will recognize sales-based milestone payments in the period in which we achieve the milestone under the sales-based royalty exception allowed under accounting rules.

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, when we achieve a milestone payment from a partner for advancing a clinical study under a collaboration agreement, we add the milestone payment to the transaction price if the milestone relates to an ongoing R&D services performance obligation and recognize revenue related to the milestone payment over our estimated period of performance. If we have partially completed our performance obligation, then we record a cumulative-effect adjustment in the period we add the milestone payment to the transaction price.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation.

License fees: We recognize as revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery.

WAINUA (Eplontersen) Collaboration with AstraZeneca

In 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize WAINUA for the treatment of transthyretin amyloidosis, or ATTR. We jointly developed and are commercializing WAINUA with AstraZeneca in the U.S. for the treatment of adults with polyneuropathy caused by hereditary ATTR, or ATTRv-PN. In addition, we are jointly developing WAINUA for the treatment of ATTR cardiomyopathy, or ATTR-CM. We initially granted AstraZeneca exclusive rights to commercialize WAINUA outside the U.S., except for certain Latin American countries. In 2023, we expanded those rights to include Latin America. Under the terms of the agreement, we received a $200 million upfront payment in 2021.

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

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

We also concluded that the co-development activities, the co-commercialization activities and the co-medical affairs activities are within the scope of ASC Topic 808, *Collaborative Arrangements*, or ASC 808, because we and AstraZeneca are active participants exposed to the risks and benefits of the activities under the collaboration and therefore do not have a vendor-customer relationship. AstraZeneca is currently responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading the Phase 3 development program, we made an accounting policy election to recognize as non-customer revenue the cost-share funding from AstraZeneca, net of our share of AstraZeneca's development expenses, in the same period we incur the related development expenses. As AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing WAINUA to market outside the U.S., we made an accounting policy election to recognize cost-share funding we receive from AstraZeneca related to commercial and medical affairs activities as reductions of our selling, general and administrative, or SG&A, expense and R&D expense, respectively.

5. Collaborative Arrangements and Licensing Agreements

Below, we have included our AstraZeneca, Biogen, Otsuka and Roche collaborations, which are the collaborations with substantive changes during 2024 from those included in Part IV, Item 15, Note 4, *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, 2023.

AstraZeneca

We have two collaborations with AstraZeneca: one focused on the joint development and commercialization of WAINUA and one focused on the treatment of cardiovascular, renal and metabolic diseases. From inception through September 30, 2024, we have received more than $935 million from these collaborations.

Over the term of our WAINUA collaboration, we are eligible to receive up to $3.6 billion, which is comprised of a $200 million upfront payment, up to $485 million in development and approval milestone payments and up to $2.9 billion in sales milestone payments. The agreement includes territory-specific development, commercial and medical affairs cost-sharing provisions. In addition, we are eligible to receive up to mid-20 percent royalties for sales in the U.S. and tiered royalties up to the high teens for sales outside the U.S.

In January 2024, we and AstraZeneca launched WAINUA in the U.S. for the treatment of adults with ATTRv-PN. As a result, we began earning royalties from WAINUA sales, which we recognize as commercial revenue in our condensed consolidated statements of operations.

During the three and nine months ended September 30, 2024 and 2023, we earned the following revenue from our relationship with AstraZeneca (in thousands, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Revenue from our relationship with AstraZeneca	$ 19,461	$ 15,959	$ 47,106	$ 99,885
Percentage of total revenue	15%	11%	10%	22%

In October 2024, we earned a $30 million milestone payment from AstraZeneca when the Medicines and Healthcare products Regulatory Agency approved WAINUA for ATTRv-PN in the United Kingdom as WAINZUA. We will achieve the next payment of $200 million or $115 million upon regulatory approval of WAINUA for ATTR-CM in the U.S. or Europe, respectively, under this collaboration.

Our condensed consolidated balance sheet at September 30, 2024 included deferred contract revenue of $1.0 million from our relationship with AstraZeneca. We did not have any deferred contract revenue from our relationship with AstraZeneca at December 31, 2023.

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. QALSODY, our medicine to treat patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS, received accelerated approval from the U.S. Food and Drug Administration, or FDA, in April 2023 and marketing authorization under exceptional circumstances from the European Medicines Agency, or EMA, in May 2024. In addition, we and Biogen are currently developing numerous other investigational medicines to treat neurodegenerative diseases, including medicines in development to treat people with SOD1-ALS, SMA, Alzheimer's disease, or AD, and Parkinson's disease, or PD. From inception through September 30, 2024, we have received more than $4.0 billion in payments from our Biogen collaborations, including payments to purchase our stock.

Under our 2013 strategic neurology collaboration, we earned a $20 million milestone payment from Biogen when the EMA approved Biogen's Marketing Authorization Application, or MAA, filing of QALSODY in the second quarter of 2024. We recognized this milestone payment as R&D revenue in full in the second quarter of 2024 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next milestone payment for QALSODY of $10 million if the Ministry of Health, Labour and Welfare of Japan approves Biogen's Japanese New Drug Application filing of QALSODY.

In the second quarter of 2024, Biogen's option to license ION582, an investigational antisense medicine for the potential treatment of Angelman Syndrome, expired unexercised. As a result, we recognized $30 million of R&D revenue from previously deferred milestone payments related to the ION582 study because we did not have any remaining performance obligations. We will achieve the next milestone payment of $25 million if Biogen advances IONIS-MAPT$_{Rx}$ into Phase 3 development under our 2012 neurology collaboration.

In the third quarter of 2024, we earned a $7.5 million milestone payment from Biogen when Biogen advanced an investigational medicine under our 2018 strategic neurology collaboration. We recognized this milestone payment as R&D revenue in full in the third quarter of 2024 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of up to $15 million if Biogen advances a medicine under this collaboration.

During the three and nine months ended September 30, 2024 and 2023, we earned the following revenue from our relationship with Biogen (in thousands, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Revenue from our relationship with Biogen	$ 80,291	$ 94,695	$ 277,686	$ 262,599
Percentage of total revenue	60%	66%	58%	57%

Our condensed consolidated balance sheets at September 30, 2024 and December 31, 2023 included deferred contract revenue of $226.4 million and $307.4 million, respectively, from our relationship with Biogen.

Otsuka

In 2023, we entered into an agreement with Otsuka Pharmaceutical Co., Ltd., or Otsuka, to commercialize donidalorsen in Europe. In the second quarter of 2024, we expanded the agreement to include commercialization rights for donidalorsen in the Asia-Pacific region in addition to Europe. As a result, we received a $20 million upfront payment from Otsuka. Under the amended agreement, we are eligible to receive up to $290 million, which is comprised of $85 million in upfront payments, up to $65 million in regulatory milestone payments and up to $140 million in sales milestone payments over the term of the collaboration. In addition, we are eligible to receive tiered royalties up to 30 percent on net sales. We are responsible for completing the ongoing development of donidalorsen. We retained the rights to commercialize donidalorsen in the U.S. and in the rest of the world, assuming regulatory approvals. From inception through September 30, 2024, we have received $85 million in payments from Otsuka.

We identified two performance obligations under our amended agreement for the Asia-Pacific region, comprised of our license of donidalorsen to Otsuka and R&D services for donidalorsen. We allocated the transaction price of $20 million based on the estimated stand-alone selling price of each performance obligation as follows:

- $17.5 million for the license of donidalorsen; and
- $2.5 million for the R&D services for donidalorsen.

In the second quarter of 2024, we recognized $17.5 million as revenue in full because Otsuka had full use of the license without any continuing involvement from us. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our R&D services performance obligation in March 2026. We will achieve the next payment of $15 million if the EMA accepts a MAA filing for donidalorsen in the European Union, or EU, under this collaboration.

During the three and nine months ended September 30, 2024 and 2023, we earned the following revenue from our relationship with Otsuka (in thousands, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Revenue from our relationship with Otsuka	$ 1,083	$ —	$ 20,773	$ —
Percentage of total revenue	1%	0%	4%	0%

Our condensed consolidated balance sheets at September 30, 2024 and December 31, 2023 included deferred contract revenue of $7.7 million and $8.5 million, respectively, from our relationship with Otsuka.

Roche

We have three collaborations with Hoffmann-La Roche Inc. and F. Hoffmann-La Roche Ltd, collectively Roche: one to develop treatments for Huntington's disease, or HD, one to develop IONIS-FB-L_{Rx} for the treatment of immunoglobulin A, or IgA, nephropathy, or IgAN, and one to develop RNA-targeted programs for AD and HD. From inception through September 30, 2024, we have received more than $345 million in payments from our Roche collaborations.

In July 2024, Roche discontinued development of IONIS-FB-L_{Rx} for the treatment of geographic atrophy, or GA, following the completion of the Phase 2 study, which showed a favorable safety profile and target engagement, but insufficient efficacy to advance into Phase 3 development. As a result, we recognized $8.5 million of R&D revenue from previously deferred revenue in the third quarter of 2024 because we do not have any remaining performance obligations under the IONIS-FB-L_{Rx} collaboration.

Over the term of the IONIS-FB-L_{Rx} collaboration for the treatment of IgAN, we are eligible to receive up to $430 million, which is comprised of a $35 million license fee, up to $25 million in development milestone payments, up to $90 million in regulatory milestone payments and up to $280 million in sales milestone payments. We will achieve the next payment of $23.5 million if Roche advances IONIS-FB-L_{Rx} for the treatment of IgAN under this collaboration.

During the three and nine months ended September 30, 2024 and 2023, we earned the following revenue from our relationship with Roche (in thousands, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Revenue from our relationship with Roche	$ 11,084	$ 8,858	$ 33,679	$ 16,979
Percentage of total revenue	8%	6%	7%	4%

Our condensed consolidated balance sheets at September 30, 2024 and December 31, 2023 included deferred contract revenue of $4.5 million and $36.7 million, respectively, from our relationship with Roche.

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 nine months ended September 30, 2024 and 2023 by dividing our net loss by our weighted-average number of common shares outstanding during the period. In September 2024, we issued 11,500,000 shares of common stock through a public offering. Refer to Note 13, *Public Common Stock Offering*, for further details on the public offering.

Diluted net loss per share

For the three and nine months ended September 30, 2024 and 2023, 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 September 30, 2024 and 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 September 30, 2024:

One year or less	70%
After one year but within two years	23%
After two years but within three and a half years	7%
Total	100%

As illustrated above, at September 30, 2024, 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 September 30, 2024, 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):

September 30, 2024	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 653,028	$ 1,120	$ (213)	$ 653,935
Debt securities issued by U.S. government agencies	149,658	464	(20)	150,102
Debt securities issued by the U.S. Treasury (1)	678,977	1,283	(114)	680,146
Debt securities issued by states of the U.S. and political subdivisions of the states	10,652	18	(2)	10,668
Total debt securities with a maturity of one year or less	1,492,315	2,885	(349)	1,494,851
Corporate debt securities	433,542	1,813	(312)	435,043
Debt securities issued by U.S. government agencies	78,241	526	(51)	78,716
Debt securities issued by the U.S. Treasury	175,390	847	(50)	176,187
Total debt securities with a maturity of more than one year	687,173	3,186	(413)	689,946
Total available-for-sale debt securities	$ 2,179,488	$ 6,071	$ (762)	$ 2,184,797
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 426	$ (4,624)	$ 7,699
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(7,093)	41,023
Total equity securities	35,012	25,427	(11,717)	48,722
Total available-for-sale debt and equity securities	$ 2,214,500	$ 31,498	$ (12,479)	$ 2,233,519

December 31, 2023	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 559,967	$ 157	$ (2,625)	$ 557,499
Debt securities issued by U.S. government agencies	224,711	64	(611)	224,164
Debt securities issued by the U.S. Treasury (1)	513,784	152	(1,889)	512,047
Debt securities issued by states of the U.S. and political subdivisions of the states	17,757	42	(113)	17,686
Total debt securities with a maturity of one year or less	1,316,219	415	(5,238)	1,311,396
Corporate debt securities	243,151	1,270	(692)	243,729
Debt securities issued by U.S. government agencies	110,138	547	(21)	110,664
Debt securities issued by the U.S. Treasury	294,873	1,239	(480)	295,632
Debt securities issued by states of the U.S. and political subdivisions of the states	3,466	7	(4)	3,469
Total debt securities with a maturity of more than one year	651,628	3,063	(1,197)	653,494
Total available-for-sale debt securities	$ 1,967,847	$ 3,478	$ (6,435)	$ 1,964,890
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 236	$ (5,832)	$ 6,301
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(5,125)	42,991
Total equity securities	35,012	25,237	(10,957)	49,292
Total available-for-sale debt and equity securities	$ 2,002,859	$ 28,715	$ (17,392)	$ 2,014,182

(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 nine months ended September 30, 2024, we recorded a $1.4 million net unrealized gain in our condensed consolidated statements of operations related to changes 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 nine months ended September 30, 2024, we recorded a loss of $2.0 million in our condensed consolidated statements of operations related to observable price changes of our investments in privately held companies.

The following is a summary of our investments we consider to be temporarily impaired at September 30, 2024 (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	209	$ 331,968	$ (351)	$ 47,159	$ (174)	$ 379,127	$ (525)
Debt securities issued by U.S. government agencies	26	49,966	(70)	3,068	(1)	53,034	(71)
Debt securities issued by the U.S. Treasury	12	48,664	(30)	59,416	(134)	108,080	(164)
Debt securities issued by states of the U.S. and political subdivisions of the states	8	534	—	919	(2)	1,453	(2)
Total temporarily impaired securities	255	$ 431,132	$ (451)	$ 110,562	$ (311)	$ 541,694	$ (762)

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 September 30, 2024 and December 31, 2023 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 September 30, 2024	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 255,924	$ 255,924	$ —
Corporate debt securities (2)	1,088,978	—	1,088,978
Debt securities issued by U.S. government agencies (3)	228,818	—	228,818
Debt securities issued by the U.S. Treasury (4)	856,333	856,333	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	10,668	—	10,668
Publicly traded equity securities included in other current assets (5)	7,699	7,699	—
Total	$ 2,448,420	$ 1,119,956	$ 1,328,464

	At December 31, 2023	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 185,424	$ 185,424	$ —
Corporate debt securities (6)	801,228	—	801,228
Debt securities issued by U.S. government agencies (3)	334,828	—	334,828
Debt securities issued by the U.S. Treasury (3)	807,679	807,679	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	21,155	—	21,155
Publicly traded equity securities included in other current assets (5)	6,301	6,301	—
Total	$ 2,156,615	$ 999,404	$ 1,157,211

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

(1) Included in cash and cash equivalents.

(2) $21.2 million was included in cash and cash equivalents, with the difference included in short-term investments.

(3) Included in short-term investments.

(4) $14.9 million was included in cash and cash equivalents, with the difference included in short-term investments.

(5) Included in other current assets.

(6) $33.0 million was included in cash and cash equivalents, with the difference included in short-term investments.

Convertible Notes

Our 1.75% Notes, 0% Notes and 0.125% Notes had a fair value of $589.8 million, $630.7 million and $44.0 million at September 30, 2024, respectively. Our 1.75% Notes, 0% Notes and 0.125% Notes had a fair value of $661.1 million, $667.8 million and $42.4 million at December 31, 2023, 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

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2024 and 2023 (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Cost of sales	$ 159	$ 118	$ 609	$ 355
Research, development and patent expense	22,120	18,727	67,111	57,543
Selling, general and administrative expense	9,705	7,119	26,332	21,575
Stock-based compensation expense, net of amounts capitalized	$ 31,984	$ 25,964	$ 94,052	$ 79,473
Capitalized stock-based compensation expense	506	—	506	—
Total stock-based compensation expense	$ 32,490	$ 25,964	$ 94,558	$ 79,473

As of September 30, 2024, total unrecognized estimated stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $54.1 million, $87.2 million and $12.1 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 1.2 years, 1.5 years and 1.7 years, respectively.

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, 2023 for further details on how we determine the fair value of stock options granted, RSUs, PRSUs and stock purchase rights under the ESPP.

For the nine months ended September 30, 2024 and 2023, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2024	2023
Risk-free interest rate	4.1%	3.7%
Dividend yield	0.0%	0.0%
Volatility	43.8%	47.1%
Expected life	6.3 years	6.3 years

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2024	2023
Risk-free interest rate	4.5%	3.8%
Dividend yield	0.0%	0.0%
Volatility	49.8%	53.0%
Expected life	7.5 years	7.7 years

ESPP:

	Nine Months Ended September 30,	
	2024	2023
Risk-free interest rate	5.2%	5.3%
Dividend yield	0.0%	0.0%
Volatility	37.8%	36.0%
Expected life	6 months	6 months

RSUs:

The weighted-average grant date fair value of RSUs granted to employees for the nine months ended September 30, 2024 and 2023 was $52.08 and $39.78 per share, respectively.

PRSUs:

Under the terms of the PRSUs we granted in 2024 and 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.

The weighted-average grant date fair value of PRSUs we granted to our executive officers for the nine months ended September 30, 2024 and 2023 was $78.41 and $58.99 per share, respectively.

10. Income Taxes

We recorded income tax benefit of $3.6 million and $3.5 million for the three and nine months ended September 30, 2024, respectively, compared to income tax expense of $6.6 million and $25.8 million for the same periods in 2023, respectively.

The benefit for the three and nine months ended September 30, 2024 primarily relates to the 2023 tax return position for the royalty purchase agreement with Royalty Pharma that we finalized during the third quarter of 2024. We reflected the Royalty Pharma transaction as a taxable sale, which required us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023.

The decrease in income tax expense for the three and nine months ended September 30, 2024 compared to the same periods in 2023 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. 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 September 30, 2024 and 2023, the estimated effective interest rate under the agreement was 13.5 percent.

The following table sets forth information on our liability related to sale of future royalties (in thousands):

Proceeds from sale of future royalties in January 2023	$	500,000
Issuance costs related to sale of future royalties		(10,434)
Royalty payments to Royalty Pharma		(44,628)
Interest expense related to sale of future royalties		68,238
Amortization of issuance costs related to sale of future royalties		560
Net liability related to sale of future royalties as of December 31, 2023		513,736
Royalty payments to Royalty Pharma		(30,422)
Interest expense related to sale of future royalties		54,330
Amortization of issuance costs related to sale of future royalties		458
Net liability related to sale of future royalties as of September 30, 2024	$	538,102

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 2023, we completed a $575.0 million offering of our 1.75% Notes and used $488.2 million of the net proceeds from the issuance of our 1.75% Notes to repurchase $504.4 million in principal of our 0.125% Notes. We expect to use the remaining net proceeds to settle the 0.125% Notes that remain outstanding and for general corporate and working capital purposes.

At September 30, 2024, 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	$	10.7
Maturity date		June 2028
Interest rate		1.75%
Effective interest rate		2.3%
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 2021, we completed a $632.5 million offering of our 0% Notes. We used $319.0 million of the net proceeds from the issuance of our 0% Notes to pay the remaining $309.9 million principal balance of our 1 percent convertible senior notes, or 1% Notes, in 2021.

At September 30, 2024, 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	$	4.8
Maturity date		April 2026
Interest rate		0%
Effective interest rate		0.5%
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 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, 2023 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

In 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our 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. As discussed above, in 2023, we repurchased $504.4 million of our 0.125% Notes.

At September 30, 2024, 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	$ 44.5
Unamortized debt issuance costs	$ 0.1
Maturity date	December 2024
Interest rate	0.125%
Effective interest rate	0.5%
Conversion price per share	$ 83.28
Effective conversion price per share with call spread	$ 123.38
Total shares of common stock subject to conversion, excluding shares related to 0.125% Notes that we have repurchased and are currently holding in treasury	0.5

In conjunction with the issuance of our 0.125% Notes in 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. As of September 30, 2024, 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. Public Common Stock Offering

In September 2024, we completed the sale of 11,500,000 shares of our common stock through a public offering at a price of $43.50 per share. We received net proceeds of $489.1 million from the sale of these shares net of underwriting discounts and commissions and other offering expenses of $11.2 million.

14. 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.

There are no pending material legal proceedings to which we are a party or of which our property is the subject.

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 our commercial medicines, additional medicines in development and technologies. 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 and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report and described in additional detail in our annual report on Form 10-K for the year ended December 31, 2023, 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements.

Overview

For three decades as a pioneer in RNA-targeted medicines, we have focused on bringing better futures to people with serious diseases. Today, we continue to drive innovation in RNA therapies. A deep understanding of disease biology and an industry-leading drug discovery technology propels our work, coupled with a passion and urgency to deliver better futures for patients.

We currently have five marketed medicines to treat serious diseases: SPINRAZA (nusinersen), QALSODY (tofersen), WAINUA (eplontersen), TEGSEDI (inotersen) and WAYLIVRA (volanesorsen). We also have a rich innovative late- and mid-stage pipeline in neurology, cardiology and other areas of high patient need. We currently have nine medicines in Phase 3 development and multiple additional medicines in early and mid-stage development.

We are using our multiple sources of revenue and our capital structure to continue investing in our commercial readiness efforts for multiple late-stage programs, our innovative pipeline and our technology. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to bring next-level value to patients and shareholders.

Marketed Medicines

SPINRAZA is an antisense medicine 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 September 30, 2024, we have earned more than $2.2 billion in revenues from our SPINRAZA collaboration, including more than $1.8 billion in royalties on sales of SPINRAZA.

QALSODY is an antisense medicine that received accelerated approval from the United States, or U.S., Food and Drug Administration, or FDA, in April 2023 and marketing authorization under exceptional circumstances from the European Medicines Agency, or EMA, in May 2024 for the treatment of adult patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or 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.

WAINUA (WAINZUA in Europe) is a once monthly, self-administered subcutaneous LIgand-Conjugated Antisense, or LICA, medicine that is approved in the U.S. and other countries for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis, or ATTRv-PN, a debilitating, progressive, and fatal disease. In addition, WAINUA recently received a positive opinion supporting marketing authorization from the Committee for Medicinal Products for Human Use, or CHMP. WAINUA is the only approved medicine for the treatment of ATTRv-PN that can be self-administered via an auto-injector. We and AstraZeneca are commercializing WAINUA in the U.S. with the launch having commenced in January 2024. We and AstraZeneca are seeking regulatory approval for WAINUA in other parts of the world. AstraZeneca has exclusive rights to commercialize WAINUA outside of the U.S.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with ATTRv-PN. We currently sell TEGSEDI in Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi. In October 2023, our agreement for TEGSEDI in North America was terminated and Sobi began transitioning responsibilities to us. Following the transition, we discontinued TEGSEDI in North America in 2024. 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 approved in Europe and Brazil as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We sell 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.

Medicines in Registration and Phase 3 Studies

We currently have nine medicines in registration or Phase 3 studies for eleven indications, which are:

WAINUA (WAINZUA in Europe) is our medicine to treat patients with transthyretin amyloidosis, or ATTR, that is approved in the U.S., Canada and United Kingdom, or UK, for the treatment of adults with ATTRv-PN and is under regulatory review in other countries. The approval of WAINUA for ATTRv-PN was based on the positive results from the Phase 3 NEURO-TTRansform study showing that WAINUA halted disease progression and continuously improved quality of life at the 35-, 66- and 85-week analyses, which were published in the *Journal of the American Medical Association*, or *JAMA*. We launched WAINUA for the treatment of adults with ATTRv-PN in the U.S. in January 2024 and in Canada in October 2024 after securing a reimbursement program. In October 2024, WAINZUA was approved by the Medicines and Healthcare products Regulatory Agency, or MHRA, for the treatment of adults with ATTRv-PN in the UK with an accelerated National Institute for Health and Care Excellence, or NICE, recommendation. Additionally, in October 2024, WAINUA received a positive opinion supporting marketing authorization from CHMP. We are also developing WAINUA for ATTR cardiomyopathy, or ATTR-CM. We continue to progress our Phase 3 development program of WAINUA for ATTR-CM, with enrollment completed in the Phase 3 CARDIO-TTRansform study in July 2023 and data is expected in the second half of 2026. The FDA granted Fast Track designation to WAINUA for the treatment of patients with ATTR-CM in February 2024. Additionally, the FDA and EMA granted Orphan Drug designation to WAINUA for the treatment of ATTR in January 2022 and October 2023, respectively.

Olezarsen is our medicine in development for FCS, an ultra-rare indication, and severe hypertriglyceridemia, or sHTG, a much broader indication. Olezarsen is currently under Priority Review in the U.S. with a Prescription Drug User Fee Act, or PDUFA, action date of December 19, 2024 for FCS. Our regulatory submission was based on the positive results from the Phase 3 Balance study in patients with FCS showing statistically significant triglyceride lowering and a substantial reduction in acute pancreatitis events in addition to a favorable safety and tolerability profile that we reported in September 2023 and presented and published in the *New England Journal of Medicine*, or *NEJM*, in April 2024. We opened our Expanded Access Program for patients with FCS in the U.S. in April 2024. Olezarsen has been granted Breakthrough Therapy designation, Orphan Drug designation and Fast Track designation for the treatment of FCS by the FDA. We are currently conducting a broad Phase 3 development program for olezarsen for the treatment of sHTG including three Phase 3 studies supporting development (CORE, CORE2 and ESSENCE), which achieved full enrollment in 2024.

Donidalorsen is our medicine in development for the prophylactic treatment of hereditary angioedema, or HAE. Donidalorsen is currently under regulatory review in the U.S. with a PDUFA action date of August 21, 2025. Our regulatory submission was based on the positive results from our comprehensive Phase 2 and Phase 3 development program for donidalorsen. This included the Phase 3 OASIS-HAE study in patients treated every four weeks and every eight weeks that were simultaneously published in *NEJM*, and positive results from OASISplus, our trial that includes an open-label, or OLE, cohort for patients rolling over from the Phase 3 study and a separate cohort for patients who have transitioned to donidalorsen from other prophylactic HAE medications that we refer to as the "switch study." In December 2023 and June 2024, we licensed commercialization rights for donidalorsen to Otsuka Pharmaceutical Co., Ltd., or Otsuka, in Europe and the Asia-Pacific region, respectively. Otsuka is preparing to submit a Marketing Authorization Application, or MAA, to the EMA. Donidalorsen was granted Orphan Drug designation by the FDA and EMA.

Zilganersen is our medicine in development for Alexander disease, or AxD. We completed enrollment in the Phase 3 portion of the ongoing study for patients with AxD in July 2024. Zilganersen was granted Fast Track designation for the treatment of AxD and Rare Pediatric designation by the FDA. Additionally, zilganersen was granted Orphan Drug designation by the FDA and EMA.

Ulefnersen is 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. Ulefnersen was granted Orphan Drug designation by the FDA and EMA.

QALSODY is our medicine to treat patients with SOD1-ALS that is marketed by Biogen. QALSODY was granted accelerated approval by the FDA in April 2023 and marketing authorization under exceptional circumstances by the EMA in May 2024 for patients with SOD1-ALS. Biogen is also evaluating QALSODY as a potential treatment for presymptomatic SOD1-ALS patients in the ongoing ATLAS study. QALSODY was granted Orphan Drug designation by the FDA and EMA.

Pelacarsen is our medicine in development to treat patients with elevated lipoprotein(a)-driven cardiovascular disease, or Lp(a)-driven CVD. Novartis is developing pelacarsen, including conducting the ongoing Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with elevated Lp(a)-driven CVD, which achieved full enrollment in July 2022 with more than 8,000 patients. Pelacarsen was granted Fast Track designation by the FDA.

Bepirovirsen is our medicine in development for chronic hepatitis B virus, or HBV. GSK is developing bepirovirsen, including conducting the ongoing B-Well Phase 3 program in patients with HBV, which achieved full enrollment in June 2024. GSK reported positive results from Phase 2 studies in 2023, including 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. The FDA granted Fast Track designation and the Japanese Ministry of Health, Labour and Welfare granted SENKU designation to bepirovirsen for the treatment of patients with HBV.

IONIS-FB-L_{Rx} is our medicine in development for immunoglobulin A, or IgA, nephropathy, or IgAN. In the second quarter of 2023, Roche advanced IONIS-FB-L_{Rx} into Phase 3 development in patients with IgAN based on interim Phase 2 data. In October 2024, we reported positive data from the Phase 2 study of IONIS-FB-L_{Rx} in patients with IgAN.

Critical Accounting Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the U.S. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with the audit committee of our board of directors. The following are our significant accounting estimates, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Assessing the appropriate estimate of anticipated future royalty payments under our royalty purchase agreement

There have been no material changes to our critical accounting estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our Annual Report on Form 10-K for the year ended December 31, 2023.

Results of Operations

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Total revenue	$ 133.8	$ 144.2	$ 478.6	$ 463.1
Total operating expenses	$ 282.5	$ 287.5	$ 842.8	$ 810.7
Loss from operations	$ (148.7)	$ (143.3)	$ (364.3)	$ (347.6)
Net loss	$ (140.5)	$ (147.4)	$ (349.5)	$ (357.0)

Revenue

Total revenue for the three and nine months ended September 30, 2024 were $133.8 million and $478.6 million, respectively, compared to $144.2 million and $463.1 million for the same periods in 2023 and were comprised of the following (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 57.2	$ 67.3	$ 152.4	$ 178.5
WAINUA royalties	5.4	—	10.3	—
Other commercial revenue:				
TEGSEDI and WAYLIVRA revenue, net	8.9	8.3	25.7	25.4
Licensing and other royalty revenue	4.2	8.5	19.0	25.8
Total other commercial revenue	13.1	16.8	44.7	51.2
Total commercial revenue	75.7	84.1	207.4	229.7
Research and development revenue:				
Amortization from upfront payments	28.2	18.0	104.9	46.8
Milestone payments	16.2	16.2	76.1	89.8
License fees	—	4.6	37.5	24.6
Other services	0.5	5.3	17.3	12.3
Collaborative agreement revenue	44.9	44.1	235.8	173.5
WAINUA joint development revenue	13.2	16.0	35.4	59.9
Total research and development revenue	58.1	60.1	271.2	233.4
Total revenue	$ 133.8	$ 144.2	$ 478.6	$ 463.1

Commercial revenue in the three and nine months ended September 30, 2024 included a new source of royalty revenue with the launch of WAINUA in the U.S. in late January 2024. Our commercial revenue in the three and nine months ended September 30, 2024 and 2023 also included royalties from the net sales of QALSODY, which Biogen launched in the U.S. in the second quarter of 2023 and in the EU in the second quarter of 2024. SPINRAZA product sales for the three months ended September 30, 2024 compared to the same period in 2023 increased slightly in the U.S. and decreased outside of the U.S. primarily due to an annual order from a single country that did not recur in 2024.

R&D revenue was relatively consistent in the three months ended September 30, 2024 compared to the same period in 2023, and increased in the nine months ended September 30, 2024 compared to the same period in 2023 primarily due to the amortization of upfront payments from the new collaborations with Roche and Novartis that we entered into during the second half of 2023. In addition, license fees increased year over year as a result of new collaborations we entered into during the second quarter of 2024, including the expanded donidalorsen licensing agreement with Otsuka, which now includes the Asia-Pacific region in addition to Europe. These increases were partially offset by the decrease in WAINUA joint development revenue, which decreased as development activities relating to ATTRv-PN wound down with the launch of WAINUA for this indication.

WAINUA (Eplontersen) Collaboration with AstraZeneca

Our financial results for the three and nine months ended September 30, 2024 and 2023 reflected the cost-sharing provisions related to our collaboration with AstraZeneca to develop and commercialize WAINUA 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 WAINUA 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 with the launch of WAINUA for ATTRv-PN in the U.S. and as WAINUA advances toward the market for ATTR-CM under our collaboration with AstraZeneca.

The following table sets forth information on revenue and expenses under this collaboration (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
WAINUA joint development revenue	$ 13.2	$ 16.0	$ 35.4	$ 59.9
Research and development expenses related to Phase 3 development of WAINUA	28.9	32.4	77.1	117.8
Medical affairs expenses for WAINUA	1.6	1.1	4.8	2.9
Commercialization expenses for WAINUA	6.3	4.5	19.0	8.3

Operating Expenses

The following table sets forth information on operating expenses (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 250.5	$ 261.6	$ 748.7	$ 731.3
Non-cash compensation expense related to equity awards	32.0	25.9	94.1	79.4
Total operating expenses	$ 282.5	$ 287.5	$ 842.8	$ 810.7

Operating expenses, excluding non-cash compensation expense related to equity awards, decreased in the three months ended September 30, 2024 compared to the same period in 2023, and increased in the nine months ended September 30, 2024 compared to the same period in 2023. Our SG&A expenses decreased in the three months ended September 30, 2024 compared to the same period in 2023 due to a one-time expense of $18 million related to a lease agreement termination in the third quarter of 2023, and increased in the nine months ended September 30, 2024 compared to the same period in 2023 primarily due to the launch of WAINUA in the U.S. and launch preparation activities for olezarsen and donidalorsen, including establishing the field team for olezarsen. Our R&D expenses were relatively consistent in the three and nine months ended September 30, 2024 compared to the same periods in 2023 as several late-stage studies have ended. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the remainder of 2024 as we advance our commercialization activities.

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 TEGSEDI and WAYLIVRA 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.

The following table sets forth information on cost of sales (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 0.9	$ 2.1	$ 6.8	$ 5.8
Non-cash compensation expense related to equity awards	0.2	0.1	0.6	0.3
Total cost of sales	$ 1.1	$ 2.2	$ 7.4	$ 6.1

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for drug discovery, drug development, medical affairs, 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 September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 197.7	$ 196.5	$ 588.9	$ 585.5
Non-cash compensation expense related to equity awards	22.1	18.8	67.1	57.6
Total research, development and patent expenses	$ 219.8	$ 215.3	$ 656.0	$ 643.1

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.

The following table sets forth information on drug discovery expenses (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 25.8	$ 26.6	$ 80.7	$ 78.8
Non-cash compensation expense related to equity awards	4.4	4.0	13.3	11.9
Total drug discovery expenses	$ 30.2	$ 30.6	$ 94.0	$ 90.7

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, were relatively consistent in the three and nine months ended September 30, 2024 compared to the same periods in 2023.

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 September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
WAINUA	$ 28.3	$ 25.1	$ 74.3	$ 90.8
TEGSEDI and WAYLIVRA	3.4	3.0	11.0	5.6
Olezarsen	36.8	38.5	116.3	96.6
Donidalorsen	3.5	6.9	13.4	19.4
Zilganersen	2.5	1.9	6.2	6.5
Ulefnersen	3.1	2.5	10.0	7.7
Other development projects	20.4	26.3	63.8	74.9
Development overhead expenses	34.2	28.3	97.2	83.8
Total drug development expenses, excluding non-cash compensation expense related to equity awards	132.2	132.5	392.2	385.3
Non-cash compensation expense related to equity awards	9.7	8.6	30.4	25.7
Total drug development expenses	$ 141.9	$ 141.1	$ 422.6	$ 411.0

Our drug development expenses, excluding non-cash compensation expense related to equity awards, were relatively consistent in the three and nine months ended September 30, 2024 compared to the same periods in 2023. We expect our development expenses will continue to be stable as several late-stage studies end and we reallocate resources toward earlier stage programs.

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.

The following table sets forth information on medical affairs expenses (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 5.5	$ 4.9	$ 17.3	$ 13.8
Non-cash compensation expense related to equity awards	1.1	0.8	3.2	2.7
Total medical affairs expenses	$ 6.6	$ 5.7	$ 20.5	$ 16.5

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, increased in the three and nine months ended September 30, 2024 compared to the same periods in 2023 as we continued advancing 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.

The following table sets forth information on manufacturing and development chemistry expenses (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 14.1	$ 12.3	$ 39.7	$ 49.2
Non-cash compensation expense related to equity awards	2.3	2.2	6.9	6.5
Total manufacturing and development chemistry expenses	$ 16.4	$ 14.5	$ 46.6	$ 55.7

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, were relatively consistent in the three months ended September 30, 2024 compared to the same period in 2023, and decreased in the nine months ended September 30, 2024 compared to the same period in 2023 due to the timing of manufacturing performed by our contract manufacturing organizations for drug product related to several late-stage programs.

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 September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Personnel costs	$ 6.9	$ 6.2	$ 21.9	$ 19.4
Occupancy	7.5	7.2	21.3	21.4
Computer software and licenses	2.4	0.8	5.7	2.0
Insurance	0.7	0.9	2.4	2.7
Patent expenses	1.3	0.9	2.7	2.8
Other	1.3	4.2	5.1	10.1
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	20.1	20.2	59.1	58.4
Non-cash compensation expense related to equity awards	4.6	3.2	13.2	10.8
Total R&D support expenses	$ 24.7	$ 23.4	$ 72.3	$ 69.2

R&D support expenses, excluding non-cash compensation expense related to equity awards, were relatively consistent in the three and nine months ended September 30, 2024 compared to the same periods in 2023.

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 SG&A 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 and QALSODY.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 51.9	$ 62.9	$ 153.1	$ 140.0
Non-cash compensation expense related to equity awards	9.7	7.1	26.3	21.6
Total selling, general and administrative expenses	$ 61.6	$ 70.0	$ 179.4	$ 161.6

SG&A expenses, excluding non-cash compensation expense related to equity awards, decreased in the three months ended September 30, 2024 compared to the same period in 2023 due to a one-time expense of $18 million related to a lease agreement termination in the third quarter of 2023. SG&A expenses, excluding non-cash compensation expense related to equity awards, increased in the nine months ended September 30, 2024 compared to the same period in 2023 due to increased expenses related to our launch of WAINUA in the U.S. and launch preparation activities for olezarsen and donidalorsen, including establishing the field team for olezarsen.

Investment Income

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Investment income	$ 26.2	$ 23.9	$ 78.1	$ 63.4

Our investment income increased primarily due to an increase in interest rates associated with our investments during a majority of the three and nine months ended September 30, 2024 compared to the same periods in 2023, partially offset by a decrease in interest rates in the second half of September 2024. In addition, our cash available for investing increased due to the $489 million net proceeds we received from our public common stock offering in September 2024. Refer to Note 13, *Public Common Stock Offering*, for further details on the public offering.

Interest Expense

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Convertible notes:				
Non-cash amortization of debt issuance costs	$ 1.5	$ 1.6	$ 4.5	$ 4.3
Interest expense payable in cash	2.6	2.5	8.0	3.5
Interest on mortgage for manufacturing facility	0.1	0.1	0.3	0.3
Total interest expense	$ 4.2	$ 4.2	$ 12.8	$ 8.1

In 2023, we completed a $575.0 million offering of our 1.75% Notes and repurchased $504.4 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 $18.5 million and $54.8 million of interest expense related to the sale of future royalties in the three and nine months ended September 30, 2024, respectively, compared to $17.8 million and $50.9 million in the same periods in 2023, respectively. These amounts are related to the Royalty Pharma transaction, in which we sold a minority interest in our future SPINRAZA and pelacarsen 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 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 September 30,		Nine Months Ended September 30,	
	2024	2023	2024	2023
Gain (loss) on investments	$ 0.9	$ (1.9)	$ (0.3)	$ (1.8)

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.

Other Income

In 2023, we completed a $575.0 million offering of our 1.75% Notes and used $488.2 million of the net proceeds to repurchase $504.4 million in principal of our 0.125% Notes. As a result of these repurchases, we recorded a $13.4 million gain on early retirement of debt in the nine months ended September 30, 2023, 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 Condensed Consolidated Financial Statements for further details regarding our convertible debt.

Income Tax Benefit (Expense)

We recorded income tax benefit of $3.6 million and $3.5 million for the three and nine months ended September 30, 2024, respectively, compared to income tax expense of $6.6 million and $25.8 million for the same periods in 2023, respectively.

The benefit for the three and nine months ended September 30, 2024 primarily relates to the 2023 tax return position for the royalty purchase agreement with Royalty Pharma that we finalized during the third quarter of 2024. We reflected the Royalty Pharma transaction as a taxable sale, which required us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023.

The decrease in income tax expense for the three and nine months ended September 30, 2024 compared to the same periods in 2023 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 $140.5 million and $349.5 million for the three and nine months ended September 30, 2024, respectively. We had a net loss of $147.4 million and $357.0 million for the same periods in 2023. 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 nine months ended September 30, 2024 were $0.95 and $2.38, respectively, compared to $1.03 and $2.50 for the same periods in 2023. The period-over-period fluctuations in our net loss per share were primarily driven by factors discussed in the sections above and partially driven by the increase in our weighted-average number of common shares outstanding due to the issuance of 11.5 million shares of common stock from our public offering in September 2024.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also financed our operations from revenue from SPINRAZA and QALSODY royalties and TEGSEDI and WAYLIVRA commercial revenue. In addition, we began receiving commercial revenue from WAINUA royalties in 2024. From our inception through September 30, 2024, we have earned approximately $7.7 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 September 30, 2024, we have raised net proceeds of approximately $2.6 billion from the sale of our equity securities, which includes our sale of 11.5 million shares of common stock for net proceeds of $489 million in September 2024. Additionally, from our inception through September 30, 2024, we have borrowed approximately $2.7 billion under long-term debt arrangements and received proceeds of approximately $0.5 billion from the sale of future royalties to finance a portion of our operations.

From December 31, 2023 to September 30, 2024 our working capital increased as our cash, cash equivalents and short-term investments increased due to net proceeds from the public common stock offering in September 2024. During the same period, our long-term obligations did not change significantly.

The following table summarizes our contractual obligations, excluding our liability related to the sale of future royalties, as of September 30, 2024. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

Contractual Obligations

	Payments Due by Period (in millions)		
(selected balances described below)	**Total**	**Less than 1 year**	**More than 1 year**
1.75% Notes (principal and interest payable)	$ 615.3	$ 10.1	$ 605.2
0% Notes (principal payable)	632.5	—	632.5
0.125% Notes (principal and interest payable)	44.6	44.6	—
Operating leases	264.6	20.7	243.9
Building mortgage payments (principal and interest payable)	9.8	0.5	9.3
Other obligations (principal and interest payable)	0.7	0.1	0.6
Total	$ 1,567.5	$ 76.0	$ 1,491.5

Our contractual obligations consist primarily of our convertible debt. In addition, we also have a facility mortgage, facility leases, equipment financing arrangements and other obligations. We believe our cash, cash equivalents and short-term investments, as well as plans for cash in the future, will be sufficient to fund our planned operations and these 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 Condensed Consolidated Financial Statements for the significant terms of each convertible debt instrument.

Operating Facilities

Refer to Part IV, Item 15, Note 7, *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, 2023 for further details on our operating facilities.

Operating Leases

Refer to Part IV, Item 15, Note 7, *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, 2023 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 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 September 30, 2024 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, securing lines of credit or executing royalty monetization agreements. 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 September 30, 2024. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2024.

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 14, *Legal Proceedings*, in the Notes to 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, 2023.

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 health epidemics, climate change, war and other global events;
- Our dependence upon our own and third-party information technology systems;
- Our compliance with laws; 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 continue 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 continue 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 continue 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 our commercial medicines and our medicines in development, we are not likely to generate substantial revenues or become consistently profitable.

Even if our medicines are authorized for marketing, our success will depend upon the medical community, patients and third-party payers accepting our medicines as medically useful, cost-effective, safe and convenient. Even when the United States, or U.S., Food and Drug Administration, or 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 our commercial medicines 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 our commercial medicines 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 or our partners 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, or REMS program. In addition, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main external 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 government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including our commercial medicines 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, our commercial medicines and our medicines in development will face competition from other therapies and medicines for limited financial resources. Furthermore, 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, includes key actions aimed at reducing the costs of prescription drugs and allows HHS to negotiate the price of certain single-source drugs covered under Medicare and establish a price cap on such drugs. Specifically, in an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation under the IRA requires, among other things, (1) a cap on out-of-pocket drug spending under Part D, (2) drug manufacturers to pay a rebate to the federal government if prices for drugs covered under Part D and Part B increase faster than the rate of inflation, and (3) drug manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. In response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs using march-in rights under the Bayh-Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future.

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.

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. For example, on January 5, 2024, the FDA approved Florida's Section 804 Importation Program, or SIP, proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs. 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 our commercial medicines 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 our commercial medicines 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 our commercial medicines and our 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;
- Taldefgrobep alfa, Evrysdi + GYM329 and NMD670 could compete with SPINRAZA;
- Patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with TEGSEDI and WAINUA;
- Acoramidis, NTLA-2001 and NNC6019-0001 could compete with TEGSEDI and WAINUA;
- ARO-APOC3 and pegozafermin could compete with WAYLIVRA and olezarsen;
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, deucrictibant, NTLA-2002 and STAR-0215 could compete with donidalorsen;
- Olpasiran, zerlasiran, lepodisiran and muvalaplin could compete with pelacarsen;
- NI-005/AP-101 could compete with QALSODY;
- VIR-2218 + PEG-IFN-α, VIR-3434 ± VIR-2218 ± PEG-IFN-α, VIR-2218 + BRII-179, NI-204VIR-2218 + GS-9688 + nivolumab, AB-729, imdusiran + Peg-IFNa-2α + NA, xalnesiran + RG6084 + NA, xalnesiran + NA, xalnesiran + pegIFN + NA, xalnesiran + RO7049389 + NA, xalnesiran + ruzotolimod + NA, RO7049389 + ruzotolimod + NA could complete with bepirovirsen; and
- Budesonide, sparsentan, atrasentan, iptacopan, zigakibart, sibeprenlimab, atacicept, ravulizumab, vemircopan, felzartamab, povetacicept, avacincaptad pegol, pegcetacoplan, tinlarebant, danicopan, GT005, AVD-104 and ANX007 could compete with IONIS-FB-L_{Rx}.

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 our commercial medicines 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 regulatory authorities 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 CMOs 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, and successfully commercialize SPINRAZA and QALSODY. 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, or successfully commercialize SPINRAZA or QALSODY, 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 WAINUA.

We have entered into a collaborative arrangement with AstraZeneca to develop and commercialize WAINUA. Under the terms of the collaboration agreement, we and AstraZeneca will co-develop and co-commercialize WAINUA in the U.S. and AstraZeneca will have the sole right to commercialize WAINUA in all other countries. 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 WAINUA is not successful for any reason, WAINUA may not meet our commercial objectives and our revenues for WAINUA 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 WAINUA 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 WAINUA.

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. While we believe our current capabilities and those we obtain through third-party manufacturers support our manufacturing needs now, it will be important to expand our manufacturing infrastructure in the future, which will likely require substantial expenditures. 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.

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

We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAINUA and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities could limit the commercial success of our medicines.

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 our commercial medicines, 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 our commercial medicines 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 authorities will not approve our medicines for marketing or our commercial medicines in additional markets or for additional indications. If the FDA or another regulatory authority believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including our commercial medicines or our medicines in development, the authority 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 Notice of Non-Compliance Withdrawal Letter, or 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; 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 in development, or failure to receive additional marketing authorizations for our commercial medicines, 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 do not show sufficient safety and 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.

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 or 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.

Further, the FDA or other regulatory authorities 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. In addition, under accelerated approval the FDA is requiring completion of the ongoing Phase 3 trial for QALSODY to confirm the clinical benefit of QALSODY.

Moreover, our commercial medicines 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. Any failure or delay in our clinical studies 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 WAINUA for the treatment of ATTR-CM, donidalorsen, olezarsen, ulefnersen and zilganersen. 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 have in the past experienced labor shortages, which impacted their ability to perform services for us for certain of our clinical trials. Subsequent failures of these third parties to carry out their obligations, or a termination of our relationship with such third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines.

In addition, while we do not have any clinical trial sites in Russia, Ukraine or Gaza, we do have a limited number of clinical trial sites in Israel that may be materially impacted by the ongoing military conflicts in Israel and elsewhere in the Middle East and could result in difficulties enrolling or completing our clinical trials in such areas on schedule.

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 WAINUA;
- 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, Otsuka 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, Otsuka 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, WAINUA, bepirovirsen, donidalorsen, 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 olezarsen for the treatment of patients with FCS, to ulefnersen for the treatment of patients with FUS-ALS, and to ION582 for the treatment of patients with Angelman syndrome. The FDA and European Medicines Agency, or EMA, have granted Orphan Drug designation to WAINUA for the treatment of patients with ATTR, to donidalorsen for the treatment of patients with HAE, to TEGSEDI for the treatment of patients with ATTRv-PN, to WAYLIVRA for the treatment of patients with FCS, to tominersen for the treatment of patients with HD, and to ION356 for the treatment of patients with Pelizaeus-Merzbacher disease. 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 or a substantially similar 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 expansion of our manufacturing capabilities. All of these activities will require significant cash. As of September 30, 2024, we had cash, cash equivalents and short-term investments equal to $2.5 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including our commercial medicines, 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 our commercial medicines;
- the profile and launch timing of our medicines in development;
- 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. For example, in September 2024, we completed an underwritten public offering of 11,500,000 shares of our common stock for total net proceeds, after deducting underwriting discounts and commissions and other offering expenses payable by us, of approximately $489.1 million. 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, or commercial operations. 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 September 30, 2024, we had an accumulated deficit of approximately $2.1 billion and stockholders' equity of approximately $0.7 billion. 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 our commercial medicines, 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 our commercial medicines 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 our commercial medicines 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 or in commercializing our medicines may make it more challenging to recruit and retain qualified personnel.

Risks related to health epidemics, climate change and other events

Our business may be adversely affected by health epidemics, 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, enrollment in some of our clinical trials was delayed due to the COVID-19 pandemic.

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, WAINUA 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, social media and artificial intelligence

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, particularly as companies (including us) moved to more remote work structures during and following 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 and military conflicts in Israel and the surrounding areas, as well as related political or economic responses and counter-responses by various global actors, or collectively, conflicts in Eastern Europe and the Middle East.

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, delay progress on the development of our medicines, 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.

The increasing use of social media platforms and artificial intelligence based software presents new risks and challenges.

Social media is increasingly being used to communicate about our medicines and the diseases our therapies are designed to treat. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear and create uncertainty and risk of noncompliance with regulations applicable to our business. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on social media. We may also encounter criticism on social media regarding our company, management, or medicines. Our reputation could be damaged by negative publicity or if adverse information concerning us is posted on social media platforms or similar mediums, which we may not be able to reverse. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face restrictive regulatory actions or incur other harm to our business.

Additionally, artificial intelligence, or AI, based software is increasingly being used in the biopharmaceutical industry. Use of AI based software may lead to the release of confidential proprietary information, which may impact our ability to realize the benefit of our intellectual property.

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. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to our commercial medicines and medicines in development, 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 September 30, 2024, the closing market price of our common stock ranged from $53.55 to $36.45 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, financing transactions, 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, recent events such as the COVID-19 pandemic, the ongoing conflicts in Eastern Europe and the Middle East, and the failure of Silicon Valley Bank have caused 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, bylaws, 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 2023, we completed a $575 million offering of 1.75% Notes and used $488.2 million of the net proceeds from the issuance of the 1.75% Notes to repurchase $504.4 million of our 0.125% Notes. In 2021, we completed a $632.5 million offering of 0% Notes and used $319.0 million of the net proceeds from the issuance of the 0% Notes to repurchase the remaining $309.9 million of our 1% Notes. In 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 28.2 million shares of our common stock upon conversion of our 1.75% Notes, 0% Notes and 0.125% Notes. In connection with the issuance of the 0% Notes and 0.125% Notes, we entered into certain call spread transactions covering 10.9 million shares and 6.6 million shares, respectively, that we expect will offset the dilution to holders of common stock upon any conversion of those notes. In addition, of the shares reserved, 6.1 million shares are reserved for issuance upon conversion of 0.125% Notes that we have repurchased and are currently held by us in treasury (and thus would not be dilutive). As a result, to the extent we elect to convert the 0.125% Notes held by us in treasury, we expect we would receive up to 6.1 million shares upon settlement of related convertible note hedges (without any additional dilution caused by the conversion of the 0.125% Notes held in treasury). However, the anti-dilutive effect of the convertible note hedges is offset by certain warrant transactions we entered into in connection with the issuance of the 0% Notes and the 0.125% Notes. 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 COVID-19 pandemic, ongoing conflicts in Eastern Europe and the Middle East, and 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.

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 and export 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, acts of terrorism, political instability or public health issues or health epidemics, 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 contract research organizations, contract manufacturing organizations, distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. Importantly, 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 extensive legal and regulatory requirements affecting the health care industry.

Our operations are subject to extensive legal and regulatory requirements affecting the health care industry, 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 our merger with Akcea Therapeutics, Inc. in 2020, or 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 NOLs 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. In 2021, the Organization for Economic Cooperation and Development, or OECD, announced an Inclusive Framework on Base Erosion and Profit Shifting including Pillar Two Model Rules defining a global minimum tax rate of 15% on a country-by-country basis for multinational corporations with annual consolidated revenue above €750 million. The ultimate impact from changes in legislation of countries in which we operate remains uncertain and such changes could have a material impact on our future effective tax rate. In addition, 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 September 30, 2024, 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.

* 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.

			Trading Arrangement			
	Action	Date	Rule 10b5-1*	Non-Rule 10b5-1**	Total Shares to be Sold	Expiration Date
Eric Swayze EVP, Research	Termination	August 12, 2024	X		85,614	Upon the execution of all instructions provided in the plan
Brian Birchler EVP, Corporate and Development Operations	Adoption	August 12, 2024	X		71,400	The earlier to occur of (i) January 2, 2026, and (ii) upon the execution of all instructions provided in the plan
Brett P. Monia Chief Executive Officer	Adoption	August 12, 2024	X		431,245	The earlier to occur of (i) May 7, 2026, and (ii) upon the execution of all instructions provided in the plan
C. Frank Bennett EVP, Chief Scientific Officer	Adoption	August 12, 2024	X		111,149	The earlier to occur of (i) January 2, 2026, and (ii) upon the execution of all instructions provided in the plan
Joseph Loscalzo Board Member	Adoption	August 12, 2024	X		62,677	The earlier to occur of (i) November 10, 2025, and (ii) upon the execution of all instructions provided in the plan
Eric Swayze EVP, Research	Adoption	August 14, 2024	X		177,770	The earlier to occur of (i) December 31, 2027, and (ii) upon the execution of all instructions provided in the plan
Shannon L. Devers EVP, Chief Human Resources Officer	Adoption	September 3, 2024	X		123,508	The earlier to occur of (i) January 31, 2026, and (ii) upon the execution of all instructions provided in the plan
Spencer Berthelsen Director	Adoption	September 11, 2024	X		16,000	The earlier to occur of (i) June 30, 2025, and (ii) upon the execution of all instructions provided in the plan

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
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 September 30, 2024, 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)	November 6, 2024
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	November 6, 2024