UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 2025

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)
2855 Gazelle Court, Carlsbad, California	**92010**
(Address of Principal Executive Offices)	(Zip Code)

760-931-9200

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol	Name of each exchange on which registered
Common Stock, $.001 Par Value	"IONS"	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer ☒	Accelerated Filer ☐
Non-accelerated Filer ☐	Smaller Reporting Company ☐ Emerging Growth Company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

The number of shares of voting common stock outstanding as of April 24, 2025 was 159,159,099.

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)

	March 31, 2025 (unaudited)	December 31, 2024
ASSETS		
Current assets:		
Cash and cash equivalents	$ 264,192	$ 242,077
Short-term investments	1,880,960	2,055,579
Contracts receivable	39,707	92,188
Inventories	11,502	12,512
Other current assets	222,571	217,934
Total current assets	2,418,932	2,620,290
Property, plant and equipment, net	102,925	94,251
Right-of-use assets	159,269	161,856
Deposits and other assets	131,822	127,278
Total assets	$ 2,812,948	$ 3,003,675
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 17,456	$ 42,964
Accrued compensation	26,575	69,614
Accrued liabilities	102,735	108,438
Income taxes payable	126	34
Current portion of deferred contract revenue	81,097	78,989
Other current liabilities	22,304	9,279
Total current liabilities	250,293	309,318
Long-term deferred contract revenue	140,678	156,504
1.75 percent convertible senior notes, net	565,721	565,026
0 percent convertible senior notes, net	629,326	628,535
Liability related to sale of future royalties, net	536,141	542,212
Long-term lease liabilities	159,392	161,805
Long-term obligations	55,671	51,924
Total liabilities	2,337,222	2,415,324
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 159,041,259 and 157,908,815 shares issued and outstanding at March 31, 2025 (unaudited) and December 31, 2024, respectively	159	158
Additional paid-in capital	2,901,262	2,868,812
Accumulated other comprehensive loss	(28,949)	(30,811)
Accumulated deficit	(2,396,746)	(2,249,808)
Total stockholders' equity	475,726	588,351
Total liabilities and stockholders' equity	$ 2,812,948	$ 3,003,675

See accompanying notes.

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

	Three Months Ended March 31,	
	2025	**2024**
Revenue:		
Commercial revenue:		
Product sales, net	$ 6,287	$ —
Royalty revenue	64,166	49,385
Other commercial revenue	5,715	10,208
Total commercial revenue	76,168	59,593
Research and development revenue:		
Collaborative agreement revenue	45,031	49,345
WAINUA joint development revenue	10,413	10,559
Total research and development revenue	55,444	59,904
Total revenue	131,612	119,497
Expenses:		
Cost of sales	1,463	2,151
Research, development and patent	200,759	214,215
Selling, general and administrative	76,250	52,644
Total operating expenses	278,472	269,010
Loss from operations	(146,860)	(149,513)
Other income (expense):		
Investment income	24,667	26,285
Interest expense	(4,108)	(4,151)
Interest expense related to sale of future royalties	(18,822)	(17,959)
Gain (loss) on investments	(2,164)	2,333
Other income	465	277
Loss before income tax expense	(146,822)	(142,728)
Income tax expense	(116)	(75)
Net loss	$ (146,938)	$ (142,803)
Basic and diluted net loss per share	$ (0.93)	$ (0.98)
Shares used in computing basic and diluted net loss per share	158,735	145,538

See accompanying notes.

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

	Three Months Ended March 31,	
	2025	**2024**
Net loss	$ (146,938)	$ (142,803)
Unrealized gains (losses) on debt securities, net of tax	1,630	(2,205)
Currency translation adjustment	232	(114)
Comprehensive loss	$ (145,076)	$ (145,122)

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, 2023	144,341	$ 144	$ 2,215,098	$ (32,645)	$ (1,795,911)	$ 386,686
Net loss	—	—	—	—	(142,803)	(142,803)
Change in unrealized losses, net of tax	—	—	—	(2,205)	—	(2,205)
Foreign currency translation	—	—	—	(114)	—	(114)
Issuance of common stock in connection with employee stock plans, net	1,504	2	23,609	—	—	23,611
Stock-based compensation expense	—	—	31,340	—	—	31,340
Balance at March 31, 2024	145,845	$ 146	$ 2,270,047	$ (34,964)	$ (1,938,714)	$ 296,515
Balance at December 31, 2024	157,909	$ 158	$ 2,868,812	$ (30,811)	$ (2,249,808)	$ 588,351
Net loss	—	—	—	—	(146,938)	(146,938)
Change in unrealized gains, net of tax	—	—	—	1,630	—	1,630
Foreign currency translation	—	—	—	232	—	232
Issuance of common stock in connection with employee stock plans, net	1,132	1	2,241	—	—	2,242
Stock-based compensation expense	—	—	30,209	—	—	30,209
Balance at March 31, 2025	159,041	$ 159	$ 2,901,262	$ (28,949)	$ (2,396,746)	$ 475,726

See accompanying notes.

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

	Three Months Ended March 31,	
	2025	**2024**
Operating activities:		
Net loss	$ (146,938)	$ (142,803)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	2,228	2,547
Amortization of right-of-use operating lease assets	2,587	2,465
Amortization of other assets	582	639
Amortization of discount on investments, net	(7,108)	(9,257)
Amortization of debt issuance costs	1,642	1,667
Non-cash royalty revenue related to sale of royalties	(12,891)	(6,623)
Non-cash interest related to sale of future royalties	18,670	17,806
Stock-based compensation expense	29,718	31,340
Loss (gain) on investments	1,849	(2,332)
Non-cash losses related to other assets	61	133
Changes in operating assets and liabilities:		
Contracts receivable	52,481	92,638
Inventories	1,010	499
Other current and long-term assets	(12,366)	11,048
Accounts payable	(25,968)	(13,869)
Income taxes	92	59
Accrued compensation	(43,039)	(46,190)
Accrued liabilities and other current liabilities	333	(42,887)
Deferred contract revenue	(13,718)	(46,818)
Net cash used in operating activities	(150,775)	(149,938)
Investing activities:		
Purchases of short-term investments	(311,068)	(519,001)
Proceeds from sale of short-term investments	494,755	600,836
Purchases of property, plant and equipment	(12,577)	(4,493)
Acquisition of licenses and other assets, net	(651)	(1,237)
Net cash provided by investing activities	170,459	76,105
Financing activities:		
Proceeds from issuance of common stock through equity plans, net	2,241	23,609
Principal payments on mortgage debt	(42)	(39)
Net cash provided by financing activities	2,199	23,570
Effects of exchange rates on cash	232	(114)
Net increase (decrease) in cash and cash equivalents	22,115	(50,377)
Cash and cash equivalents at beginning of period	242,077	399,266
Cash and cash equivalents at end of period	$ 264,192	$ 348,889
Supplemental disclosures of cash flow information:		
Interest paid	$ 92	$ 95
Income taxes paid (refunds received)	$ (400)	$ 13
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 460	$ 924

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2025
(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 months ended March 31, 2025 and 2024 on the same basis as the audited financial statements for the year ended December 31, 2024. 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, 2024 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 operating decision maker, or CODM, reviews operating results on an aggregate basis and manages our operations as a single operating segment. Refer to Note 14, *Segment Information*, for further details on our segment information.

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

Below, we have included our accounting policies for revenue recognition related to product sales, net and cost of sales as a result of our launch of TRYNGOLZA in the U.S. Our other significant accounting policies have not changed substantially from those included in our Annual Report on Form 10-K for the year ended December 31, 2024.

Revenue Recognition

Product Sales, Net

We recognize revenue from product sales when the customer obtains control of our product in the amount of the transaction price, which is the amount that reflects the consideration which we expect to receive. We estimate reserves for variable consideration related to applicable discounts, rebates, chargebacks and other allowances included in our agreements with customers, payors and other third parties. We include the amount of variable consideration in the transaction price to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. If actual results vary significantly from our estimates, we adjust our estimates in the period that we become aware of such variances.

Cost of Sales

Our cost of sales is comprised of costs related to our commercial revenue, including manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of our products. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of sales.

Cost of sales for a newly launched product, such as TRYNGOLZA, does not include the full cost of manufacturing until we manufacture and sell additional inventory after exhausting pre-launch inventory, which we previously recorded as research and development, or R&D, expense.

Recent Accounting Standards

In November 2023, the Financial Accounting Standards Board, or FASB, issued Accounting Standard Update, or ASU, 2023-07, which provides updated guidance on segment reporting. The guidance requires public companies to disclose significant expenses that are regularly provided to the CODM, other segment items for each reportable segment and measures of segment profit or loss used by the CODM for allocating resources. In addition, the updated guidance requires public companies with a single reportable segment to provide all disclosures required under Accounting Standards Codification, or ASC, Topic 280, *Segment Reporting*, and public companies to include in interim reports all disclosures related to a reportable segment's profit or loss and assets that are currently required in annual reports. We adopted the reporting requirements in our 2024 Annual Report on Form 10-K and in this Quarterly Report on Form 10-Q for the first quarter of 2025. Refer to Note 14, *Segment Information*, for further details on our segment information.

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, 2024 to have a material impact to our financial results.

3. Supplemental Financial Data

Inventories

Our inventories consisted of the following (in thousands):

	March 31, 2025	December 31, 2024
Raw materials	$ 640	$ 5,557
Work in process	8,744	6,679
Finished goods	2,118	276
Total inventories	$ 11,502	$ 12,512

Accrued Liabilities

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

	March 31, 2025	December 31, 2024
Clinical expenses	$ 67,614	$ 77,436
In-licensing expenses	7,374	7,951
Commercial expenses	7,257	3,589
Other miscellaneous expenses	20,490	19,462
Total accrued liabilities	$ 102,735	$ 108,438

4. Revenues

During the three months ended March 31, 2025 and 2024, our revenues were comprised of the following (in thousands):

	Three Months Ended March 31,	
	2025	2024
Revenue:		
Commercial revenue:		
Product sales, net:		
TRYNGOLZA sales, net	$ 6,287	$ —
Total product sales, net	6,287	—
Royalty revenue:		
SPINRAZA royalties	48,010	38,455
WAINUA royalties	9,372	1,125
Other royalties	6,784	9,805
Total royalty revenue	64,166	49,385
Other commercial revenue:		
TEGSEDI and WAYLIVRA revenue, net	5,715	8,628
Other revenue	—	1,580
Total other commercial revenue	5,715	10,208
Total commercial revenue	76,168	59,593
Research and development revenue:		
Collaborative agreement revenue	45,031	49,345
WAINUA joint development revenue	10,413	10,559
Total research and development revenue	55,444	59,904
Total revenue	$ 131,612	$ 119,497

Revenue Sources

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

Commercial Revenue

In December 2024, the U.S. Food and Drug Administration, or FDA, approved TRYNGOLZA (olezarsen) for the treatment of familial chylomicronemia syndrome, or FCS. Following the approval, we launched TRYNGOLZA and began earning revenue from TRYNGOLZA sales. We recognize product sales, net of variable considerations related to applicable discounts and allowances, when the customer obtains control of our product.

We earn royalty payments primarily on net sales of SPINRAZA, WAINUA and QALSODY.

We earn commercial revenue from TEGSEDI and WAYLIVRA sales under our distribution agreements with Swedish Orphan Biovitrum AB, or Sobi. In addition, we receive royalties from PTC Therapeutics International Limited, or PTC, for TEGSEDI and WAYLIVRA sales. Refer to 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, 2024 for details on our commercialization partnerships with Sobi and PTC.

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, R&D services and manufacturing services.

For R&D services that we recognize over time, we measure our progress using an input method. The input methods we use are based on the effort we expend or costs we incur toward the satisfaction of our performance obligation. We estimate the amount of effort we expend, including the time we estimate it will take us to complete the activities, or costs we incur in a given period, relative to the estimated total effort or costs to satisfy the performance obligation. This results in a percentage that we multiply by the transaction price to determine the amount of revenue we recognize each period. This approach requires us to make numerous estimates that may involve judgement. If our estimates or judgements change over the course of the collaboration, they may affect the timing and amount of revenue that we recognize in the current and future periods.

Upfront payments: When we enter into a collaboration agreement and receive an upfront payment, we 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 consider milestone payments to be variable consideration and include them 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 there is considerable uncertainty in the research and development processes that trigger these payments. Similarly, we include regulatory 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 remaining 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. Under the terms of the agreement, we received a $200 million upfront payment in 2021.

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

We determined that we had a vendor-customer relationship within the scope of ASC 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 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.

Swedish Orphan Biovitrum AB (Sobi)

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

5. Collaborative Arrangements and Licensing Agreements

Below, we have included our Ono collaboration, which is the only collaboration that had either substantive changes or was new 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, 2024.

Ono

In March 2025, we entered into an agreement with Ono Pharmaceutical, Ltd, or Ono, to develop and commercialize sapablursen, an investigational RNA-targeted medicine for the potential treatment of polycythemia vera, or PV, a rare and potentially life-threatening hematologic disease. We are responsible for completing the ongoing Phase 2 IMPRSSION study, while Ono will be solely responsible for subsequent development, regulatory filings and commercialization of sapablursen.

Over the term of our sapablursen collaboration, we are eligible to receive up to $940 million, which is comprised of a $280 million upfront payment and up to $660 million in development, regulatory and sales milestone payments. In addition, we are eligible to receive royalties in the mid-teen percentage range on net sales.

In April 2025, we achieved a $280 million upfront payment when this transaction received clearance under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, or HSR Act.

6. Basic and Diluted Net Loss Per Share

Basic net loss per share

We calculated our basic net loss per share for the three months ended March 31, 2025 and 2024 by dividing our net loss by our weighted-average number of common shares outstanding during the period.

Diluted net loss per share

For the three months ended March 31, 2025 and 2024, 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;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

For the three months ended March 31, 2024, common stock underlying the 0.125 percent convertible senior notes, or 0.125% Notes, and note hedges related to the 0.125% Notes would also have had an anti-dilutive effect on net loss per share.

Additionally, as of March 31, 2025 and 2024, 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 March 31, 2025:

One year or less	67%
After one year but within two years	27%
After two years but within three and a half years	6%
Total	100%

As illustrated above, at March 31, 2025, 94 percent of our available-for-sale securities had a maturity of less than two years.

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

We invest in 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 March 31, 2025, 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):

March 31, 2025	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 516,458	$ 299	$ (247)	$ 516,510
Debt securities issued by U.S. government agencies	120,961	156	(32)	121,085
Debt securities issued by the U.S. Treasury (1)	592,770	393	(270)	592,893
Debt securities issued by states of the U.S. and political subdivisions of the states	3,072	2	—	3,074
Total debt securities with a maturity of one year or less	1,233,261	850	(549)	1,233,562
Corporate debt securities	471,479	1,086	(1,009)	471,556
Debt securities issued by U.S. government agencies	61,184	188	(116)	61,256
Debt securities issued by the U.S. Treasury	145,922	373	(52)	146,243
Debt securities issued by states of the U.S. and political subdivisions of the states	1,595	1	—	1,596
Other municipal debt	698	—	—	698
Total debt securities with a maturity of more than one year	680,878	1,648	(1,177)	681,349
Total available-for-sale debt securities	$ 1,914,139	$ 2,498	$ (1,726)	$ 1,914,911
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 41	$ (8,856)	$ 3,082
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(7,093)	41,023
Total equity securities	35,012	25,042	(15,949)	44,105
Total available-for-sale debt and equity securities	$ 1,949,151	$ 27,540	$ (17,675)	$ 1,959,016

December 31, 2024	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 593,810	$ 487	$ (240)	$ 594,057
Debt securities issued by U.S. government agencies	143,647	287	(39)	143,895
Debt securities issued by the U.S. Treasury (1)	657,285	825	(120)	657,990
Debt securities issued by states of the U.S. and political subdivisions of the states	7,516	8	—	7,524
Total debt securities with a maturity of one year or less	1,402,258	1,607	(399)	1,403,466
Corporate debt securities	439,561	723	(2,275)	438,009
Debt securities issued by U.S. government agencies	65,255	137	(289)	65,103
Debt securities issued by the U.S. Treasury	149,086	124	(476)	148,734
Other municipal debt securities	698	—	(2)	696
Total debt securities with a maturity of more than one year	654,600	984	(3,042)	652,542
Total available-for-sale debt securities	$ 2,056,858	$ 2,591	$ (3,441)	$ 2,056,008
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 26	$ (6,660)	$ 5,263
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(7,093)	41,023
Total equity securities	35,012	25,027	(13,753)	46,286
Total available-for-sale debt and equity securities	$ 2,091,870	$ 27,618	$ (17,194)	$ 2,102,294

(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 three months ended March 31, 2025, we recorded a $2.2 million net unrealized loss 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.

The following is a summary of our investments we consider to be temporarily impaired at March 31, 2025 (in thousands, except for number of investments):

	Number of Investments	Less than 12 Months of Temporary Impairment: Estimated Fair Value	Less than 12 Months of Temporary Impairment: Unrealized Losses	More than 12 Months of Temporary Impairment: Estimated Fair Value	More than 12 Months of Temporary Impairment: Unrealized Losses	Total Temporary Impairment: Estimated Fair Value	Total Temporary Impairment: Unrealized Losses
Corporate debt securities	244	$ 466,130	$ (1,236)	$ 9,945	$ (20)	$ 476,075	$ (1,256)
Debt securities issued by U.S. government agencies	26	45,578	(148)	—	—	45,578	(148)
Debt securities issued by the U.S. Treasury	40	271,642	(266)	12,931	(56)	284,573	(322)
Debt securities issued by states of the U.S. and political subdivisions of the states	2	471	—	—	—	471	—
Total temporarily impaired securities	312	$ 783,821	$ (1,650)	$ 22,876	$ (76)	$ 806,697	$ (1,726)

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 March 31, 2025 and December 31, 2024 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 March 31, 2025	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 176,876	$ 176,876	$ —
Corporate debt securities (2)	988,066	—	988,066
Debt securities issued by U.S. government agencies (3)	182,341	—	182,341
Debt securities issued by the U.S. Treasury (3)	739,136	739,136	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	4,670	—	4,670
Other municipal debt (3)	698	—	698
Publicly traded equity securities included in other current assets (4)	3,082	3,082	—
Total	$ 2,094,869	$ 919,094	$ 1,175,775

	At December 31, 2024	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 180,445	$ 180,445	$ —
Corporate debt securities (3)	1,032,066	—	1,032,066
Debt securities issued by U.S. government agencies (3)	208,998	—	208,998
Debt securities issued by the U.S. Treasury (3)	806,724	806,724	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	7,524	—	7,524
Other municipal debt securities (3)	696	—	696
Publicly traded equity securities included in other current assets (4)	5,263	5,263	—
Total	$ 2,241,716	$ 992,432	$ 1,249,284

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

(1) Included in cash and cash equivalents.

(2) $34.0 million was included in cash and cash equivalents, with the difference included in short-term investments.

(3) Included in short-term investments.

(4) Included in other current assets.

Convertible Notes

Our 1.75% Notes and 0% Notes had a fair value of $559.0 million and $623.0 million at March 31, 2025, respectively. Our 1.75% Notes and 0% Notes had a fair value of $569.3 million and $612.8 million at December 31, 2024, 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 months ended March 31, 2025 and 2024 (in thousands):

	Three Months Ended March 31,	
	2025	2024
Cost of sales	$ 100	$ 204
Research, development and patent expense	20,298	22,225
Selling, general and administrative expense	9,320	8,911
Stock-based compensation expense, net of amounts capitalized	29,718	31,340
Capitalized stock-based compensation expense	491	—
Total stock-based compensation expense	$ 30,209	$ 31,340

As of March 31, 2025, total unrecognized estimated stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $51.9 million, $117.1 million and $17.8 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized stock-based compensation expense for future forfeitures, including any PRSUs that do not vest. We expect to recognize the cost of stock-based compensation expense related to our non-vested stock options, RSUs and PRSUs over a weighted average amortization period of 1.3 years, 1.8 years and 1.9 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, 2024 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 three months ended March 31, 2025 and 2024, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2025	2024
Risk-free interest rate	4.5%	4.0%
Dividend yield	0.0%	0.0%
Volatility	41.9%	44.0%
Expected life	6.3 years	6.3 years

ESPP:

	Three Months Ended March 31,	
	2025	2024
Risk-free interest rate	4.3%	5.3%
Dividend yield	0.0%	0.0%
Volatility	41.3%	38.4%
Expected life	6 months	6 months

RSUs:

The weighted-average grant date fair value of RSUs granted to employees for the three months ended March 31, 2025 and 2024 was $33.21 and $53.54 per share, respectively.

PRSUs:

Under the terms of the PRSUs we granted in 2025 and 2024, 100 percent of the PRSUs may vest at the end of the three-year performance period based on our relative total shareholder return, or 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 three months ended March 31, 2025 and 2024 was $48.81 and $78.41 per share, respectively.

10. Income Taxes

We recorded income tax expense of $0.1 million for the three months ended March 31, 2025 compared to $0.1 million for the same period in 2024.

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

11. Liability Related to Sale of Future Royalties

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

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

We determine the effective interest rate used to record interest expense under this agreement based on an estimate of future royalty payments to Royalty Pharma. As of March 31, 2025 and 2024, 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):

Liability related to sale of future royalties, net as of December 31, 2024	$	542,212
Royalty payments to Royalty Pharma		(12,891)
Interest expense related to sale of future royalties		18,670
Amortization of issuance costs related to sale of future royalties		152
Liability related to sale of future royalties, net as of March 31, 2025	$	548,143
Less: Current portion (1)		(12,002)
Liability related to sale of future royalties, net as of March 31, 2025 – Non-current	$	536,141

(1) Included in other current liabilities in our condensed consolidated balance sheet.

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. We used $532.7 million of the net proceeds from the issuance of our 1.75% Notes to repurchase and settle our 0.125% Notes, which matured in December 2024.

At March 31, 2025, 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	$	9.3
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 March 31, 2025, 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	$	3.2
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 warrants will expire in July 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, 2024 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.

Other Terms of Convertible Senior Notes

The 1.75% and 0% Notes are convertible under certain conditions, at the option of the note holders. We can settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the notes prior to maturity, and we do not have to provide a sinking fund for them. Holders of the notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indentures governing the notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus any accrued and unpaid interest.

13. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If we consider the potential loss from any legal proceeding to be probable and we can reasonably estimate the amount, we accrue a liability for the estimated loss. The outcome of any proceeding is not determinable in advance. Therefore, we are required to use significant judgment to determine the probability of a loss and whether the amount of the loss is reasonably estimable. Our assessment of a potential liability and the amount of accruals we recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding and may revise our estimates.

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

14. Segment Information

We operate as a single operating segment, Ionis operations, focused on the research, development and commercialization of our RNA-targeted medicines to bring better futures to people with serious diseases. As the CODM, our Chief Executive Officer manages our company, reviews operating results, assesses performance and allocates resources on an aggregate basis using consolidated net income or loss as the key measure of segment profit or loss. As such, results of our operations are reported on a consolidated basis for purposes of management and segment reporting.

Ionis operations derives its revenues from commercial and R&D revenue sources. Refer to Note 4, *Revenues*, for further details on our sources of revenue.

The following table sets forth information on segment profit or loss, including significant segment expenses (in thousands):

	Three Months Ended March 31,	
	2025	2024
Revenue	$ 131,612	$ 119,497
Less:		
Cost of sales	1,363	1,952
Drug discovery	26,989	28,171
Drug development	112,946	125,751
Medical affairs	5,642	4,676
Manufacturing and development chemistry	14,281	11,441
R&D support	20,553	21,946
Selling, general and administrative	66,980	43,733
Other segment items (1)	29,796	24,630
Consolidated net loss	$ (146,938)	$ (142,803)

(1) Other segment items include stock-based compensation expense, investment income, interest expense, gain or loss on investments, other income or expense and income tax expense or benefit.

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," the "Company," "we," "our," and "us," means Ionis Pharmaceuticals, Inc. and its subsidiaries.

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, 2024, 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, we have invented medicines that bring better futures to people with serious diseases. As a pioneer in RNA-targeted medicines with a deep understanding of disease biology and an industry-leading drug discovery technology, we are driven to deliver innovative, life-changing advances for patients.

With our commercial launch of TRYNGOLZA (olezarsen) in the United States, or U.S., following its approval by the U.S. Food and Drug Administration, or FDA, we began a new chapter as a fully integrated commercial-stage biotechnology company. We currently have six marketed medicines to treat serious diseases: TRYNGOLZA, WAINUA (eplontersen), SPINRAZA (nusinersen), QALSODY (tofersen), TEGSEDI (inotersen) and WAYLIVRA (volanesorsen). In addition, we are also positioned to independently launch multiple medicines in the next two years, including donidalorsen for the treatment of hereditary angioedema, or HAE. Donidalorsen is currently under regulatory review in the U.S., positioning us for our second independent commercial launch in the second half of this year. We are also on track for Phase 3 readouts later this year, which include olezarsen for severe hypertriglyceridemia, or sHTG, and zilganersen for Alexander disease, or AxD. We also have a rich innovative pipeline across our focus areas of neurology, cardiology and select areas of high patient need. We currently have three wholly owned medicines and six partnered medicines in Phase 3 development and additional medicines in early and mid-stage development, including ION528 for Angelman syndrome, or AS, which we plan to advance into a Phase 3 study in the second quarter of 2025.

Our multiple sources of revenue and capital structure enable our continued investments to support ongoing and upcoming planned launches and to advance our wholly owned medicines in development. Our key recent achievements, combined with our independent and partnered product launches anticipated over the next three years, position us well to help millions of patients with serious diseases and to deliver increasing product and royalty revenue.

Our Marketed Medicines

TRYNGOLZA is a once monthly, self-administered LIgand-Conjugated Antisense, or LICA, medicine approved in the U.S. as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome, or FCS. TRYNGOLZA is the first and only FDA-approved treatment that significantly and substantially reduces triglyceride levels in adults with FCS and provides a clinically meaningful reduction in acute pancreatitis, or AP, events. TRYNGOLZA is the first medicine we are commercializing independently in the U.S. TRYNGOLZA is currently under regulatory review in the European Union, or EU. Sobi has exclusive rights to commercialize TRYNGOLZA in most countries outside of the U.S., Canada and China.

WAINUA (WAINZUA in Europe) is a once monthly, self-administered subcutaneous LICA medicine that is approved in the U.S., EU and other countries for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis, or ATTRv-PN, a debilitating, progressive, and fatal disease. WAINUA is the only approved medicine for the treatment of ATTRv-PN that can be self-administered via an auto-injector. The launch of WAINUA is underway in numerous countries, including the EU, following the approval by the European Commission, or EC, in March 2025. AstraZeneca has exclusive rights to commercialize WAINUA outside of the U.S. From inception through March 31, 2025, we have earned more than $545 million in revenues from our WAINUA collaboration, including approximately $30 million in royalties on sales of WAINUA.

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 March 31, 2025, we have earned more than $2.3 billion in revenues from our SPINRAZA collaboration, including more than $1.9 billion in royalties on sales of SPINRAZA.

QALSODY is an antisense medicine that received accelerated approval from the 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. QALSODY was the first treatment approved to target a genetic cause of ALS. Our partner, Biogen, is responsible for commercializing QALSODY worldwide. 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.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in Europe 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 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 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.

Our Innovative Late-Stage Pipeline of Ionis-Owned Investigational Medicines

Olezarsen is our medicine in development for sHTG, a second potential indication which has a more prevalent patient population. 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. In March 2025, we published the Phase 3 study design and baseline characteristics for the CORE, CORE2 and ESSENCE studies in the *American Heart Journal*. We licensed commercialization rights for olezarsen to Sobi in most countries outside of the U.S., Canada and China, and Theratechnologies in Canada.

Donidalorsen is our medicine in development for the prophylactic treatment of HAE. Donidalorsen is currently under regulatory review in the U.S. with a Prescription Drug User Fee Act, or PDUFA, action date of August 21, 2025. Donidalorsen is also under regulatory review in the EU. Our regulatory submissions are 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 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.” We licensed commercialization rights for donidalorsen to Otsuka Pharmaceutical Co., Ltd., or Otsuka, in Europe and the Asia-Pacific region. In addition, we licensed commercialization rights for donidalorsen to Theratechnologies in Canada. The FDA and EMA granted Orphan Drug designation to donidalorsen.

Zilganersen is our medicine in development for 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.

ION582 is our medicine in development for AS. We are conducting the ongoing open label Phase 1/2 study, HALOS, of ION582 in patients with AS designed to assess the safety, tolerability and activity of multiple ascending doses of ION582 administered intrathecally. In 2024, we presented positive results from the completed multiple ascending dose, or MAD, portion of the study in people with AS. Based on the positive results from the HALOS study and alignment with the FDA, we plan to advance ION582 into Phase 3 development in the second quarter of 2025. The FDA and EMA granted Orphan Drug designation to ION582. Additionally, the FDA granted Fast Track and Rare Pediatric designations to ION582.

Our Innovative Late-Stage Pipeline of Partnered Investigational Medicines

Eplontersen is our medicine in development to treat patients with transthyretin amyloidosis cardiomyopathy, or ATTR-CM. We completed enrollment in the Phase 3 CARDIO-TTRansform study in July 2023. The FDA granted Fast Track designation to eplontersen for the treatment of patients with ATTR-CM. Additionally, the FDA and EMA granted Orphan Drug designation to eplontersen for the treatment of ATTR.

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 Phase 3 Lp(a) HORIZON cardiovascular outcome study in patients with elevated Lp(a)-driven CVD, which achieved full enrollment in July 2022 with more than 8,000 patients. The study design and baseline characteristics of the Phase 3 Lp(a) HORIZON study were published in the *American Heart Journal* in April 2025. The FDA granted Fast Track designation and the Center for Drug Evaluation of China National Medical Products Administration granted Breakthrough Therapy designation to pelacarsen for the treatment of patients with elevated Lp(a) and established CVD.

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. 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.

Sefaxersen is our medicine in development for immunoglobulin A, or IgA, nephropathy, or IgAN. In the second quarter of 2023, Roche advanced sefaxersen into Phase 3 development in patients with IgAN based on interim Phase 2 data.

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. We licensed global commercialization rights for ulefnersen to Otsuka. The FDA and EMA granted Orphan Drug designation to ulefnersen.

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, 2024.

Results of Operations

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

	Three Months Ended March 31	
	2025	2024
Total revenue	$ 131.6	$ 119.5
Total operating expenses	$ 278.5	$ 269.0
Loss from operations	$ (146.9)	$ (149.5)
Net loss	$ (146.9)	$ (142.8)

Revenue

Total revenue for the three months ended March 31, 2025 was $131.6 million compared to $119.5 million for the same period in 2024 and was comprised of the following (in millions):

	Three Months Ended March 31,	
	2025	2024
Revenue:		
Commercial revenue:		
Product sales, net:		
TRYNGOLZA sales, net	$ 6.3	$ —
Total product sales, net	6.3	—
Royalty revenue:		
SPINRAZA royalties	48.0	38.5
WAINUA royalties	9.4	1.1
Other royalties	6.8	9.8
Total royalty revenue	64.2	49.4
Other commercial revenue:		
TEGSEDI and WAYLIVRA revenue, net	5.7	8.6
Other revenue	—	1.6
Total other commercial revenue	5.7	10.2
Total commercial revenue	76.2	59.6
Research and development revenue:		
Collaborative agreement revenue	45.0	49.3
WAINUA joint development revenue	10.4	10.6
Total research and development revenue	55.4	59.9
Total revenue	$ 131.6	$ 119.5

Commercial revenue for the three months ended March 31, 2025 increased 28% compared to the same period in 2024, driven in part by revenue from U.S. product sales from the launch of TRYNGOLZA. Higher royalty revenues from SPINRAZA, WAINUA and QALSODY also contributed to the year over year increase.

The remainder of our revenue came from programs under our research and development, or R&D, collaborations, reflecting the value that our pipeline and technology continue to generate.

WAINUA (Eplontersen) Collaboration with AstraZeneca

Our financial results for the three months ended March 31, 2025 and 2024 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 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 March 31,	
	2025	2024
WAINUA joint development revenue	$ 10.4	$ 10.6
Research and development expenses related to Phase 3 development of WAINUA	21.5	22.7
Medical affairs expenses for WAINUA	1.6	1.3
Commercialization expenses for WAINUA	7.7	6.0

Operating Expenses

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

	Three Months Ended March 31,	
	2025	2024
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 248.8	$ 237.7
Non-cash compensation expense related to equity awards	29.7	31.3
Total operating expenses	$ 278.5	$ 269.0

Operating expenses, excluding non-cash compensation expense related to equity awards, for the three months ended March 31, 2025 increased slightly compared to the same period in 2024. SG&A expenses increased year over year primarily due to the launches of WAINUA and TRYNGOLZA, and advancing launch preparation activities for donidalorsen. R&D expenses decreased year over year as several late-stage studies ended. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the remainder of 2025 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 commercial revenue, which consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TRYNGOLZA, TEGSEDI and WAYLIVRA and certain associated period costs.

Cost of sales for a newly launched product, such as TRYNGOLZA, does not include the full cost of manufacturing until we manufacture and sell additional inventory after exhausting pre-launch inventory, which we previously recorded as R&D expense.

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

	Three Months Ended March 31,	
	2025	2024
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 1.4	$ 2.0
Non-cash compensation expense related to equity awards	0.1	0.2
Total cost of sales	$ 1.5	$ 2.2

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 March 31,	
	2025	2024
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 180.4	$ 192.0
Non-cash compensation expense related to equity awards	20.4	22.2
Total research, development and patent expenses	$ 200.8	$ 214.2

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 March 31,	
	2025	2024
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 27.0	$ 28.2
Non-cash compensation expense related to equity awards	4.1	4.3
Total drug discovery expenses	$ 31.1	$ 32.5

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, were essentially flat in the three months ended March 31, 2025 compared to the same period in 2024.

Drug Development

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

	Three Months Ended March 31,	
	2025	2024
Eplontersen	$ 21.1	$ 21.7
Olezarsen	24.9	39.5
Donidalorsen	5.1	4.8
Zilganersen	5.2	2.1
Ulefnersen	3.0	3.5
Other development projects	22.2	25.1
Development overhead expenses	31.4	29.1
Total drug development expenses, excluding non-cash compensation expense related to equity awards	112.9	125.8
Non-cash compensation expense related to equity awards	9.5	10.4
Total drug development expenses	$ 122.4	$ 136.2

Our development expenses, excluding non-cash compensation expense related to equity awards, decreased for the three months ended March 31, 2025 compared to the same period in 2024 as several late-stage studies ended. We expect our development expenses will continue to stabilize 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 March 31,	
	2025	2024
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 5.6	$ 4.7
Non-cash compensation expense related to equity awards	0.3	0.9
Total medical affairs expenses	$ 5.9	$ 5.6

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2025 compared to the same period in 2024 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 March 31,	
	2025	2024
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 14.3	$ 11.4
Non-cash compensation expense related to equity awards	2.1	2.3
Total manufacturing and development chemistry expenses	$ 16.4	$ 13.7

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2025 compared to the same period in 2024 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 March 31,	
	2025	2024
Occupancy	$ 7.3	$ 7.1
Personnel costs	6.8	7.8
Computer software and licenses	3.2	1.6
Insurance	1.0	0.9
Patent expenses	0.6	0.7
Consulting expenses	0.1	0.6
Other	1.6	3.2
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	20.6	21.9
Non-cash compensation expense related to equity awards	4.4	4.3
Total R&D support expenses	$ 25.0	$ 26.2

R&D support expenses, excluding non-cash compensation expense related to equity awards, were essentially flat in the three months ended March 31, 2025 compared to the same period in 2024.

Selling, General and Administrative Expenses

SG&A expenses include personnel, information technology systems and outside costs associated with the commercialization and pre-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 and cost sharing payments associated with co-commercialization activities under our WAINUA collaboration with AstraZeneca.

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

	Three Months Ended March 31,	
	2025	2024
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 67.0	$ 43.7
Non-cash compensation expense related to equity awards	9.3	8.9
Total selling, general and administrative expenses	$ 76.3	$ 52.6

SG&A expenses, excluding non-cash compensation expense related to equity awards, increased in the three months ended March 31, 2025 compared to the same period in 2024 due to the launches of WAINUA and TRYNGOLZA and advancing launch preparation activities for donidalorsen. We expect SG&A expenses to increase as we continue to invest in our independent commercial launches.

Investment Income

Investment income for the three months ended March 31, 2025 was $24.7 million compared to $26.3 million for the same period in 2024. Our investment income decreased primarily due to a decrease in interest rates associated with our investments during the three months ended March 31, 2025 compared to the same period in 2024.

Interest Expense

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

	Three Months Ended March 31,	
	2025	2024
Convertible notes:		
Non-cash amortization of debt issuance costs	$ 1.5	$ 1.6
Interest expense payable in cash	2.5	2.5
Interest on mortgage for manufacturing facility	0.1	0.1
Total interest expense	$ 4.1	$ 4.2

Interest Expense Related to Sale of Future Royalties

We recorded $18.8 million and $18.0 million of interest expense related to the sale of future royalties in the three months ended March 31, 2025 and 2024. respectively. These amounts are related to the Royalty Pharma Investments, or 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

We recorded a net loss on investments of $2.2 million for the three months ended March 31, 2025 compared to a net gain on investments of $2.3 million for the same period in 2024 primarily due to changes in the fair value of our investments in publicly traded biotechnology companies.

Income Tax Expense

We recorded income tax expense of $0.1 million for the three months ended March 31, 2025 compared to $0.1 million for the same period in 2024.

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

Net Loss and Net Loss per Share

We had a net loss of $146.9 million for the three months ended March 31, 2025 compared to a net loss of $142.8 million for the same period in 2024, which reflects the fluctuations discussed above. Our basic and diluted net loss per share for the three months ended March 31, 2025 and 2024 was $0.93 and $0.98, respectively.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also financed our operations from commercial revenue from SPINRAZA, WAINUA and QALSODY royalties and TEGSEDI and WAYLIVRA commercial revenue. In addition, we began earning commercial revenue from TRYNGOLZA product sales in late December 2024. From our inception through March 31, 2025, we have earned approximately $8.0 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 March 31, 2025, we have raised net proceeds of approximately $2.6 billion from the sale of our equity securities. Additionally, from our inception through March 31, 2025, we have borrowed approximately $2.7 billion under long-term debt arrangements and received proceeds of $0.5 billion from the sale of future royalties to finance a portion of our operations.

From December 31, 2024 to March 31, 2025, our working capital decreased as our cash, cash equivalents and short-term investments decreased, while 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 March 31, 2025. 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)	$ 610.3	$ 10.1	$ 600.2
0% Notes (principal payable) (1)	632.5	—	632.5
Operating leases	255.0	20.9	234.1
Building mortgage payments (principal and interest payable)	9.5	0.5	9.0
Other obligations (principal and interest payable)	0.7	0.1	0.6
Total	$ 1,508.0	$ 31.6	$ 1,476.4

(1) Our 0% Notes become due in April 2026.

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 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2024 for further details on our operating facilities.

Operating Leases

Refer to Part IV, Item 15, Note 7 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2024 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 March 31, 2025 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 March 31, 2025. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2025.

We also performed an evaluation of any changes in our internal controls over financial reporting that occurred during our last fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting. We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. That evaluation did not identify any changes in our internal controls over financial reporting that occurred during our latest fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

For details of legal proceedings, refer to Part I, Item 1, Note 13, *Legal Proceedings*, in the Notes to 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, 2024.

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 events;
- Our dependence upon our own and third-party information technology systems; 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 effectively establish or maintain an effective commercialization infrastructure, or enter into agreements with third parties to commercialize our medicines, we may not be able to successfully commercialize our medicines.

We have historically relied on third parties to commercialize our marketed medicines and have limited experience as a company in commercializing medicines. TRYNGOLZA is our first independently launched medicine and we expect to independently launch additional medicines in the future. Any failure to effectively commercialize our medicines, including our failure to allocate resources to our commercial launches efficiently or timely, could adversely impact the revenue we generate from our medicines. If the commercialization of TRYNGOLZA and future sales are less successful than anticipated by us or our investors or securities analysts, our stock price could decline and our business may be harmed.

We will have to continue to invest significant financial and management resources to build and maintain the infrastructure required to successfully commercialize our medicines. We will need to establish and maintain effective sales teams for each of our independently launched medicines and there are significant risks involved in 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 must also continue to scale-up existing internal support functions to aid our commercialization efforts. Further, these existing support functions will need to work effectively in coordination with new commercial functional areas. Any failure to establish or maintain an effective commercialization infrastructure, including our sales, marketing, market access, distribution, and related capabilities, scale-up our existing support functions, or effectively integrate new functional areas, could adversely affect our ability to successfully commercialize our medicines.

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. In addition, 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.

The proximity of our planned upcoming independent launches could increase the likelihood that the risks set forth above will occur.

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 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 several 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, public perception regarding 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, the product label for WAYLIVRA in the EU requires regular blood monitoring, which has negatively affected our ability to attract and retain patients for this medicine.

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. The IRA, among other things, (1) directs HHS to negotiate the price of certain single-source drugs and biologics that have been on the market for at least seven years covered under Medicare, or the Medicare Drug Price Negotiation Program, and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions began to take effect progressively starting in fiscal year 2023, although the Medicare Drug Price Negotiation Program is currently subject to legal challenges. Under this program, HHS has already announced the agreed-upon prices of the first drugs that were subject to price negotiations and will announce the agreed-upon prices of additional drugs in the coming years. In response to an October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center that 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, particularly in light of the recent U.S. presidential and congressional elections.

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 that our own 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 or of medicines we are commercializing. For example:

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Acoramidis, patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with WAINUA;
- Nexiguran ziclumeran, ALXN2220 and NNC6019-0001 could compete with WAINUA;
- Plozasiran, pegozafermin and NST-1024 could compete with TRYNGOLZA and WAYLIVRA;
- 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, VIR-3434, BRII-179, AB-729, selgantolimod, bersacapavir, REP 2139-Mg and VTP-300 could complete with bepirovirsen;
- Budesonide, sparsentan, atrasentan, iptacopan, zigakibart, sibeprenlimab, atacicept, ravulizumab, vemircopan, felzartamab, telitacicept and povetacicept could compete with sefaxersen; and
- GTX-102, alogabat and NNZ-2591 could compete with ION582.

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. The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine through the product label. 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.

Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. Additionally, 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 the 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 are co-developing and co-commercializing WAINUA in the U.S. and AstraZeneca has 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 (1) the amount and timing of resources that AstraZeneca devotes to our collaboration, particularly outside of the U.S; (2) the pricing and reimbursement strategies for WAINUA; and (3) whether AstraZeneca elects to terminate the collaborative arrangement. 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. We will also need to ensure that we have the manufacturing capabilities in place to support advances in our drug development activities, such as new chemistries. 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. If a supplier chooses to devote more resources to other products, especially products with higher manufacturing capacity needs, that could impact such supplier's capability to deliver our requirements timely. 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.

We rely on third-party manufacturers to supply the drug substance and drug product for TRYNGOLZA and WAINUA and drug product for WAYLIVRA. The operations of our suppliers, many of which are located outside of the United States, are subject to additional risks that are beyond our control. For example, tariffs on the raw materials, components, or equipment we use to manufacture our products, or on our drug substance or finished products, will increase our manufacturing costs. There have also been Congressional legislative proposals, such as the recent bill titled the BIOSECURE Act, to discourage contracting with Chinese companies for the development or manufacturing of pharmaceutical products. In addition, merger and acquisition activity within the commercial manufacturing space could reduce the availability of resources from our third-party manufacturers. Delays or disruption to our own or third-party commercial manufacturing capabilities for any reason 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. Similarly, topline, preliminary or interim data we release for any of our clinical studies may not be indicative of full or final results from such study.

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 addition, we may release topline, preliminary or interim data for any of our clinical studies. The interim, topline or preliminary results we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. As a result, such data should be viewed with caution until the final data are available.

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 European Commission 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 part of our strategy to fund the advancement and commercialization of some 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 those 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. While we are now commercializing some of our medicines independently, we still 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 sefaxersen.

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, sefaxersen and pelacarsen.

We may not be able to benefit from designations for our medicines from regulatory authorities that are intended to confer benefits such as financial incentives or an accelerated regulatory pathway.

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 TRYNGOLZA for the treatment of patients with FCS, to WAINUA for the treatment of patients with ATTR, to ulefnersen for the treatment of patients with FUS-ALS, to ION582 for the treatment of patients with Angelman syndrome, and to some of our earlier stage medicines. The FDA and EMA have granted Orphan Drug designation to donidalorsen for the treatment of patients with HAE, to WAYLIVRA for the treatment of patients with FCS, to tominersen for the treatment of patients with HD, and to some of our earlier stage medicines. 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.

We may also seek rare pediatric disease designation for some of our medicines. The FDA defines "rare pediatric disease" as a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years or is a rare disease or condition within the meaning of the Orphan Drug Act. Designation of a medicine as a medicine for a rare pediatric disease does not guarantee that a marketing application for such medicine will meet the eligibility criteria for a rare pediatric disease priority review voucher, or PRV, at the time the application is approved. Under the FDCA, we will need to request a rare pediatric disease PRV in our original marketing application for any potential medicine for which we have received rare pediatric disease designation. The FDA may determine that a marketing application for any such medicine, if approved, does not meet the eligibility criteria for a PRV. Under the current statutory sunset provisions, after December 20, 2024, the FDA may only award a PRV for an approved rare pediatric disease application if the sponsor has rare pediatric disease designation for the drug or biologic that is the subject of such application, and that designation was granted by December 20, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease PRVs. However, it is possible the authority for FDA to award rare pediatric disease PRV will be further extended by Congress.

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 building and maintaining new support functions and scaling up existing internal support functions and expanding our manufacturing capabilities. All of these activities will require significant cash. As of March 31, 2025, we had cash, cash equivalents and short-term investments equal to $2.1 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including 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 March 31, 2025, we had an accumulated deficit of approximately $2.4 billion and stockholders' equity of approximately $0.5 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 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, scientific and commercial staff. We do not have employment agreements with any of our employees that would prevent them from leaving us. The loss of our key management, 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, fires, earthquakes, war, civil or political unrest, terrorism or disruptions of the U.S. government.*

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 fires, hurricanes, tornadoes, droughts, floods, or other events that may result from the impact of climate change on the environment, any of which could impact our business and manufacturing operations. 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, and various regions within California have recently experienced numerous catastrophic wildfires. We manufacture the finished drug product for TRYNGOLZA, WAYLIVRA and eplontersen for ongoing clinical trials at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA and QALSODY and AstraZeneca is responsible for WAINUA's commercial drug supply. 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 staffing shortages or a shutdown or other significant disruption of the U.S. government, including the FDA or the U.S. PTO.

Risks related to personal information, cybersecurity, social media and artificial intelligence

We are dependent on data as well as information technology systems and infrastructure, which exposes us to data protection risks.

We are dependent upon our own and third-party data as well as information technology systems and infrastructure, including mobile technologies, to operate our business. The personal information we process subjects us to stringent and evolving U.S. and foreign laws, rules and regulations, contractual obligations, industry standards and other obligations related to data privacy and security. Our personal information obligations require us to implement and maintain certain practices, including those in relation to cross-border transfers of personal information. The multitude and complexity of our information technology systems and infrastructure make them vulnerable to a variety of evolving threats that may result in systems or data interruption, corruption, destruction, disruption of data integrity, malicious intrusion, or random attacks or other compromise (such as due to malfunctions, software vulnerabilities, natural disasters, telecommunications failures, malicious actors and personnel error). Data privacy or security incidents or breaches 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. Cyber-attacks are increasing in their frequency, sophistication and intensity, particularly as companies (including us) continue to move to more remote work structures. 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 the Middle East and the surrounding areas, or collectively, conflicts in Eastern Europe and the Middle East, as well as related political or economic responses and counter-responses by various global actors.

Cybersecurity related events could include the deployment or use of harmful malware or malicious code, denial-of-service attacks, credential stuffing attacks, credential harvesting attacks, social engineering attacks (including deep fakes), ransomware and other means to affect the confidentiality, integrity or availability of our data as well as information systems and infrastructure. Our current, past and prospective business partners face similar risks and any security breaches of their systems could adversely affect our security posture. A security breach or privacy violation (including perceived breaches or violations) could result in any of the following, any of which could disrupt our business and result in increased costs or loss of revenue:

- harm our reputation;
- delay progress on the development of our medicines;
- compel us to comply with applicable security or data breach notification obligations (including laws);
- result in the diversion of monetary funds and other company resources;
- subject us to financial or other penalties, regulatory investigations or actions, including mandatory and costly corrective actions; and
- require us to verify the correctness of database contents and otherwise subject us to litigation or other liabilities.

Risk mitigation strategies such as liability limitations in our contracts and insurance coverage may prove inadequate if there is a security breach or privacy violation. While we have invested, and continue to invest, in the protection of our data and information technology systems and infrastructure, our efforts may not be successful. Non-compliance with relevant data protection obligations or a failure to secure our data, information technology systems or infrastructure 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 disclosing clinical data, when we anticipate completing a clinical study, 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. In addition, our share price may be dependent upon the valuations and recommendations of the analysts who cover our business. If our results do not meet these analysts' forecasts, the expectations of our investors or the financial guidance we provide to investors in any period, the market price of our common stock could decline. Our ability to meet analysts' forecasts, investors' expectations and our financial guidance is substantially dependent on our ability to maintain or increase sales of our commercial medicines, both partnered and unpartnered.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2025, the closing market price of our common stock ranged from $51.86 to $30.17 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, events such as recent tariffs announcements and the ongoing conflicts in Eastern Europe and the Middle East 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.

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 tariffs announcements and the ongoing conflicts in Eastern Europe and the Middle East. 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 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;
- the potential for a local seller, faced with higher local prices, importing medicines from an international market with lower prices rather than buying such medicines locally, which is referred to as parallel importation;
- 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.

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 2024, we used $44.5 million of the net proceeds to settle the remaining principal balance of our 0.125% Notes upon maturity. 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. For our 0.125% Notes, the note hedges expired upon maturity of the 0.125% Notes and the warrants began expiring in March 2025. Terminating or unwinding the call spread transactions for our 0% Notes 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 21.6 million shares of our common stock upon conversion of our 1.75% Notes and 0% Notes. In connection with the issuance of the 0% Notes, we entered into certain call spread transactions covering 10.9 million shares that we expect will offset the dilution to holders of common stock upon any conversion of those notes. 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. 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, 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 offset any cash payments we are required to make in excess of the principal amount of the converted 0% 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.

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.

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. For example, in June 2024, California enacted Senate Bill 167, or SB 167, which, with certain exceptions, suspends the ability to use California net operating losses to offset California income and limits the ability to use California business tax credits to offset California taxes, for taxable years beginning after 2023 and before 2027.

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

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us.

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and foreign income taxes, sales taxes in the U.S., withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. In particular, our tax obligations and effective tax rate in the jurisdictions in which we conduct business could increase in the future as a result of the base erosion and profit shifting, or BEPS, project led by the Organization for Economic Co-operation and Development, or OECD, and other initiatives led by the OECD or the European Commission. The OECD is leading work on an iteration of the BEPS project based on two "pillars" (subject to certain revenue thresholds), involving the reallocation of taxing rights in respect of certain multinational enterprises above a fixed profit margin to the jurisdictions in which they carry on business) (referred to as "Pillar One") and imposing a minimum effective corporate tax rate on certain multinational enterprises (referred to as "Pillar Two"). Based on the minimum revenue thresholds we do not expect to fall within the scope of these requirements in the near term.

We may be audited in various jurisdictions, and such jurisdictions may assess additional income, sales and value-added or other 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 March 31, 2025, our directors and officers (as defined in Rule 16a-1(f) under the Exchange Act), or Section 16 officers and directors, did not adopt or terminate contracts, instructions or written plans for the purchase or sale of our securities.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Third Amended Non-Employee Director Compensation Policy.
10.2	License Agreement between Ionis Pharmaceuticals, Inc. and Ono Pharmaceutical Co., Ltd., dated March 10, 2025. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, 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)	April 30, 2025
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	April 30, 2025

Exhibit 10.1

Third Amended Non-Employee Director Compensation Policy
As of March 6, 2025

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

Cash Compensation

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

Role	Cash Compensation
Board Member (base retainer)	$ 60,000
Non-Executive Chairman of the Board (additional)	$ 40,000
Independent Lead Director (additional)	$ 40,000
Committee Chair (additional):	
-Audit	$ 25,000
-Compliance	$ 20,000
-Compensation	$ 20,000
-Finance	$ 20,000
-Nominating, Governance and Review	$ 20,000
-Science/Medical	$ 20,000
Committee Member (additional):	
-Audit	$ 12,500
-Compliance	$ 10,000
-Compensation	$ 10,000
-Finance	$ 10,000
-Nominating, Governance and Review	$ 10,000
-Science/Medical	$ 10,000

Equity Compensation

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

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

*These equity awards are to be automatically granted pursuant to the terms of the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors Stock Option Plan as approved by our stockholders on June 4, 2020 (the ***"NED Plan"***). Notwithstanding the terms of the NED Plan, the following annual equity compensation limits will apply to all non-employee Directors through May 24, 2026: (1) incumbent non-employee Directors will receive no more than $450,000 in annual equity compensation per year based on the aggregate grant date fair value (as determined in accordance with FASB Topic ASC 718 or its successor), and (2) newly appointed non-employee Directors will receive no more than $675,000 in initial equity compensation based on the aggregate grant date fair value (as determined in accordance with FASB Topic ASC 718 or its successor).

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

As set forth in the NED Plan, one-third of the shares subject to stock options or restricted stock units for initial grants to new non-employee Directors vest on each annual anniversary of the date of grant and annual grants vest on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.

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

Review of Non-Employee Director Compensation Policy

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

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

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

Execution Version

Exhibit 10.2

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

LICENSE AGREEMENT

BETWEEN

IONIS PHARMACEUTICALS, INC.

AND

ONO PHARMACEUTICAL CO., LTD.

Dated March 10, 2025

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LICENSE AGREEMENT

This **License Agreement** (this "***Agreement***") is signed as of March 10, 2025 (the "***Execution Date***") between **Ionis Pharmaceuticals, Inc.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010, USA ("***Ionis***"), and **Ono Pharmaceutical Co., Ltd.**, a company organized and existing under the laws of Japan, having its principal place of business at 8-2 Kyutaromachi 1-chome, Chuo-ku, Osaka-shi, Osaka 541-8564, Japan ("***Ono***"). Ionis and Ono may be referred to in this Agreement individually as a "***Party***" and collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in Appendix 1. All attached appendices and schedules are part of this Agreement.

RECITALS

WHEREAS, Ionis possesses certain Patent Rights, Know-How, technology and expertise with respect to research, development, and manufacturing of RNA-targeted antisense drugs, and is currently developing the Licensed Product;

WHEREAS, Ono (itself and through its Affiliates) has expertise in the development of biopharmaceutical products and has regulatory, development, and commercial capabilities to bring the Licensed Products to patients in the Territory; and

WHEREAS, Ono wishes to receive from Ionis, and Ionis desires to grant to Ono a worldwide license to develop, manufacture, and commercialize the Licensed Products as set forth in, and subject to the terms of, this Agreement.

NOW THEREFORE, the Parties agree as follows:

ARTICLE 1
OVERVIEW

1.1 **Development and Commercialization**. As of the Execution Date, Ionis is Developing the Licensed Product in an ongoing Clinical Trial in the Territory (such study is further described and defined in Section 7.1 (Ongoing Clinical Trial)). Under this Agreement, the Parties intend that, as between the Parties: (a) Ionis will continue to conduct the Ongoing Clinical Trial, at [***] cost and expense, in accordance with the Ongoing Clinical Trial Development Plan, (b) if requested by Ono, Ionis will conduct an extension of the Ongoing Clinical Trial at [***] cost and expense, (c) other than the Ongoing Clinical Trial, including any extension of such study, Ono will conduct all further Development of the Licensed Product in the Territory, which Development will be at [***] cost and expense, and (d) Ono will seek Regulatory Approval for the Licensed Product in the Territory and, following Regulatory Approval, Commercialize the Licensed Product in the Territory.

1.2 **Governance**. The Parties have agreed to form a joint steering committee to oversee and coordinate the Development activities with respect to the Licensed Products under this Agreement through the [***] Regulatory Approval of the [***] Licensed Product [***].

1.3 **Purpose**. The purpose of this Article 1 (Overview) is to provide a high-level overview of the roles, responsibilities, rights, and obligations of each Party under this Agreement, and therefore, this Article 1 (Overview) is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

ARTICLE 2
LICENSES

2.1 **License Grant to Ono**. Subject to the terms of this Agreement (including Ionis' retained rights set forth in Section 2.6 (No Other Rights and Retained Rights)), and effective as of the Effective Date, Ionis hereby grants to Ono:

2.1.1 an exclusive (even as to Ionis and its Affiliates), royalty-bearing license, with the right to grant sublicenses (through multiple tiers, solely in accordance with Section 2.2.1(a) (Rights of Ono to Grant Sublicenses)), under the Ionis Product-Specific Technology and Ionis Core Technology, in each case to Develop, Manufacture, Commercialize and otherwise Exploit the Licensed Compounds and the Licensed Products in the Field in the Territory; and

2.1.2 a non-exclusive, royalty-bearing license, with the right to grant sublicenses (solely in accordance with Section 2.2.1(b) (Rights of Ono to Grant Sublicenses)), under the Ionis Manufacturing and Analytical Technology to Manufacture the Licensed Compounds and the Licensed Products in the Field in the Territory, solely for the Development and Commercialization of the Licensed Products in the Field in the Territory.

2.2 **Sublicensing Terms**.

2.2.1 **Rights of Ono to Grant Sublicenses**.

(a) Subject to the terms of this Agreement, Ono may grant sublicenses of the rights granted under Section 2.1.1 to its Affiliates and to Third Parties[***].

(b) Subject to the terms of this Agreement, Ono may grant sublicenses of the rights granted under Section 2.1.2 (i) to its Affiliates to [***], (ii) to [***]; and (iii) to [***] (A) to [***], and (B) to [***].

2.2.2 **Requests to Grant Sublicenses to CMOs**. If Ono provides Ionis with a written request for Ionis to grant a license under the Ionis Manufacturing and Analytical Technology to a Third Party designated by Ono solely for such Third Party to Manufacture the Licensed Compounds in the Territory for Ono, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such Third Party, and such Third Party does not have a valid license granted by Ionis under the Ionis Manufacturing and Analytical Technology, then Ionis will [***]. Before Ionis grants such a license to such Third Party, Ionis will require such Third Party to complete a CMO qualification process, substantially similar to such process Ionis has required of contract manufacturing organizations it has previously enabled under the Ionis Manufacturing and Analytical Technology. Ono and the Third Party will enter into a quality agreement, which will govern quality matters pertaining to the Manufacturing and supply of the Licensed Compounds for Development, Commercialization, and Exploitation purposes in the Territory.

2.2.3 **Sublicense Agreements**. Each sublicense granted by Ono pursuant to this Section 2.2 (Sublicensing Terms) will (a) be subject and subordinate to this Agreement, (b) be consistent with the terms of this Agreement, (c) include obligations of confidentiality and non-use applicable to the Confidential Information of the other Party that are at least as stringent as those set forth in Article 14 (Confidentiality), and (d) include terms that are consistent with the intellectual property provisions set forth in this Agreement. Without limiting the generality of the foregoing, Ono's right to sublicense to Third Parties, including through multiple tiers, is conditioned on every sublicense agreement with a Third Party entered into after the Effective Date [***]. At Ionis' request, Ono will provide Ionis with a copy of any executed sublicense agreement with a Third Party that will perform [***], which copy may be redacted as necessary to protect confidential information that is not necessary to confirm compliance with this Agreement.

2.3 Subcontracting Terms.

2.3.1 **Right to Subcontract**. Each Party may engage one or more Third Party subcontractors to perform services in furtherance of the performance of its obligations or exercise of its rights under this Agreement; *provided* that (a) neither Party will engage any such Third Party that has been Debarred/Excluded, (b) no engagement of any such Third Party subcontractors will relieve the engaging Party of its obligations under this Agreement or any liability hereunder, and (c) the engagement of such Third Party subcontractors is consistent with the engaging Party's standard business practices.

2.3.2 **Subcontract Agreements**. Each agreement pursuant to which a Party engages any Third Party subcontractor to perform its obligations or exercise its rights under this Agreement will (a) be subject and subordinate to this Agreement, (b) be consistent with the terms of this Agreement, (c) include obligations of confidentiality and non-use applicable to the Confidential Information of the other Party that are at least as stringent as those set forth in Article 14 (Confidentiality), and (d) include terms that are consistent with the intellectual property provisions set forth in this Agreement.

2.4 Responsibility for Sublicensees and Subcontractors. Notwithstanding any sublicense or subcontract granted in accordance with Section 2.2 (Sublicensing Terms), Section 2.3 (Subcontracting Terms), or Section 2.5 (Improvement Enabling License), the sublicensing or subcontracting Party will remain primarily liable to the other Party for the performance of all of its obligations under, and such Party's compliance with all provisions of, this Agreement. Each Party agrees that it will be fully responsible and liable for any breach of the terms of this Agreement by any of its Sublicensees or subcontractors to the same extent as if such Party itself had committed any such breach.

2.5 [***].

2.6 No Other Rights and Retained Rights. Nothing in this Agreement will be interpreted to grant a Party any rights under any intellectual property rights owned or Controlled by the other Party, including Ionis Technology or Ono Technology, in each case, that are not expressly granted herein, whether by implication, estoppel, or otherwise. Ono will not practice the Ionis Technology other than as expressly licensed and permitted under this Agreement [***]. Any rights not expressly granted to Ono by Ionis under this Agreement are hereby retained by Ionis, [***]. Without limiting the foregoing, Ionis hereby expressly retains the right to perform (a) Development activities for the Licensed Products worldwide in accordance with the Ongoing Clinical Trial Development Plan, (b) Manufacturing activities worldwide to support Ionis' Development activities under the Ongoing Clinical Trial Development Plan, and (c) Ionis' other obligations under this Agreement.

2.7 Existing Third-Party IP Agreements.

2.7.1 **Compliance**. Ono acknowledges and agrees that (a) the rights and licenses granted to Ono under this Agreement are subject to the applicable terms of all Existing Third-Party IP Agreements with respect to the Ionis Technology that is being sublicensed thereunder, (b) Ionis' ability to comply with its obligations, and grant rights and licenses to Ono, under this Agreement are limited by any and all requirements and restrictions imposed on Ionis under the Existing Third-Party IP Agreements with respect to the Ionis Technology that is being sublicensed by Ionis under such Existing Third-Party IP Agreements, and (c) Ionis will not be required to take any action or inaction pursuant to this Agreement that would cause Ionis to be in breach of any Existing Third-Party IP Agreement or to grant any rights to Ono hereunder that are in violation of, or inconsistent with, any Existing Third-Party IP Agreement, [***]. Ono will, and will cause its Affiliates, licensees, and Sublicensees to, abide by the applicable terms of the Existing Third-Party IP Agreements (to the extent such Existing Third-Party IP Agreements were disclosed to Ono), and, subject to Ionis' compliance with Section 2.7.2 (Existing Third Party IP Amendments), any amendments thereto, to the extent disclosed in the copies of the Existing Third-Party IP Agreements. If [***], which [***], then [***] shall promptly, but in no event less than [***] thereafter, provide written notice thereof to [***]. Subject to [***]. If [***] within [***] of [***], then [***]. Notwithstanding any provision to the contrary in this Agreement, [***].

2.7.2 **Existing Third-Party IP Amendments**. During the Term, Ionis will not[***] terminate any Existing Third-Party IP Agreement or amend any Existing Third-Party IP Agreement, in each case, to the extent that doing so would conflict with, or materially and adversely affect, Ono's rights under this Agreement.

2.8 Future Third-Party IP Agreements.

2.8.1 **Identification of Future Third Party Patent Rights**. If either Party identifies additional Third Party Patent Rights that would be considered Ionis Product-Specific Technology or Ionis Core Technology if Ionis Controlled such Third Party Patent Rights ("***Future Third Party IP***"), then such Party will provide the other Party with written notice of such Future Third Party IP.

2.8.2 **Future Third Party** [***].

(a) **Ono First Right**. If such Party believes that such Future Third Party IP is [***] and would be considered Ionis Product-Specific Patents or Ionis Product-Specific Know-How if Ionis Controlled such Patent Rights or Know-How (such Patent Rights and Know-How, "***Future Third Party*** [***]"), then Ono will have the first right, but not the obligation, to negotiate, and enter into an agreement, with a Third Party to acquire or obtain a license, covenant not to sue, or other similar right to such Future Third Party [***]. If Ono enters into an agreement with such Third Party for rights to such Future Third Party [***], then Ono will pay the financial obligations due under such agreement that are attributable to the Development or Commercialization of any Licensed Product, and, [***].

(b) **Ionis Step-In Right**. If Ono elects not to obtain rights to such Future Third Party [***], then Ono will so notify Ionis, and Ionis may obtain rights to such Future Third Party [***]. If Ionis obtains such rights, then, upon Ono's request, Ionis will include such Future Third Party [***] in the license granted to Ono under Section 2.1 (License Grant to Ono), *so long as* [***].

2.8.3 **Future Third Party** [***].

(a) **Ono First Right**. If such Party believes that such Future Third Party IP is [***] and would be considered Ionis Product-Specific Patents or Ionis Product-Specific Know-How if Ionis Controlled such Patent Rights or Know-How (such Patent Rights and Know-How, "***Future Third Party*** [***]"), then Ono will have the first right, but not the obligation, to negotiate, and enter into an agreement, with a Third Party to acquire or obtain a license, covenant not to sue, or other similar right to such Future Third Party [***]. If Ono enters into an agreement with such Third Party for rights to such Future Third Party [***], then [***].

(b) **Ionis Step-In Right**. If Ono elects not to obtain rights to such Future Third Party [***], then Ono will so notify Ionis, and Ionis may obtain rights to such Future Third Party [***]. If Ionis obtains such rights, then, upon Ono's request, Ionis will include such Future Third Party [***] in the license granted to Ono under Section 2.1 (License Grant to Ono), *so long as* [***].

2.8.4 **Future Third Party Core IP**.

(a) **Ionis First Right**. If such Future Third Party IP would be considered Ionis Core Patents or Ionis Core Know-How if Ionis Controlled such Patent Rights or Know-How (such Patent Rights and Know-How, "***Future Third Party Core IP***"), then Ionis will have the first right, but not the obligation, to negotiate, and enter into an agreement, with a Third Party to acquire or obtain a license, covenant not to sue, or other similar right to such Future Third Party Core IP. If Ionis enters into an agreement with such Third Party for rights to such Future Third Party Core IP, then Ionis will include such Future Third Party Core IP in the license granted to Ono under Section 2.1 (License Grant to Ono), and, subject to Section 11.3.3(d) (Royalty Floor), [***] will pay the financial obligations due under such agreement with respect to such Future Third Party Core IP.

(b) **Ono Step-In Right**. If Ionis elects not to obtain rights to such Future Third Party Core IP, then Ionis will so notify Ono, and Ono may obtain rights to such Future Third Party Core IP. [***].

2.9 [***].

2.9.1 [***].

2.9.2 [***].

ARTICLE 3
EXCLUSIVITY

3.1 **Exclusivity Covenants of the Parties**. Except in the performance of its obligations or exercise of its rights under this Agreement, and except as set forth in Section 3.2 (Limitations and Exceptions to Exclusivity Covenants):

3.1.1 from the Effective Date until the earliest to occur of (a) [***], (b) [***], and (c) the termination of this Agreement, neither Party nor its Affiliates will [***], itself or through a Third Party, [***]; and

3.1.2 from the Effective Date until the earliest to occur of (a) [***] and (b) the termination of this Agreement, neither Party nor its Affiliates will [***], itself or through a Third Party, [***].

3.2 Limitations and Exceptions to Exclusivity Covenants. Notwithstanding anything to the contrary in this Agreement, a Party's practice of the following will not violate Section 3.1 (Exclusivity Covenants of the Parties):

3.2.1 performance of the activities designated to such Party under the Ongoing Clinical Trial Development Plan;

3.2.2 performance of any activities or fulfillment of any obligations under any Prior Agreement;

3.2.3 the granting of, or performance of obligations under, Permitted Licenses;

3.2.4 the performance of non-clinical Development activities; and

3.2.5 the granting of, or performance of obligations or exercise of rights under, [***].

3.3 Effect of Exclusivity on Indications. Ionis and Ono are subject to certain exclusivity covenants under Section 3.1 (Exclusivity Covenants of the Parties); *however*, the Parties acknowledge and agree that each Party (on its own or with or through a Third Party or an Affiliate) may develop and commercialize products for the same indication as a Licensed Product so long as such product is [***]. Unless otherwise agreed in a separate agreement between the Parties, after the expiration of the exclusivity covenants set forth in Section 3.1 (Exclusivity Covenants of the Parties), neither Party will be prohibited from pursuing (on its own or with or through a Third Party or an Affiliate) any products for any target or therapeutic area.

ARTICLE 4
GOVERNANCE

4.1 Joint Steering Committee.

4.1.1 **Formation and Purpose of the JSC**. Within [***] after the Effective Date, Ionis and Ono will establish a joint steering committee ("***JSC***") to oversee, review, monitor, coordinate, and, where specified in this Section 4.1 (Joint Steering Committee), [***] the Parties' [***] activities under this Agreement for the Licensed Products in the Territory and updates to the Ongoing Clinical Trial Development Plan in accordance with this Section 4.1 (Joint Steering Committee). The JSC will dissolve upon [***]. From time to time, the JSC may establish working groups to oversee particular activities, as it deems necessary or advisable (each, a "***Working Group***"). Each Working Group shall consist of such number of representatives of each Party as the JSC determines is appropriate from time to time. Such representatives shall be individuals with expertise relevant to the particular Working Group. Each Working Group shall meet with such frequency as the Working Group, once formed, deems to be advisable. If the Working Group cannot reach unanimity on any topic, the matter shall be immediately referred to the JSC, which shall resolve such matter in accordance with Section 4.3 (Decision-Making) and Section 4.4 (Resolution of Committee Disputes).

4.1.2 **Membership**. The JSC will be composed of an equal number of representatives from each Party who have the appropriate and direct knowledge and expertise and requisite decision-making authority. Each Party may replace any of its representatives on the JSC and appoint a person to fill the vacancy arising from each such replacement. A Party that replaces a representative will notify the other Party at least [***] prior to the next scheduled meeting of the JSC. Ionis will designate one of its JSC members as one of the co-chairpersons of the JSC and Ono will designate one of its members as the other co-chairperson of the JSC (each, a "***JSC Co-Chairperson***"). The JSC Co-Chairpersons or their designees, in collaboration with the Liaisons, will be responsible for calling meetings, preparing and circulating an agenda in advance of each meeting, and preparing and issuing minutes of each meeting promptly thereafter. Such minutes will not be finalized until all JSC members have had [***] to review and confirm the accuracy of such minutes.

4.1.3 **Meetings**. The JSC will hold meetings at such times as it elects to do so, but, (a) until [***], will meet no less frequently than [***], and (b) commencing with the [***], will meet no less frequently than every [***], in each case ((a) and (b)), unless otherwise agreed by the Parties. The JSC may meet in person or by means of audio or video conference as determined by the JSC. Each Party will be responsible for all its own costs and expenses of participating in any JSC meeting.

4.1.4 **Meeting Agendas**. Each Party will disclose to the other Party the proposed agenda items along with appropriate information at least [***] in advance of each meeting of the JSC; *provided* that under exigent circumstances requiring JSC input, a Party may provide its agenda items to the other Party within a shorter period of time in advance of a meeting, or may propose that there not be a specific agenda for a particular meeting, so long as such other Party consents to such later addition of such agenda items or the absence of a specific agenda for such JSC meeting.

4.1.5 **Specific Responsibilities of the JSC**. The responsibilities of the JSC will be to:

(a) manage the overall strategic alignment between the Parties under this Agreement and maintain the relationship between the Parties;

(b) review, discuss, and manage the activities related to the Technology Transfers;

(c) [***];

(d) share information related to, and review and discuss activities and progress under, the Ongoing Clinical Trial Development Plan;

(e) [***];

(f) review and discuss the study design, high-level plan, and timeline for [***] Pivotal Clinical Trial for [***] Licensed Product, as described in Section 7.7 (Pivotal Clinical Trial Design and Regulatory Strategy);

(g) review and discuss the regulatory strategy for [***] Regulatory Approval of [***] Licensed Product [***], as described in Section 7.7 (Pivotal Clinical Trial Design and Regulatory Strategy);

(h) review and discuss any matters related to the Development of the Licensed Products referred to the JSC by either Party's representatives;

(i) review and discuss, either at meetings of the JSC or through any manufacturing Working Group of the JSC, any matters related to Manufacturing and supply chain plans for the Licensed Compounds and Licensed Products, the performance of CMOs that Manufacture the Licensed Compounds and Licensed Products, and any other issues pertaining to the Manufacturing of the Licensed Compounds and Licensed Products; and

(j) perform such other functions as appropriate to further the purposes of this Agreement as determined by the Parties.

4.2 Additional Participants. Employees of a Party or any of its Affiliates involved in the Exploitation of the Licensed Products may attend meetings of the JSC as non-voting participants with the prior notice of the other Party. In addition, with the prior notice of each Party, consultants, representatives, or advisors involved in the same activities and under written obligations of confidentiality and non-use applicable to the Confidential Information of each Party that are at least as stringent as those set forth in Article 14 (Confidentiality) may attend meetings of the JSC as non-voting observers.

4.3 Decision-Making.

4.3.1 **General Decision-Making Process**. Each Party's representatives on the JSC will, collectively, have [***]. The JSC will [***], which will be reflected in the minutes of the committee meeting or [***]. Except as otherwise expressly set forth in this Agreement, the phrase [***] the JSC and similar phrases used in this Agreement will mean [***] in accordance with this Section 4.3 (DecisionMaking-), [***]. [***].

4.3.2 **Decisions of the JSC**. The JSC will use good faith efforts, in compliance with this Section 4.3.2 (Decisions of the JSC), to promptly resolve any such matter for which it has authority. If the JSC does not resolve any such matter within [***], then the Parties may refer such matter to their respective Executive Officers for resolution in accordance with Section 4.4.1 (Referral to Executive Officers).

4.3.3 Except as otherwise expressly stated in this Agreement, the JSC will have no decision-making authority and will act as a forum for sharing information about the activities conducted by the Parties hereunder and as an advisory body, in each case only on the matters described in, and to the extent set forth in, this Agreement.

4.4 Resolution of Committee Disputes.

4.4.1 **Referral to Executive Officers**. If a Party refers a matter to the Executive Officers under Section 4.3.2 (Decisions of the JSC), then the Executive Officers will use good faith efforts to resolve any such matter so referred to them as soon as practicable but, in any event, within [***] after such matter is referred to them, and any final decision that the Executive Officers agree to in writing will be conclusive and binding on the Parties.

4.4.2 **Final Decision-Making Authority**. If the Executive Officers do not reach agreement on any matter referred to them in accordance with Section 4.4.1 (Referral to Executive Officers) within [***] after such matter is referred to them (or such longer period as the Executive Officers may agree upon), then, subject to Section 4.4.3 (Limitations on Decision Making):

(a) **Ionis Final Decision-Making Authority**. Ionis will have final decision-making authority over [***].

(b) **Ono Final Decision-Making Authority**. Ono will have final decision-making authority over [***].

(c) **No Change; Status Quo**. Neither Party will have final decision-making authority with respect to the final resolution of any disagreement related to (a) [***], or (b) [***].

4.4.3 **Limitations on Decision Making**. Notwithstanding anything to the contrary set forth in this Agreement, no decision of the JSC, or a Party's Executive Officer (in the exercise of a Party's decisionmaking authority on any such matters), in each case may, without the other Party's prior written consent, (a) [***], (b) [***], (c) [***], or (d) [***].

4.5 **Day-to-Day Responsibilities**. Each Party will: (a) be responsible for day-to-day implementation and conduct of the activities hereunder for which it has or is otherwise assigned responsibility under this Agreement, *provided* that [***]; and (b) provide the other Party with [***].

4.6 **Liaisons**. Each Party will appoint a representative of such Party to act as its liaison under this Agreement no later than [***] after the Effective Date (each, a "***Liaison***"). The role of the Liaison is to act as a single point of contact between the Parties to ensure a successful relationship under this Agreement. The Liaisons will attend all JSC meetings and will support the JSC Co-Chairpersons in the discharge of their responsibilities. Liaisons will be non-voting participants in all JSC meetings, but a Liaison may bring any matter to the attention of the JSC if such Liaison reasonably believes that such matter warrants such attention. Each Party may change its designated Liaison at any time upon written notice to the other Party. Any Liaison may designate a substitute to temporarily perform the functions of that Liaison by written notice to the other Party. Each Liaison will also: (a) be the point of first referral in all matters of conflict resolution; (b) provide a single point of communication for seeking consensus between the Parties regarding key strategy and plan issues; (c) identify and bring disputes to the attention of the JSC in a timely manner; (d) plan and coordinate cooperative efforts and internal and external communications; and (e) take responsibility for ensuring that governance activities, such as the conduct of required committee meetings and production of meeting minutes, occur as set forth in this Agreement, and that the relevant action items resulting from such meetings are appropriately carried out or otherwise addressed.

ARTICLE 5
CLOSING

5.1 **Closing**. Subject to the last sentence of Section 16.1 (Term), the closing of the transaction contemplated by this Agreement will be deemed to have taken place on the date that all necessary authorizations, consents, orders or approval of, or declarations or filings with, or expirations of waiting periods under the HSR Act, as applicable to the consummation of the transactions contemplated by this Agreement ("***HSR Clearance***") have been received, authorized, permitted, or expired (the "***Effective Date***"). Ono shall immediately provide written notice to Ionis of such Effective Date. Except for the Parties' rights and obligations under Section 7.4 (Development Activities Prior to Effective Date), Article 13 (Representations, Warranties, and Covenants), Article 14 (Confidentiality), Article 17 (Dispute Resolution; Governing Law), and this Article 5 (Closing), which will be effective as of the Execution Date, this Agreement will not become effective until the Effective Date. Upon the occurrence of the Effective Date, all other provisions of this Agreement will become effective automatically without the need for further action by the Parties.

5.2 Antitrust Filings.

5.2.1 The Parties shall, as promptly as practicable (but no later than [***] after the Execution Date, or as otherwise mutually agreed by the Parties and their respective antitrust counsel), and before the expiration of any relevant legal deadline, prepare and file with the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice (collectively, the "***Antitrust Authorities***"), the Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) required for the transactions contemplated hereby, together with all required documentary attachments thereto and any supplement information requested in connection therewith pursuant to the HSR Act (the "***Antitrust Filings***"). Notwithstanding the foregoing, the Parties may, upon mutual agreement, delay the filing of any of the Antitrust Filings if they reasonably believe that such delay would result in obtaining any clearance required under the HSR Act for the consummation of this Agreement and the transactions contemplated hereby more expeditiously. The Parties shall cooperate in the antitrust clearance process, including by furnishing to each other's counsel such necessary information and reasonable assistance as the other may request in connection with its preparation of any filing or submission that is necessary under the HSR Act and to furnish promptly with the Antitrust Authorities any information reasonably requested by them in connection with such filings. Each Party shall be responsible for its own fees, costs, and expenses associated with any Antitrust Filings or in connection with its obligations pursuant to this Section 5.2 (Antitrust Filings).

5.2.2 The Parties shall use their commercially reasonable efforts to promptly obtain HSR Clearance and shall keep each other apprised of the status of any communications with, and any inquiries or requests for additional information from, any Antitrust Authority and shall use commercially reasonable efforts to comply promptly with any such inquiry or request. Commercially reasonable efforts as used in this Section 5.2.2 will not include proposing, negotiating, committing to or effecting, by consent decree, hold separate order, or otherwise, (a) the sale, divestiture, disposition, licensing or sublicensing of any of a Party's or its Affiliates' assets, properties, or business, (b) behavior limitations, conduct restrictions, or commitments with respect to such assets, properties, or business, or of any of the rights or obligations of a Party under this Agreement, or (c) defending through litigation any claim asserted in court by any Third Party that would restrain, prevent, or delay the Effective Date.

5.2.3 Subject to Section 5.2.2, the Parties shall instruct their respective counsel to cooperate with each other and use commercially reasonable efforts to facilitate and expedite the identification and resolution of any issues arising under the HSR Act at the earliest practicable dates. Such commercially reasonable efforts and cooperation include counsel's undertaking to (a) keep each other informed of communications, inquiries, and requests from and to personnel of the reviewing Antitrust Authorities, including by providing copies thereof to the other Party (subject to reasonable redactions for privilege or confidentiality concerns), and (b) confer with each other regarding appropriate contacts with and response to personnel of such Antitrust Authorities and the content of any such contacts or presentations. Each Party shall consult with the other Party, to the extent practicable in advance of participating in any substantive meeting or discussion with any Antitrust Authority with respect to any such filings, applications, investigation, or other inquiry and, to the extent permitted by the relevant Antitrust Authority, give the other Party the opportunity to attend and participate in such meeting or discussion. Each Party shall give the other Party the opportunity to review in advance, and shall consider in good faith the other Party's reasonable comments in connection with, the content of any presentations, white papers, or other written materials to be submitted to any Antitrust Authority. Neither Party shall withdraw its filing under the HSR Act or agree to delay the Effective Date without the prior written consent of the other Party. The Parties' rights and obligations hereunder apply only in so far as they relate to this Agreement and to the transactions contemplated under this Agreement.

ARTICLE 6
TECHNOLOGY TRANSFER

6.1 **Initial Know-How Transfer**. Subject to Section 6.4 (Technology Transfer Costs and Support), at a time period to be agreed upon by the Parties after the Effective Date, Ionis will provide and transfer to Ono copies of the Ionis Know-How (other than Ionis Manufacturing and Analytical Know-How, the transfer of which will be conducted pursuant to Section 6.3 (Manufacturing Technology Transfer)) that (a) exists on the Effective Date, (b) was not previously provided to Ono, (c) is [***] for Ono to Develop, Manufacture, Commercialize, and otherwise Exploit the Licensed Compounds and the Licensed Products in the Territory, and (d) is [***], in each case ((a)-(d)), in the form in which Ionis maintains such Know-How (such transfer, the "***Initial Know-How Transfer***") [***]. Upon Ono's request, Ionis will [***]. Such Initial Know-How Transfer shall include: (i) [***]; (ii) [***]; (iii) [***]; (iv) [***], in each case ((i)-(iv)), [***] for Ono to obtain Regulatory Approvals for the Licensed Products in the Field in the Territory.

6.2 **Additional Know-How Transfer**. Subject to Section 6.4 (Technology Transfer Costs and Support), following the Initial Know-How Transfer, Ionis will make available to Ono all such Ionis Know-How, other than Ionis Manufacturing and Analytical Know-How, in Ionis' possession that (a) is [***], or, (b) [***], in each case ((a) and (b)), that is [***] for the Development, Manufacture, Commercialization, or other Exploitation of the Licensed Compounds and the Licensed Products in the Territory (the "***Additional Know-How Transfer***," and together with the Initial Know-How Transfer, the "***Non-Manufacturing Technology Transfer***"). Ono may only use the Ionis Know-How to perform its obligations or exercise its rights under this Agreement (including, for the avoidance of doubt, the licenses granted under Section 2.1 (License Grant to Ono)) and in accordance with the terms hereof and will not use such Know-How for any other purpose.

6.3 **Manufacturing Technology Transfer**. Subject to Section 6.4 (Technology Transfer Costs and Support), upon Ono's request after the Effective Date at a time mutually agreed by the Parties, Ionis will make available to Ono all Ionis Manufacturing and Analytical Know-How and materials that are [***], for Ono to Manufacture the Licensed Product and Licensed Compound in the Territory, in the form in which Ionis maintains such Know-How and materials (the "***Manufacturing Technology Transfer***"). Upon Ono's request, Ionis will [***]. Any materials provided by Ionis to Ono in connection with the transfer of the Ionis Manufacturing and Analytical Know-How will remain the sole property of Ionis, and Ono will (a) use such materials only in the fulfillment of obligations or exercise of rights under this Agreement (including, for the avoidance of doubt, the licenses granted under Section 2.1 (License Grant to Ono)), and (b) not provide such Ionis Manufacturing and Analytical Know-How or materials to any Third Party, without Ionis' prior written consent, except to its Sublicensees in accordance with Section 2.2.1 (Rights of Ono to Grant Sublicenses).

6.4 **Technology Transfer Costs and Support**. Ionis will perform the Non-Manufacturing Technology Transfer and the Manufacturing Technology Transfer (collectively, the "***Technology Transfers***") including [***] until the earlier of (a) [***], and (b) [***]. Thereafter, if Ono requests, and Ionis agrees to provide, additional support for the Technology Transfers, Ionis will provide [***], and Ono will [***]. In addition, [***], *provided* that any such [***]. [***].

ARTICLE 7
DEVELOPMENT

7.1 **Ongoing Clinical Trial**. As of the Execution Date, Ionis is conducting a Clinical Trial with respect to the Licensed Product under a protocol entitled, "A Phase 2a, Randomized, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ISIS 702843 Administered to Patients with Phlebotomy Dependent Polycythemia Vera (PD-PV)" (the "***Ongoing Clinical Trial***"). The development plan for the Ongoing Clinical Trial mutually approved by the Parties is set forth on SCHEDULE 7.1 (such development plan as it may be modified in accordance with the terms and conditions of this Agreement, the "***Ongoing Clinical Trial Development Plan***"). From time to time during the Term, either Party may submit to the JSC any proposed update to the Ongoing Clinical Trial Development Plan. The JSC will [***] Ongoing Clinical Trial Development Plan. [***], each update to the Ongoing Clinical Trial Development Plan will become effective and supersede the previous Ongoing Clinical Trial Development Plan, as of the date of [***].

7.2 **Extension of Ongoing Clinical Trial.** After the Effective Date, if Ono wishes Ionis to extend the treatment period in the Ongoing Clinical Trial to a treatment period of [***] (the "***Ongoing Clinical Trial Extension***"), then Ono will notify Ionis in writing as soon as possible after the Effective Date, but in any event no later than [***] after the Effective Date, and the Parties, through the JSC, will meet as soon as possible after Ono has notified Ionis of its desire to extend the Ongoing Clinical Trial [***]. Ionis' estimate of such updated development plan and budget are set forth in SCHEDULE 7.2.

7.3 **Performance by Ionis**. With respect to the Ongoing Clinical Trial, including any Ongoing Clinical Trial Extension, Ionis shall update Ono at least [***] every [***] at the meetings of the JSC regarding the progress of the Ongoing Clinical Trial, including any Ongoing Clinical Trial Extension. Such update may be in the form in which Ionis presented such information to its senior management in the regular course of its business. Ionis will use Commercially Reasonable Efforts to complete the Ongoing Clinical Trial, including any Ongoing Clinical Trial Extension, in accordance with the Ongoing Clinical Trial Development Plan. Ionis will conduct all Development activities with respect to the Licensed Compound and the Licensed Product in a good scientific manner, in accordance with GLP and GCP, as applicable, and in compliance with Professional Requirements and Applicable Law. Ionis [***].

7.4 **Development Activities Prior to Effective Date**. After the Execution Date and prior to the Effective Date, Ionis will [***] in accordance with the Ongoing Clinical Trial Development Plan. Ionis will promptly notify Ono if Ionis is required to make any material changes to such performance (a) to comply with any changes in Applicable Law, (b) to comply with specific requirements imposed by Regulatory Authorities, or (c) as Ionis reasonably determines in good faith are necessary for safety reasons.

7.5 **Development Diligence**. From and after the Effective Date, Ionis will be responsible for conducting, and will use Commercially Reasonable Efforts to conduct, the Ongoing Clinical Trial until [***], in accordance with the Ongoing Clinical Trial Development Plan, and, subject to Section 7.6 (Development Costs), any extension of such Ongoing Clinical Trial approved in accordance with Section 7.2 (Extension of Ongoing Clinical Trial). Other than the Ongoing Clinical Trial, Ono will be responsible for Developing, and will use Commercially Reasonable Efforts to [***]. Subject to Section 4.4.3 (Limitations on Decision-Making) and Section 8.8 (No Harmful Actions), [***]. Each Party will conduct all Development activities for which it is responsible under this Agreement in a good scientific manner, in accordance with GLP and GCP, as applicable, and in compliance with Professional Requirements and Applicable Law.

7.6 **Development Costs**.

7.6.1 **Ionis Costs**. Ionis will be solely responsible for (a) [***], and (b) [***].

7.6.2 **Ono Costs**. After the Effective Date, Ono will be solely responsible for [***]. On a Calendar Quarter-by-Calendar Quarter basis, Ionis will issue an invoice for the [***] incurred in each Calendar Quarter no later than [***] after the end of such Calendar Quarter, and Ono will pay the invoiced amounts within [***] after receipt of such invoice.

7.6.3 **Cost Overruns**. Ionis will use Commercially Reasonable Efforts to [***]. Ionis will notify the JSC without undue delay if it anticipates that [***] (a "***Cost Overrun***"). Ionis will [***]. Thereafter, the JSC will promptly meet to evaluate whether [***], and if not, the JSC will discuss what steps to take to [***]. If the JSC [***], then [***].

7.7 **Pivotal Clinical Trial Design and Regulatory Strategy**. Within [***], or a longer period agreed by the Parties, after the Effective Date, Ono will provide to the JSC for review and discussion the proposed design and an initial draft of the high-level development plan, including a timeline, for [***] Pivotal Clinical Trial for [***] Licensed Product, as well as the regulatory strategy for [***] Regulatory Approval of [***] Licensed Product [***]. After submission of the initial draft plan, Ono [***]. The JSC will meet promptly thereafter to discuss the proposed design, plan, and timeline for such study and the proposed regulatory strategy.

7.8 **Development Reports**. At each JSC meeting, (a) Ionis will [***], and (b) Ono will [***]. For [***] after dissolution of the JSC, on a Calendar Year-by-Calendar Year basis, Ono will [***]. Each Party will also promptly provide written notice to the other Party of any significant Development events with respect to the Licensed Products that [***] the other Party under this Agreement.

7.9 **Development Records**. Each Party and its Affiliates will maintain written or electronic records, in sufficient detail, in a good scientific manner (in accordance with GLP, GCP, GMP, and Applicable Laws, as applicable), and appropriate for regulatory and patent purposes, and that are complete and accurate in all material respects and reflect all Development work performed and results achieved, in each case, by or on behalf of such Party and its Affiliates for the Licensed Products.

ARTICLE 8
REGULATORY AFFAIRS

8.1 **Regulatory Responsibility**. Subject to the obligations in this Article 8 (Regulatory Affairs), after the Effective Date, Ono will be responsible for[***] all Regulatory Submissions, communications, and other dealings with Regulatory Authorities related to the Licensed Products in the Territory and the regulatory strategy for the Licensed Products; *provided* that, (a) Ionis shall have the right to [***], (b) Ionis will [***], and (c) Ionis shall have the right to [***]. At a time period to be agreed upon by the Parties after the Effective Date, Ionis will transfer and assign to Ono the Regulatory Submissions, and all related documentation, as applicable, related to the Licensed Products, except, with respect to regulatory filings for Development activities for the Licensed Products for which Ionis is responsible under this Agreement. Without limiting Section 8.4 (Regulatory Submissions) and Section 8.8 (No Harmful Actions), Ono will not be required to delay any submission, correspondence, or communication with any Regulatory Authorities in a manner that affects Ono's ability to comply with any Regulatory Authority requirement or deadline or Applicable Law in such jurisdiction.

8.2 **Correspondence with Regulatory Authorities**. Each Party will provide the other Party with (a) copies of any material written correspondence submitted to or received from any Regulatory Authority, and (b) summaries of any material oral communications with any Regulatory Authority, in each case ((a) and (b)), relating to Regulatory Submissions for the Licensed Products, reasonably promptly after receipt or delivery by such Party of such correspondence or communication with any Regulatory Authority [***].

8.3 **Regulatory Meetings**. At any time after the Effective Date, at Ono's reasonable request, Ionis will use Commercially Reasonable Efforts to [***]. Ionis will [***]. Ionis will strictly follow Ono's instructions with respect to any such meeting that it attends and will not [***] except as required by Applicable Law or authorized by Ono in writing.

8.4 **Regulatory Submissions**. Ono will provide Ionis with a copy of all proposed material Regulatory Submissions (including any Regulatory Submissions related to the Approved Labeling) that it intends to file with or submit to any Regulatory Authority [***] for Ionis' review and comment reasonably in advance of Ono's filing or submission thereof, [***]. Ono will [***] any comments received from Ionis into such Regulatory Submissions.

8.5 **Investigator's Brochure**. Once prepared for any Clinical Trial of the Licensed Products, Ono will share a copy of the investigator's brochure with Ionis. Thereafter, Ono will provide updated versions of such investigator's brochure to Ionis annually and upon any substantive change to the safety or risk of the Licensed Products.

8.6 **Cooperation and Support**. The Parties will cooperate with each other to achieve the regulatory objectives contemplated herein in a timely, accurate, and responsive manner. Upon Ono's reasonable request, Ionis will [***], *provided* that [***]. Ono will reimburse Ionis for [***]. Ionis may invoice Ono for [***] incurred each Calendar Quarter no later than [***] after the end of such Calendar Quarter in connection with [***] under this Section 8.6 (Cooperation and Support), and Ono will pay the invoiced amounts within [***] after receipt of such invoice.

8.7 **Cost of Regulatory Activities**. Ionis will be responsible for the costs it incurs in conducting its regulatory activities [***]. Ono will be responsible for [***] in connection with all other activities under this Article 8 (Regulatory Affairs), including the preparation of Regulatory Submissions and the maintenance of Regulatory Approvals with respect to the Licensed Products and any associated filing and transfer fees.

8.8 **No Harmful Actions**. Notwithstanding any provision to the contrary in this Agreement, Ono will not (a) [***], or (b) [***], in each case ((a) and (b)), [***].

8.9 **Adverse Event Reporting; Global Safety Database**. The Parties will cooperate with regard to the reporting and handling of safety information involving the Licensed Products in accordance with Applicable Law, regulatory requirements, and regulations on pharmacovigilance and clinical safety. Ionis will transfer the global safety database to Ono on a mutually agreed and appropriate timeline before [***]. After the transfer of such database is complete, Ono will be responsible for all processing of information related to any adverse events for the Licensed Products in the Territory, including any information regarding such adverse events that is received from a Third Party. Each Party will promptly provide to the other Party in a timely manner the relevant safety information it receives (either directly or indirectly) related to the Licensed Products. Within [***] following the Effective Date (or such longer time as agreed upon by the Parties), the Parties will negotiate in good faith and enter into a Pharmacovigilance Agreement related to the Licensed Products, which will define the pharmacovigilance responsibilities of the Parties and include safety data exchange procedures governing the exchange of information affecting the class and products (*e.g.*, serious adverse events, emerging safety issues) to enable each Party to comply with all of its legal and regulatory obligations related to such Licensed Product. Ono will own and maintain the global safety database for the Licensed Products in accordance with its internal policies and procedures, consistently applied.

8.10 **Ionis Internal Oligonucleotide Safety Database**.

8.10.1 Ionis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during non-clinical and clinical Development (the "***Ionis Internal Oligonucleotide Safety Database***"). To maximize understanding of the safety profile and pharmacokinetics of Ionis compounds, Ionis will have the right to use any safety-related information provided by Ono pursuant to the Pharmacovigilance Agreement or this Section 8.10 (Ionis Internal Oligonucleotide Safety Database) solely for the purposes of maintaining the Ionis Internal Oligonucleotide Safety Database or with the prior approval of Ono. In addition, with respect to Clinical Trials of the Licensed Products conducted by or on behalf of Ono, Ono will provide Ionis with copies of annual safety updates filed with each IND and the safety sections of any final Clinical Trial reports within [***] following the date such information is filed, as applicable. Furthermore, Ono will promptly provide Ionis with supporting data and answer any follow-up questions reasonably requested by Ionis or its Affiliates to the extent such data and answers are reasonably available to Ono, subject to any confidentiality obligations that are imposed on Ono by Third Parties or Applicable Law. With respect to any confidentiality obligations that are imposed on Ono after the Effective Date by any Third Party in connection with any Clinical Trial of a Licensed Product, Ono will use Commercially Reasonable Efforts [***]. All such information disclosed by Ono to Ionis will be Ono's Confidential Information; *provided*, *however*, that so long as Ionis does not disclose the identity of a Licensed Product or Ono's identity, and such information is included in the Ionis Internal Oligonucleotide Safety Database, Ionis may disclose any such Confidential Information of Ono to (i) Ionis' other partners if such information is regarding class generic properties of oligonucleotides, (ii) any Third Party that contributes to the populating of the Ionis Internal Oligonucleotide Safety Database, or (iii) any Regulatory Authority. Ono will deliver all such information to Ionis at [***] (or to such other address/contact designated in writing by Ionis). Ono will also cause its Affiliates and Sublicensees to comply with this Section 8.10 (Ionis Internal Oligonucleotide Safety Database).

8.10.2 From time to time, Ionis utilizes the information in the Ionis Internal Oligonucleotide Safety Database to conduct analyses to keep Ionis and its partners informed regarding class generic properties of oligonucleotides, including with respect to safety. As such, if and when Ionis identifies safety or other related issues that may be relevant to a Licensed Product (including any potential class-related toxicity), Ionis will promptly inform Ono of such issues and provide the data supporting Ionis' conclusions.

8.10.3 During the Term, Ono may submit written requests to Ionis for Ionis to have queries run of the Ionis Internal Oligonucleotide Safety Database relevant to the Licensed Products, and Ionis will cause such queries to be run and will use Commercially Reasonable Efforts to promptly deliver to Ono the results of such queries. Any information disclosed between the Parties under this Section 8.10.3 will be treated as Confidential Information of Ionis in accordance with Article 14 (Confidentiality), to the extent such information would not constitute Confidential Information of Ono.

ARTICLE 9
COMMERCIALIZATION

9.1 **Commercialization Responsibilities for Licensed Product**. Subject to the terms and conditions of this Agreement, including but not limited to Section 9.3 (Commercialization Diligence Obligations), Ono and its Affiliates will have [***] with respect to the Commercialization of the Licensed Products in the Territory [***].

9.2 **Commercialization Reporting**. For each Fiscal Year following the [***] Regulatory Approval for a Licensed Product in the Territory, Ono will provide to Ionis a [***] of the [***] Commercialization activities conducted by Ono or its Affiliates, licensees, or Sublicensees for such Licensed Product [***] during such Fiscal Year and the [***] Commercialization activities expected to be conducted by Ono or its Affiliates, licensees, or Sublicensees for such Licensed Product [***] during the upcoming Fiscal Year. Each such report will contain sufficient detail [***] and may be in the form in which Ono presented such information to its senior management in the regular course of its business. In addition, Ono will provide to Ionis a report of the forecasted Net Sales of Licensed Products anticipated to be generated by Ono or its Affiliates, licensees, or Sublicensees during the upcoming Fiscal Year, which forecast will be broken down [***] by Calendar Quarter[***]. Ono will provide the first preliminary report of forecasted Net Sales for the Fiscal Year in which a Licensed Product is expected to be launched no later than [***] before the expected [***] Regulatory Approval for such Licensed Product and will revise the preliminary report as necessary after such Regulatory Approval, if applicable. Ono will provide subsequent reports of forecasted Net Sales for each subsequent Fiscal Year no later than [***] after the end of each Fiscal Year. As both Parties' mutual understanding of the foregoing, it will not constitute a breach of this Agreement if the forecasted Net Sales for any Fiscal Year as set forth in such reports differs from actual Net Sales for such Fiscal Year.

9.3 **Commercialization** [***]. On a Licensed Product-by-Licensed Product basis, following receipt of Regulatory Approval for a Licensed Product [***], Ono will use [***].

9.4 **Standards of Conduct; Compliance**. Ono will perform, or will require that its Affiliates, Sublicensees, and subcontractors perform, all Commercialization activities in a professional and ethical business manner and in compliance with Applicable Law and applicable Professional Requirements.

ARTICLE 10
MANUFACTURING

10.1 **Ionis Manufacturing and Supply**. Ionis will have sole responsibility [***], the Manufacture of all supplies of the Licensed Compounds and Licensed Products required for its Development activities under the Ongoing Clinical Trial Development Plan (other than the costs of [***]. In addition, Ono will purchase from Ionis, and Ionis will sell to Ono, the Licensed Compounds and the Licensed Products as set forth in Schedule 10.1(A) at [***]. Ionis may dispose of any such inventory and drug products that Ono has not taken possession of by [***]. Notwithstanding the foregoing, [***]. [***]. The Parties will enter into a definitive supply agreement and quality agreement, which will include provisions stipulating the quality standards agreed upon by the Parties, and Manufacturing for [***] will be carried out under such supply agreement and quality agreement.

10.2 **Related Drug Substance Supply**. Upon Ono's request after the Effective Date, at a time mutually agreed by the Parties, Ionis will supply to Ono [***]. Ionis may dispose of such substances that Ono has not taken possession of by [***]. Ionis shall provide the foregoing in this Section 10.2 (Related Drug Substance Supply) [***]. Ono will be responsible for [***] pursuant to this Section 10.2 (Related Drug Substance Supply) that is [***] under this Agreement.

10.3 **Ono Manufacturing**. Subject to Section 8.8 (No Harmful Actions), during the Term, except as set forth in Section 10.1 (Ionis Manufacturing and Supply), Ono will have sole responsibility for and sole decision-making authority over all Manufacturing activities and [***] for the Development and Commercialization of the Licensed Compounds and Licensed Products in the Field in the Territory. Ionis shall provide Ono with assistance as set forth in Section 6.3 (Manufacturing Technology Transfer), and the Parties, through the JSC or a Working Group of the JSC, will discuss manufacturing and supply issues to the extent they arise, as set forth in Section 4.1.5(i).

10.4 **Third Party CMOs**. Upon Ono's written request after the Effective Date, Ionis will provide Ono with an introduction to a Licensed CMO and a CMO Ionis has used to manufacture finished drug product and will reasonably cooperate to authorize such parties to manufacture the Licensed Compounds and Licensed Products for Ono to Exploit in accordance with this Agreement.

ARTICLE 11
PAYMENTS

11.1 **Upfront Payment**. In partial consideration of the licenses and rights granted to Ono hereunder, Ono will pay to Ionis, by wire transfer of immediately available funds, a non-refundable, non-creditable upfront payment of $280,000,000 on or after the Effective Date and within [***] (the "***Upfront Payment***").

11.2 **Milestone Payments**.

11.2.1 **Development Milestone Payments**. In further consideration of the licenses and rights granted to Ono hereunder, Ono will pay to Ionis the corresponding milestone payment, as set forth below (each milestone event set forth in Table 11.2.1, a "***Development Milestone Event***," and each milestone payment set forth in Table 11.2.1, a "***Development Milestone Payment***").

Table 11.2.1 – Development Milestones	
Development Milestone Event	***Development Milestone Payment (in [***])***
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

If Ono or its Affiliates or Sublicensees achieve all the Development Milestone Events, then the Development Milestone Payments payable by Ono under this Section 11.2.1 (Development Milestone Payments) will not exceed [***].

11.2.2 **Sales Milestone Payments**. In further consideration of the licenses and rights granted to Ono hereunder, Ono will pay to Ionis the corresponding milestone payment, as set forth below (each milestone event set forth in Table 11.2.2, a "***Sales Milestone Event***" and each milestone payment set forth in Table 11.2.2, a "***Sales Milestone Payment***").

Table 11.2.2 –Sales Milestones	
Sales Milestone Event	***Sales Milestone Payment (in [***])***
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

If Ono or its Affiliates or Sublicensees achieve all the Sales Milestone Events, then the Sales Milestone Payments payable by Ono under this Section 11.2.2 (Sales Milestone Payments) will not exceed [***].

11.2.3 **Notice and Payment.** Ono will notify Ionis in writing of the achievement of each Development Milestone Event within [***] after achievement of such Development Milestone Event by Ono, its Affiliates or Sublicensees, and the corresponding Development Milestone Payment will be due within [***] after receipt of the corresponding invoice and Taxation Forms from Ionis. Ono will notify Ionis in writing of the achievement of each Sales Milestone Event no later than [***] after the end of the Calendar Quarter in which the Sales Milestone Event is achieved, and the corresponding Sales Milestone Payment will be due within [***] after receipt of the corresponding invoice and Taxation Forms from Ionis. If more than one of the Sales Milestone Events is achieved for the first time in a given Calendar Quarter during the Term, then Ono will pay to Ionis a separate Sales Milestone Payment with respect to each such Sales Milestone Event. A failure or delay by Ono to deliver such notice of achievement of any Milestone Event will not relieve Ono of its obligation to pay Ionis the corresponding Milestone Payment for achievement of such Milestone Event. For the avoidance of doubt, each Milestone Payment is payable only on the first occurrence of the achievement of the corresponding Milestone Event, regardless of how many Licensed Products achieve such Milestone Event or the number of times a Milestone Event is achieved by the same Licensed Product (i.e., no Milestone Payment would be due for subsequent or repeated achievements of the same Milestone Event, whether by the same Licensed Product or a different Licensed Product).

11.3 Royalties.

11.3.1 **Royalty Rate**. In further consideration of the licenses and rights granted to Ono hereunder, subject to the provisions of Section 11.3 (Royalties), on a Licensed Product-by-Licensed Product and country-by-country basis, Ono will pay to Ionis royalties on the Annual Net Sales of the applicable Licensed Product sold by Ono, its Affiliates and Sublicensees in the Territory (the "***Royalties***") at a rate of [***] (the "***Full Royalty Rate***").

11.3.2 **Royalty Term**.

(a) Ono's obligation to pay Royalties to Ionis under this Agreement will commence, on a Licensed Product-by-Licensed Product and country-by-country basis, on the date of the First Commercial Sale of the applicable Licensed Product in the applicable country in the Territory and, subject to Section 11.3.2(b), will end on the latest to occur of (a) [***] after First Commercial Sale of such Licensed Product in such country, (b) [***] of such Licensed Product in such country, and (c) [***] and that Cover such Licensed Product in such country (the "***Royalty Term***").

(b) Notwithstanding anything to the contrary in Section 11.3.2(a), on a country-by-country and Licensed Product-by-Licensed Product basis, if at any time during the applicable Royalty Term [***], then the Royalty Term will end at 11:59 p.m. Pacific Time on the last day of the Calendar Quarter in which [***] occurred.

11.3.3 **Royalty Adjustments**.

(a) **Generic Entry**. On a country-by-country and Licensed Product-by-Licensed Product basis, if at any time during the Royalty Term a Generic Product obtains Regulatory Approval in such country and the aggregate unit equivalent volume of such Licensed Product in such country in any Calendar Quarter thereafter decreases by at least [***]% as compared to [***], the Full Royalty Rate will be reduced by [***]% for such Licensed Product in such country commencing with such Calendar Quarter and for all Calendar Quarters thereafter during the applicable Royalty Term.

(b) **Offset for Third Party Payments**. Subject to Section 11.3.3(d) (Royalty Floor), Ono may offset [***]% of any Third Party Payments made for a Licensed Product in a country in the Territory in a Calendar Quarter during the Royalty Term against the Royalties due and payable by Ono to Ionis on the Net Sales for such Licensed Product in such country in such Calendar Quarter; *provided* that the terms of this Section 11.3.3(b) (Offset for Third Party Payments) will not apply to any license agreement entered into in violation of the terms of Section 12.5.3 (Settlement).

(c) [***]. Subject to Section 11.3.3(d) (Royalty Floor), on a country-by-country and Licensed Product-by-Licensed Product basis, if during any Calendar Quarter during the Royalty Term for such Licensed Product in such country, (i) [***], and (ii) [***] (the "***Reduction Circumstances***"), then, commencing the first Calendar Quarter when the Reduction Circumstances first exist and for all Calendar Quarters thereafter during which the Reduction Circumstances exist, the Full Royalty Rate due on Net Sales of such Licensed Product in such country for such Calendar Quarter will be reduced by [***]%; *provided* that, [***].

(d) **Royalty Floor**. In no event will the Full Royalty Rate due to Ionis for a Licensed Product in a country in the Territory in any given Calendar Quarter during the Royalty Term for such Licensed Product in such country be reduced to an amount that is less than the greater of (i) [***], and (ii) [***]. Notwithstanding the foregoing, [***].

11.3.4 **Royalty Payments and Reports**.

(a) **Flash Reports**. Commencing with the Calendar Quarter during which the First Commercial Sale of a Licensed Product is made anywhere in the Territory, within [***] after the end of each Calendar Quarter, Ono will provide to Ionis flash reports containing [***]: (i) the total aggregate Net Sales of the Licensed Products sold by Ono or its Affiliates or Sublicensees in the Territory in such Calendar Quarter; (ii) the expected Royalties to be paid to Ionis on the Net Sales of the Licensed Products sold by Ono or its Affiliates or Sublicensees in the Territory in such Calendar Quarter, including any reduction pursuant to Section 11.3.3 (Royalty Adjustments) (if applicable); and (iii) the exchange rates used to calculate the Royalties payable in U.S. Dollars (the "***Flash Report***").

(b) **Royalty Report**. In addition to the Flash Reports to be provided in accordance with Section 11.3.4(a) (Flash Reports), commencing with the Calendar Quarter during which the First Commercial Sale of a Licensed Product is made anywhere in the Territory, within [***] after the end of each Calendar Quarter, Ono will provide to Ionis a written report (each, a "***Royalty Report***") setting forth in reasonable detail: (i) the aggregate Net Sales of the Licensed Products sold by Ono or its Affiliates or Sublicensees in the Territory in such Calendar Quarter; (ii) all deductions used to determine the Net Sales of the Licensed Products for such Calendar Quarter and the Royalties payable with respect to the Licensed Products for such Calendar Quarter, including any reduction pursuant to Section 11.3.3 (Royalty Adjustments) (if applicable); (iii) the exchange rates used to calculate the Royalties payable in [***]; (iv) any withholding taxes required to be made from such Royalties; and (v) the quantity and description of the Licensed Products sold by Ono or its Affiliate or Sublicensee in the Territory during such Calendar Quarter comprising such Net Sales. The Parties will seek to resolve any questions or issues related to a Royalty Report within [***] following receipt by Ionis of each Royalty Report.

(c) **Royalty Payments**. The information contained in each Flash Report and Royalty Report will be considered the Confidential Information of Ono. Following receipt of each Royalty Report, [***], Ono will pay the Royalties due hereunder for the Calendar Quarter covered by the applicable Royalty Report.

11.4 **Other Amounts Payable**. With respect to any amounts owed under this Agreement by one Party to the other for which no other invoicing and payment procedure is specified hereunder, within [***] after the end of each Calendar Quarter, each Party will provide an invoice, together with reasonable supporting documentation, to the other Party for such amounts owed in respect of such Calendar Quarter. The owing Party will pay any undisputed invoiced amounts within [***] after the date of the invoice, and any disputed amounts owed by a Party will be paid within [***] following resolution of the dispute.

11.5 **Financial Records and Audits**. Each Party will, and will require its Affiliates, Sublicensees and subcontractors to, maintain complete and accurate records in accordance with such Party's Accounting Standards in sufficient detail to permit the other Party to confirm the accuracy of any amounts payable under this Agreement for at least the preceding [***], including (as applicable) any [***], Royalties, Sales Milestone Payments, and sales of the Licensed Products (including all calculations of Net Sales). Upon reasonable prior notice, each Party will permit such records to be open during regular business hours for examination by an independent and internationally recognized certified public accountant selected by the auditing Party and reasonably acceptable to the audited Party for the sole purpose of verifying the accuracy of the financial reports furnished by the audited Party pursuant to this Agreement or of any payments made, or required to be made, by the audited Party pursuant to this Agreement; *provided* that such independent accounting firm is subject to written obligations of confidentiality and non-use applicable to each Party's Confidential Information that are at least as stringent as those set forth in Article 14 (Confidential Information). Such audit will not be (a) performed more frequently than once per [***] period, or (b) repeated for any [***] or with respect to the same set of records (in each case, unless a prior audit indicated a discrepancy, in which case the auditing Party may conduct an additional audit with respect to such period or records). Such auditor will disclose only whether such reports or payments made by the audited Party are correct or not, and, if not, any discrepancies and the specific details concerning any such discrepancies to the auditing Party. The auditor will not share any other information with the auditing Party, and the results of the audit will be subject to Article 14 (Confidentiality). The [***] will pay any amounts shown to be owed to the auditing Party but unpaid within [***] after the accountant's report, *plus* interest (as set forth in Section 11.11 (Late Payments; Disputed Payments)) from the original due date solely if the [***] is responsible for the discrepancy. If such examination of records reveals any overpayment by Ionis, then Ono will reimburse Ionis for the amount overpaid within [***] after the accountant's report, *plus* interest (as set forth in Section 11.11 (Late Payments; Disputed Payments)) from the original due date [***]. If such examination of records reveals any overpayment by Ono, then Ionis will [***]. The [***] will bear the full cost of such audit unless such audit reveals an underpayment by the [***] of more than [***]% of the amount actually due for the time period being audited, in which case Ono will reimburse Ionis for the reasonable audit fees for such examination.

11.6 **No Refunds**. Except as expressly provided herein, all payments under this Agreement will be irrevocable, non-refundable, and non-creditable.

11.7 **Accounting Standards**. If a Party changes its general accounting principles from its then-current Accounting Standard (*e.g.*, from GAAP to IFRS) at any time during the Term, then at least [***] prior to adopting such change in principles, such Party will provide written notice to the other Party of such change.

11.8 **Method of Payment; Exchange Rate**. All amounts to be paid pursuant to this Agreement will [***] and will be paid by wire transfer in immediately available funds to a bank account designated by the receiving Party. The rate of exchange to be used in computing the amount of currency equivalent in [***] owed to a Party under this Agreement will be the Selling Party's then-current standard exchange rate methodology employed for the translation of foreign currency sales into [***] in accordance with its Accounting Standards and consistently applied during the period.

11.9 **Blocked Payments**. If by reason of Applicable Law in any country or jurisdiction, it becomes impossible or illegal for a Party to transfer, or have transferred on its behalf, payments owed the other Party hereunder, then such Party will promptly notify the other Party of the conditions preventing such transfer and use reasonable efforts to deposit such payments in [***] or [***], as applicable. If, after using reasonable efforts, such Party is not able to deposit such payments in [***] or [***], as applicable, then such payments will be deposited in [***] in the relevant country to the credit of the other Party in a recognized banking institution designated by the other Party or, if none is designated by the other Party within a period of [***], in a recognized banking institution selected by the transferring Party, as the case may be, and identified in a written notice given to the other Party.

11.10 **Taxes**.

11.10.1 **Taxes on Income**. Each Party will be solely responsible for the payment of any and all income Taxes levied on account of all payments it receives under this Agreement.

11.10.2 **Withholding Tax**. Any and all payments made pursuant to this Agreement will be paid without deduction or withholding for any Taxes, except as required by Applicable Law. To the extent a Party is required by Applicable Law to deduct or withhold Taxes on any payment to the other Party (the "***Withheld Amount***"), such Party will remit such Withheld Amount to the proper Governmental Authority in a timely manner and promptly transmit to the other Party an official Tax certificate or other reasonable evidence of any withholding sufficient to enable the other Party to claim available credits for such Withheld Amount. The withholding Party will have the right to deduct such Withheld Amount from payment due to the other Party. For the avoidance of doubt, to the extent such Withheld Amount is so withheld and remitted in accordance with this Section 11.10.2 (Withholding Tax), such Withheld Amount will be treated for all purposes of this Agreement as having been paid to the other Party.

11.10.3 **Tax Cooperation**. The Parties agree to cooperate with one another in accordance with Applicable Law and use reasonable efforts to [***] Tax withholding or similar obligations in respect of payments made by each Party to the other Party under this Agreement. Without limiting the generality of the foregoing, each Party will provide the other with any Tax forms and other information that may be reasonably necessary to [***] withholding based on an applicable treaty or otherwise, including a properly completed Internal Revenue Service ("***IRS***") Form W-9 or appropriate IRS Form W-8, as applicable, before a payment is made. If any Tax form or other information a Party previously delivered expires or becomes obsolete or inaccurate in any respect, then such Party will provide the other Party with an updated version of such form or certification or promptly notify the other Party in writing of its legal inability to do so. Each Party will provide the other Party with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding Taxes or similar obligations resulting from payments made under this Agreement, such recovery to be for the benefit of the Party bearing such withholding Tax.

11.10.4 **Changes in Domicile**. Notwithstanding any provision to the contrary in this Agreement, including Section 11.10.2 (Withholding Tax), if as a result of a Party assigning, transferring, or conveying rights under this Agreement to an Affiliate or changing its domicile, additional Taxes become due that would not otherwise have been due hereunder with respect to payments under this Agreement, then such Party will be responsible for all such additional withholding Taxes.

11.11 Late Payments; Disputed Payments. Any undisputed payments or portions thereof due hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest from the due date until the date of payment at a per-annum rate equal to the lesser of: (a) [***]; or (b) the maximum rate permitted by Applicable Law. If a Party disputes an invoice or other payment obligation under this Agreement, then such Party will timely pay the undisputed amount of the invoice or other payment obligation, and the Parties will resolve such dispute in accordance with Article 17 (Dispute Resolution; Governing Law).

ARTICLE 12
INTELLECTUAL PROPERTY

12.1 Inventions.

12.1.1 **Ownership of Background Intellectual Property**. As between the Parties, and subject to the licenses granted under this Agreement, each Party retains all rights, title, and interests in and to all Patent Rights and Know-How that such Party owns or Controls as of the Effective Date or that it develops or otherwise acquires after the Effective Date outside the performance of the activities under this Agreement. As between the Parties, each Party shall be solely responsible for any remuneration that may be due to such Party's or its Affiliates' inventors under any applicable inventor remuneration laws.

12.1.2 **Ownership of Arising Intellectual Property**. As between the Parties, ownership of all Collaboration Know-How and Collaboration Patent Rights will be as follows:

(a) Ionis will solely own or Control any and all (i) Collaboration Know-How that is developed or invented solely by Ionis or employees of Ionis or its Affiliates or its or their licensees (other than Ono), Sublicensees, or subcontractors, or any Persons contractually required to assign or license such Collaboration Know-How to Ionis or any Affiliate of Ionis ("***Ionis Collaboration Know-How***"), and (ii) Patent Rights that Cover the Ionis Collaboration Know-How ("***Ionis Collaboration Patent Rights***"), and will retain all of its rights thereto, subject to any rights or licenses expressly granted by Ionis to Ono under this Agreement.

(b) Ono will solely own or Control any and all (i) Collaboration Know-How that is developed or invented solely by Ono or employees of Ono or its Affiliates or [***] or any Affiliate of Ono ("***Ono Collaboration Know-How***"), and (ii) Patent Rights that Cover the Ono Collaboration Know-How ("***Ono Collaboration Patent Rights***"), and will retain all of its rights thereto, subject to any rights or licenses expressly granted by Ono to Ionis under this Agreement.

(c) Each Party will own an equal, undivided share of all Joint Collaboration Technology.

(d) As between the Parties, each Party shall be solely responsible for any remuneration that may be due to such Party's or its Affiliates' inventors under any applicable inventor remuneration laws.

12.1.3 **Ownership of Trademarks**. As between the Parties, Ono has the sole right in the Territory, at its sole cost and in its sole discretion, to (a) select the trademark(s), service mark(s), logo(s), and other source identifier(s) to be used on or in connection with Commercialization of the Licensed Products in the Territory, and (b) apply for, prosecute, and maintain any registrations for the Licensed Products in the Territory.

12.1.4 **Disclosure; Inventorship**.

(a) **Invention Disclosure**. Each Party will promptly disclose to the other Party all Inventions within the Collaboration Know-How developed or invented during the Term by or on behalf of such Party, in each case, as soon as practicably possible. Each Party will also promptly respond to reasonable requests from the other Party for additional information relating thereto. Ionis Collaboration Know-How shall be considered the Confidential Information of Ionis, and, subject to Section 2.5 (Improvement Enabling License), Ono Collaboration Know-How shall be considered the Confidential Information of Ono.

(b) **Inventions by a Party**. Inventorship for Inventions and discoveries (including Know-How) first invented or developed during the course of the performance of activities under this Agreement will be determined in accordance with United States Patent Laws for determining inventorship.

(c) **Joint Research Agreement under the Leahy-Smith America Invents Act**. If a Party intends to invoke its rights under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act, then it will notify the other Party and neither Party will make an election under such provision when exercising its rights under this Article 12 (Intellectual Property) without the prior written consent of the other Party (such consent not to be unreasonably withheld, conditioned, or delayed), and the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in 35 U.S.C. § 100(h).

12.1.5 **Practice Under and Other Use of Joint Collaboration Technology**. Subject to the rights granted under and the restrictions set forth in this Agreement (including the licenses granted under Article 2 (Licenses)), each Party will be entitled to the free use and enjoyment of all Joint Collaboration Technology and neither Party will have any obligation to account to the other Party for profits, or to obtain any approval of the other Party to license, assign, or otherwise exploit any Joint Collaboration Technology by reason of joint ownership thereof. Each Party hereby waives any right it may have under the Applicable Law of any jurisdiction to require any such approval or accounting. To the extent any further consent is required to enable a Party to so license or exploit its interest in the Joint Collaboration Technology, the other Party will grant consent promptly upon request. Without limitation, each Party will cooperate with the other Party if the Parties determine to apply patent protection in any jurisdiction for any Joint Collaboration Technology and will obtain the cooperation of the individual inventors of any such Joint Collaboration Technology.

12.1.6 **Employee Assignment**. Ono and its Affiliates will[***] enter into an agreement with each of its employees performing activities under this Agreement that (a) compels prompt disclosure to Ono [***] of all Collaboration Know-How and Collaboration Patent Rights discovered, developed, invented, or filed by such employee during any performance under this Agreement; and (b) automatically assigns to Ono [***] all rights, title, and interests in and to all Collaboration Know-How and Collaboration Patent Rights, and requires each employee to execute all documents and take such other actions as may be necessary to effectuate such assignment.

12.2 Patent Prosecution.

12.2.1 **Joint** [***]**, and Ionis Patent Rights**.

(a) **Right to Prosecute**. As between the Parties, Ionis will have the (i) first right to control the Patent Prosecution of all [***], and (ii) sole right, in its sole discretion, to control the Patent Prosecution of all Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents (collectively, ((i) and (ii)), the "***Ionis Prosecuted Patent Rights***"). Upon Ionis' reasonable request, Ono will obtain any necessary assignment documents for Ionis with respect to the Patent Prosecution of Ionis Prosecuted Patent Rights, will render all signatures that will be necessary for such patent filings, and will assist Ionis in all other reasonable ways that are necessary for the issuance of Ionis Prosecuted Patent Rights as well as for the Patent Prosecution of Ionis Prosecuted Patent Rights. Ono will be responsible for [***] of the reasonable costs and expenses incurred with respect to the Patent Prosecution of the [***]. Ionis will be responsible for [***] of the reasonable costs and expenses incurred with respect to the Patent Prosecution of the [***] and for [***] of the reasonable costs and expenses incurred with respect to the Patent Prosecution of [***]. Ono will be responsible for [***] of the reasonable costs and expenses incurred by or on behalf of Ionis with respect to the Patent Prosecution of the [***], and Ono will reimburse Ionis for such costs within [***] after receiving an invoice [***] for such costs.

(b) **Review and Consult**. Ionis will keep Ono reasonably informed regarding the Patent Prosecution of the [***] and will [***]. In addition, Ionis will provide Ono with drafts of proposed substantive filings with any patent authority in connection with the Patent Prosecution of the [***] for Ono's review and comment as early as practicable and at least [***] prior to the submission of such proposed filings, which comments (if any) Ono must provide no later than [***] after receipt of the applicable draft filing. Ionis will consider in good faith Ono's reasonable comments on the Patent Prosecution of the [***], but Ionis will have final decision-making authority regarding Patent Prosecution of all Ionis Prosecuted Patent Rights.

(c) **Abandonment**. If, at any time during the Term, Ionis decides to cease the Patent Prosecution of [***], then Ionis will provide written notice to Ono of such decision at least [***] prior to the date that such applicable [***] will become abandoned. If, at any time during the Term, Ionis decides to cease the Patent Prosecution of [***], then Ionis will provide written notice to Ono of such decision within [***] after the date that Ionis decides or instructs to abandon the applicable [***]. Unless such written notice with respect to [***] includes a reasonable strategic reason for ceasing such Patent Prosecution (*e.g.*, continuing such Patent Prosecution would adversely affect Ionis' Patent Prosecution or litigation strategy), Ono may, upon written notice to Ionis, assume the Patent Prosecution of such [***] at Ono's sole cost and expense. Without limiting the foregoing, with respect to any such [***] abandoned by Ionis, Ionis [***].

12.2.2 [***] **and Ono Patent Rights**.

(a) **Right to Prosecute**. As between the Parties, Ono will have the (i) first right, in its sole discretion, to control the Patent Prosecution of all [***] and (ii) sole right, in its sole discretion, to control the Patent Prosecution of all Ono Patent Rights (collectively, ((i) and (ii)), the "***Ono Prosecuted Patent Rights***"). Upon Ono's reasonable request, Ionis will obtain any necessary assignment documents for Ono with respect to the Patent Prosecution of the Ono Prosecuted Patent Rights, will render all signatures that will be necessary for such patent filings, and will assist Ono, at Ono's cost, in all other reasonable ways that are necessary for the Patent Prosecution and issuance of the Ono Prosecuted Patent Rights. Ono will be responsible for [***] of the costs and expenses incurred with respect to the Patent Prosecution of the Ono Prosecuted Patent Rights.

(b) **Review and Consult**. Ono will keep Ionis reasonably informed regarding the Patent Prosecution of the [***] and will [***]. In addition, Ono will provide Ionis with drafts of all proposed substantive filings with any patent authority in connection with the Patent Prosecution of the [***] for Ionis' review and comment as early as practicable and at least [***] prior to the submission of such proposed filings, which comments (if any) Ionis must provide no later than [***] after receipt of the applicable draft filing. Ono will consider in good faith Ionis' reasonable comments on the Patent Prosecution of the [***] but Ono will have final decision-making authority regarding Patent Prosecution of all Ono Prosecuted Patent Rights.

(c) **Abandonment**. If, at any time during the Term, Ono decides to cease the Patent Prosecution of [***], then, Ono will provide written notice to Ionis of such decision at least [***] prior to the date that such Patent Right will become abandoned. Unless such written notice includes a reasonable strategic reason for ceasing such Patent Prosecution (*e.g.*, continuing such Patent Prosecution would adversely affect Ono's Patent Prosecution or litigation strategy), Ionis may, upon written notice to Ono, assume the Patent Prosecution of any such Patent Right at Ionis' sole cost and expense. Without limiting the foregoing, with respect to any such [***] abandoned by Ono, Ono [***].

12.3 Enforcement Against Third Party Infringement or Misappropriation.

12.3.1 **Notice of Infringement or Misappropriation**. Each Party will promptly notify the other of any apparent, threatened, or actual Competitive Infringement of which it becomes aware.

12.3.2 **Ono's Enforcement Right**. Ono will have the (a) first right, but not the obligation, to enforce any [***], and (b) sole right to enforce any [***], in each case ((a) and (b)), against any Competitive Infringement at its own cost and expense and using counsel of its own choice; *provided* that (i) with respect to [***], Ionis will be entitled to attend any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit (together with its own counsel, at its own cost and expense) and to review and comment on all substantive documents related to such infringement or misappropriation suit prior to filing or submission of such documents, and (ii) with respect to [***], Ono shall keep Ionis reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit to the extent without adverse effect on such suit. If Ono fails to initiate a suit or take other action to abate any such Competitive Infringement with respect to [***] within the earlier of: (x) [***] and (y) [***], or if Ono discontinues the prosecution of any such action after filing without abating such infringement, then, in either case, Ionis will have the second right, but not the obligation, to attempt to resolve such Competitive Infringement, at its own cost and expense, including the filing of an infringement or misappropriation suit, as applicable, to enforce the applicable Patent Rights or Know-How using counsel of its own choice.

12.3.3 **Ionis' Enforcement Right**. Ionis will have the (a) sole right, but not the obligation, to enforce any [***], and (b) first right to enforce any [***], in each case ((a) and (b)) against any Competitive Infringement at its own cost and expense and using counsel of its own choice; *provided* that Ionis informs Ono of the status of enforcement of [***] related to the Licensed Compound or Licensed Product. Ionis shall keep Ono reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit, to the extent without adverse effect on such suit. If Ionis fails to initiate a suit or take other action to abate any such Competitive Infringement with respect to [***] within the earlier of (x) [***] and (y) [***], or if Ionis discontinues the prosecution of any such action after filing without abating such infringement, then, in either case, Ono will have the second right, but not the obligation, to attempt to resolve such Competitive Infringement, at its own cost and expense, including the filing of an infringement or misappropriation suit, as applicable, to enforce the applicable Patent Rights or Know-How using counsel of its own choice.

12.3.4 **Allocation of Recoveries**. Any recoveries resulting from an enforcement action relating to a claim of Competitive Infringement will be first applied against payment of each Party's costs and expenses in connection therewith. Any such recoveries in excess of such costs and expenses will be allocated as follows: (a) if the recoveries relate to [***], and (b) if the recoveries relate to [***]. Other than the above, the recoveries will be allocated to the Parties as follows: (x) if Ono initiates such suit, action, or proceeding, then such recoveries will [***], and (y) if Ionis initiates such suit, action, or proceeding, then such recoveries will [***].

12.3.5 **Cooperation; Procedures**. At the request and expense of the Party bringing an infringement or misappropriation action under this Section 12.3 (Enforcement Against Third Party Infringement or Misappropriation), the other Party will provide reasonable assistance and cooperation in any such action (including entering into a common interest agreement if reasonably deemed necessary by any Party) and agrees to be joined as a party to the suit if necessary for the initiating Party to bring or continue an infringement or misappropriation action hereunder. In addition, the Party bringing an infringement or misappropriation action under this Section 12.3 (Enforcement Against Third Party Infringement or Misappropriation) will provide the other Party with copies of all pleadings and other documents in advance of filing with the court and will consider reasonable input from the other Party during the course of the action. Neither Party may [***]. The Parties will reasonably assist each other and cooperate with each other, at their own cost and expense, in any such investigation, pre-litigation preparation, or litigation to ensure that there is an aligned global litigation and enforcement strategy.

12.4 **Defense of Third Party Challenges**. Each Party will promptly notify the other Party in writing after becoming aware of an actual or threatened challenge by a Third Party of any Ionis Patent Right, Ono Patent Right, or Joint Collaboration Patent Right (each, a "***Third Party Challenge***").

12.4.1 **Ono's Right to Defend**. Subject to the terms of Section 12.4.3 (Cooperation; Procedures) and of any applicable license pursuant to which Ionis Controls any Patent Right, and except as may be otherwise agreed by the Parties, Ono will have the (a) sole right, but not the obligation, to control the defense of any Third Party Challenge relating to an [***], and (b) first right, but not the obligation, to control the defense of any Third Party Challenge relating to [***], and to compromise, litigate, settle, or otherwise dispose of any such challenge at its own cost and expense using counsel of its own choice; *provided* that Ionis will be entitled to attend any substantive meetings, hearings, or other proceedings related to such Third Party Challenge of [***] (together with its own counsel, at its own cost and expense) and to review and comment on all substantive documents related to such Third Party Challenge of [***]. If Ono fails to initiate or continue the defense of such Third Party Challenge of [***] within [***] after the notice provided under Section 12.4 (Defense of Third Party Challenges), or otherwise abandons or elects not to continue any such defense once initiated, then Ionis will have the second right, but not the obligation, to control the defense of such Third Party Challenge relating to [***] at its own cost and expense using counsel of its own choice.

12.4.2 **Ionis' Right to Defend**. Subject to the terms of Section 12.4.3 (Cooperation; Procedures), and except as may be otherwise agreed by the Parties, Ionis will have the (i) sole right, but not the obligation, to control the defense of any Third Party Challenge relating to an [***], and (ii) first right to control the defense of any Third Party Challenge relating to [***], and, in each case ((i) and (ii)), to compromise, litigate, settle, or otherwise dispose of any such challenge, in each case, at its own cost and expense using counsel of its own choice; *provided* that Ono will be entitled to attend any substantive meetings, hearings, or other proceedings related to such Third Party Challenge of any [***] (together with its own counsel, at its own cost and expense) and to review and comment on all substantive documents related to such Third Party Challenge of any [***]. If Ionis fails to initiate the defense of such Third Party Challenge of [***] within [***] after the notice provided under Section 12.4 (Defense of Third Party Challenges), or otherwise abandons or elects not to continue any such defense once initiated, then Ono will have the second right, but not the obligation, to control the defense of such Third Party Challenge of any [***] at its own cost and expense using counsel of its own choice.

12.4.3 **Cooperation; Procedures**. At the request and expense of the Party controlling the defense of any Third Party Challenge under this Section 12.4 (Defense of Third Party Challenges), the other Party will provide reasonable assistance and cooperation in any such action. In addition, the Party controlling the defense of any Third Party Challenge under this Section 12.4 (Defense of Third Party Challenges) will provide the other Party with copies of all pleadings and other documents to be filed with the court and will consider reasonable input from the other Party during the course of the action. Ono may not settle any action or proceeding brought or defended under this Section 12.4 (Defense of Third Party Challenges) or knowingly take any other action in the course thereof without Ionis' prior consent, unless such action or proceeding solely concerns the [***]. Ionis may not settle any action or proceeding brought or defended under this Section 12.4 (Defense of Third Party Challenges) or knowingly take any other action in the course thereof without Ono's prior consent, unless such action or proceeding solely concerns the [***]. The Parties will reasonably assist each other and cooperate with each other, at their own cost and expense, in any such investigation, pre-litigation preparation, or litigation to ensure that there is an aligned global litigation strategy. Notwithstanding the above, in the case of any invalidity or unenforceability claims arising in an enforcement action under Section 12.3 (Enforcement Against Third Party Infringement or Misappropriation), the Party controlling the enforcement action pursuant to Section 12.3 (Enforcement Against Third Party Infringement or Misappropriation) shall control the response to such invalidity or unenforceability claims, *provided* that such Party may not admit invalidity or unenforceability of any Patent Right Controlled by the other Party without the prior written consent of the other Party.

12.5 Third Party Infringement Claims.

12.5.1 **Infringement Claim; Challenges of Third-Party IP**. If a Third Party asserts that a Patent Right controlled by it is, or will be, infringed by the Exploitation of a Licensed Product in the Territory in accordance with this Agreement, then the Party first obtaining knowledge of such claim will promptly provide the other Party with prompt written notice thereof and the related facts in reasonable detail.

12.5.2 **Responsibility to Defend**. During the Term of this Agreement, if a Third Party asserts that a Patent Right controlled by such Third Party is infringed, or will be infringed, by the Exploitation of a Licensed Product, then, subject to Article 15 (Indemnification), Ono will have the first right, but not the obligation, to defend such claim using counsel of its own choosing. If Ono does not take affirmative steps to defend such claim within [***] (or such shorter period of time as is legally required to answer to such claim), then Ionis may defend such claim. The Party defending such claim will (a) keep the other Party reasonably informed regarding any such assertion, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such claim, (b) consider reasonable input from the other Party during the course of the claim, and (c) provide the other Party with the opportunity to attend any substantive meetings, hearings, or other proceedings related to such claim (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such claim prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such claim. Each Party will bear its own costs and expenses with respect to any such claim.

12.5.3 **Settlement**. Subject to Article 15 (Indemnification), neither Party will pursue or enter into any settlement or license agreement with any Third Party with respect to the Patent Rights that are the subject of a claim brought by a Third Party that a Patent Right controlled by such Third Party is infringed by the Exploitation of a Licensed Product without the other Party's prior written consent, not to be unreasonably withheld, conditioned, or delayed. Subject to Article 15 (Indemnification), [***].

12.6 Patent Challenges of Third Party Patent Rights.

12.6.1 **Notice of Third Party Patent Right**. If either Party becomes aware of a Third Party Patent Right that might form the basis for a claim that the Exploitation of a Licensed Product infringes, or will infringe, such Patent Right, then the Party first obtaining knowledge of such Patent Right will promptly provide the other Party with written notice thereof and the related facts in reasonable detail, and the Parties will promptly meet to discuss the matter.

12.6.2 **Challenges of Third Party Patents**. Ionis will have the first right, but not the obligation, to initiate a challenge of such Third Party Patent Right if such Patent Right would be an [***] if it were Controlled by Ionis, and if Ionis notifies Ono that it does not intend to initiate such a challenge, then Ono will have the second right, but not the obligation to do so. With respect to all other Third Party Patent Rights, Ono will have the first right, but not the obligation, to initiate a challenge of such Third Party Patent Right, and if Ono notifies Ionis that it does not intend to initiate such a challenge, then Ionis will have the second right, but not the obligation, to do so. The Party initiating such challenge will (a) keep the other Party reasonably informed regarding any such challenge, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such challenge, (b) consider reasonable input from the other Party during the course of the challenge, and (c) provide the other Party with the opportunity to attend any substantive meetings, hearings, or other proceedings related to such challenge (together with its own counsel, at its own cost and expense) and to review and comment on all substantive documents related to such challenge prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such challenge. Each Party will bear its own costs and expenses with respect to any such challenge.

12.6.3 **Restrictions on Settlement**. Neither Party nor its Affiliates will pursue or enter into any settlement or license agreement with any Third Party with respect to the Patent Rights that are the subject of such challenge without the other Party's prior written consent.

12.7 **Orange Book Listing**. Following the Effective Date, [***] will select which Patent Rights licensed to Ono under this Agreement will be listed in the Orange Book and will promptly cause such Patent Rights to be listed in the Orange Book. [***] will have final decision-making authority to select which Patent Rights will be listed in the Orange Book; *provided, however*, that [***].

12.8 **Patent Term Extensions**. With respect to supplemental protection certificates or any similar system for extending the term of Patent Rights that are in existence as of the Effective Date or that become available during the Term ("***Patent Term Extensions***"), Ono will have sole rights for making all decisions regarding such supplemental protection certificates that become available as a result of the Regulatory Approval of a Licensed Product for the Ono Patent Rights, [***] licensed hereunder; *provided* that, with respect to the [***], Ono will consult with Ionis with respect to such decisions and [***] the reasonable comments and concerns of Ionis, and Ionis shall fully cooperate with Ono in any necessary procedures with respect thereto. Ionis shall provide Ono with an opportunity to consult with respect to which Patent Rights may be extended in the country where multiple Patent Rights may be extended. Ono will be responsible for [***]% of the costs and expenses incurred with respect to the Patent Term Extensions of the [***], and for [***]% of the costs and expenses incurred by or on behalf of Ono with respect to the Patent Term Extensions of the [***]. Ionis will be responsible for [***]% of the costs and expenses incurred with respect to the Patent Term Extensions of the [***] and for [***]% of the reasonable costs and expenses incurred by or on behalf of Ono with respect to the Patent Term Extensions of the [***], and Ionis will reimburse Ono for such costs within [***] after receiving an invoice [***] for such costs.

12.9 **Unified Patent Court**. The Parties shall determine through mutual consultation regarding the opting-out or opting-in of the Ionis Patent Rights, the Ono Patent Rights, and the Joint Collaboration Patent Rights into the jurisdiction of the Unified Patent Court or the registration of Patent Rights with unitary effect.

12.10 **Common Interest**. The Parties stipulate and agree that, with regard to such prosecution, maintenance, enforcement, and defense the interests of the Parties as collaborators and licensor and licensee are to obtain the strongest patent protection possible, and as such, are aligned and are legal in nature. The Parties stipulate and agree that they have not waived, and nothing in this Agreement constitutes a waiver of, any legal privilege concerning the Patent Rights under this Article 12 (Intellectual Property), including privilege under the common interest doctrine and similar or related doctrines. Notwithstanding any provision to the contrary set forth in this Agreement, to the extent a Party has a good faith belief that any information required to be disclosed by such Party to the other Party under this Article 12 (Intellectual Property) is protected by attorney-client privilege or any other applicable legal privilege or immunity, such Party will not be required to disclose such information and the Parties will in good faith cooperate to agree upon a procedure (including entering into a specific common interest agreement, disclosing such information on a "for counsel eyes only" basis or similar procedure) under which such information may be disclosed without waiving or breaching such privilege or immunity.

ARTICLE 13
REPRESENTATIONS, WARRANTIES, AND COVENANTS

13.1 **Mutual Representations and Warranties**. Each of Ono and Ionis hereby represents and warrants to the other Party, as of the Execution Date and as of the Effective Date, that:

13.1.1 It is a corporation or limited company duly organized, validly existing, and in good standing under the laws of the jurisdiction of its organization, and it has the full right, power, and authority to enter into this Agreement and to perform its obligations hereunder.

13.1.2 All consents, approvals, and authorizations from all Governmental Authorities or other Third Parties required to be obtained by such Party in connection with this Agreement have been obtained.

13.1.3 The execution, delivery, and performance of this Agreement by it has been duly authorized by all requisite corporate action.

13.1.4 The execution and delivery of this Agreement and the performance of its obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of its articles of incorporation, bylaws, limited partnership agreement, or any similar instrument, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent under, any Applicable Law or any contractual obligation or court or administrative order by which it is bound.

13.1.5 It has not been debarred or suspended under 21 U.S.C. §335(a) or (b), is not the subject of a conviction described in Section 306 of the FD&C Act, has not been and is not excluded from a federal or governmental health care program, debarred from federal contracting, convicted of or pled *nolo contendere* to any felony, or to any federal or state legal violation (including misdemeanors) relating to prescription drug products or fraud, is not subject to OFAC sanctions or on the OFAC list of specially designated nationals, and is not subject to any similar sanction of any Governmental Authority in the Territory ("***Debarred/Excluded***"), and no proceeding that could result in it being Debarred/Excluded is pending, and neither it nor any of its Affiliates has used, in any capacity in the performance of obligations relating to the Licensed Products, any employee, subcontractor, consultant, agent, representative, or other Person who has been Debarred/Excluded.

13.1.6 [***] there are no legal claims, judgments, or settlements against or owed by it or any of its Affiliates, or pending or, to its Knowledge, threatened, legal claims or litigation, in each case, relating to antitrust, anti-competition, or anti-corruption law violations.

13.2 **Additional Ionis Warranties and Covenants**. Ionis hereby represents and warrants to Ono, as of the Execution Date and as of the Effective Date, and where applicable, covenants to Ono, that:

13.2.1 It has the right under the Ionis Technology to grant to Ono the licenses set forth in this Agreement, and it has not granted any license or other right under the Ionis Technology that is inconsistent with the licenses granted to Ono hereunder. Without limiting the foregoing, Ionis has not granted any other licenses to Ionis Product-Specific Technology, or to Ionis Core Technology that would conflict with the licenses granted to Ono under Section 2.1.1.

13.2.2 Appendix 2 (Ionis Core Technology Patents), Appendix 3 (Ionis Manufacturing and Analytical Patents), and Appendix 4 (Ionis Product-Specific Patents), collectively, list all Ionis Patent Rights existing as of the Effective Date that are necessary or reasonably useful to Exploit the Licensed Product in the Territory in the manner contemplated as of the Effective Date and in the form existing as of the Effective Date. With respect to any such Ionis Patent Right identified as being solely owned by Ionis, Ionis owns all rights, title, and interests in and to such Ionis Patent Rights.

13.2.3 All issued Patent Rights within the Ionis Patent Rights are in full force and effect, have been filed, prosecuted and maintained in good faith, and, to Ionis' Knowledge, are valid and enforceable.

13.2.4 There is no pending or, to Ionis' Knowledge, threatened litigation, nor has Ionis received any written notice from any Third Party, asserting or alleging that the Exploitation of the Licensed Products prior to the Execution Date infringed or misappropriated the intellectual property rights of such Third Party.

13.2.5 Schedule 13.2.5 (Existing Third-Party IP Agreements) sets forth all Existing Third-Party IP Agreements in effect as of the Execution Date, redacted copies of which have been provided to Ono prior to the date hereof, and any such redactions are of information not necessary to disclose to understand the implications of such Existing Third-Party IP Agreements to this Agreement. Other than the Existing Third-Party IP Agreements, as of the Execution Date there are no agreements between Ionis and any Third Party pursuant to which Ionis Controls any Ionis Technology licensed to Ono under this Agreement.

13.2.6 There are no pending, or to Ionis' Knowledge, threatened, adverse actions, suits, proceedings, judgments, orders, decrees, or settlements against or owed by Ionis or any of its Affiliates involving the Ionis Technology.

13.2.7 To Ionis' Knowledge, no Third Party is infringing or misappropriating any Ionis Technology as such Ionis Technology relates to the Licensed Compounds in the form existing as of the Effective Date or in any manner that would adversely affect Ono's rights under this Agreement.

13.2.8 Ionis obtained assignments from the inventors of all inventorship rights relating to the Ionis Patent Rights that are solely owned by Ionis, or assignments of such Patent Rights by operation of Applicable Law, and all such assignments of inventorship rights are valid and enforceable.

13.2.9 To Ionis' Knowledge, the Development or Commercialization of the Licensed Compound in the form existing as of the Effective Date does not infringe or misappropriate the intellectual property rights of any Third Party.

13.2.10 Ionis' Development of the Licensed Products in the Ongoing Clinical Trial has, to Ionis' Knowledge, been conducted in material conformance with the protocol for the Ongoing Clinical Trial, in good scientific manner, in accordance with GLP and GCP, as applicable, in compliance with Professional Requirements and Applicable Law, and in such a manner as to enable Ono to conduct further Development, Manufacture, Commercialization of, and to seek Regulatory Approvals for, the Licensed Products in the Field in the Territory.

13.2.11 Ionis [***].

13.2.12 The Ionis Technology owned by Ionis, and, to Ionis' Knowledge, the Ionis Technology licensed by Ionis was not funded by the USA federal government or otherwise subject to any rights of the USA federal government under the Bayh-Dole Act.

13.2.13 During the Term, Ionis will not [***].

13.2.14 Ionis [***].

13.3 **Additional Ono Warranties**. Ono represents and warrants to Ionis, as of the Execution Date and as of the Effective Date that:

13.3.1 There are no [***].

13.3.2 Ono [***].

13.4 **Additional Covenants**. Each of Ono and Ionis hereby covenant to the other:

13.4.1 **Assignment of Inventions**. Each Party will require all its and its Affiliates' employees to assign all Inventions that are developed or invented by such employees under this Agreement according to the ownership principles described in Section 12.1 (Ownership).

13.4.2 **Compliance with Law**. It will, and will require that its Affiliates, comply with all Applicable Law and, to the extent applicable, Professional Requirements, with respect to the performance of its obligations under this Agreement, including, as applicable, the Approved Labeling, the European Data Protection Directive 95/46/EC, the European General Data Protection Regulation (Regulation (EU) 2016/679), and any other applicable national data protection, cybersecurity, or privacy legislation.

13.4.3 **No Bribery**; **FCPA Compliance**. It will not in the future offer, promise, pay, authorize, or give, money or anything of value, directly or indirectly, to any Government Official or Other Covered Party for the purpose, pertaining to this Agreement, of: (a) influencing any act or decision of the Government Official or Other Covered Party; (b) inducing the Government Official or Other Covered Party to do or omit to do an act in violation of a lawful duty; (c) securing any improper advantage; or (d) inducing the Government Official or Other Covered Party to influence the act or decision of a government or government instrumentality, in order to obtain or retain business, or direct business to, any Person, in each case, in any way related to this Agreement. In performing under this Agreement, it and its Affiliates agree to comply with all applicable anti-corruption laws, including the Foreign Corrupt Practices Act of 1977 and the UK Bribery Act 2010, as amended from time-to-time; the anti-corruption laws of the Territory; and all laws enacted to implement the Organization for Economic Co-operation and Development Convention on Combating Bribery of Foreign Officials in International Business Transactions.

13.4.4 **Restricted Countries**. Neither it nor its Affiliates will export, transfer, or sell any Licensed Product (a) to any country or territory that is subject to comprehensive economic sanctions administered by OFAC, unless the sale of such Licensed Product would be permissible if Ono or its Affiliates or Sublicensees were subject to OFAC's jurisdiction, (b) to any other country or territory in which such activity would violate Applicable Law in the U.S., (c) to any Restricted Party unless the sale of such Licensed Product would be permissible if Ono or its Affiliates or Sublicensees was subject to OFAC's jurisdiction, or (d) in such a manner that would violate the Global Trade Control Laws.

13.4.5 **Debarred/Excluded Persons**. It will not engage, in any capacity in connection with this Agreement or any ancillary agreements, any officer, employee, contractor, consultant, agent, representative, or other Person who has been Debarred/Excluded. Each Party will inform the other Party in writing promptly if it or any Person engaged by it or any of its Affiliates who is performing any obligations under this Agreement or any ancillary agreements is Debarred/Excluded, or if any action, suit, claim, investigation, or legal or administrative proceeding is pending or, to each Party's Knowledge, is threatened, pursuant to which a Party, any of its Affiliates or any such Person performing obligations hereunder or thereunder may become Debarred/Excluded.

13.5 **Disclaimer**. EXCEPT AS EXPRESSLY SET FORTH IN THIS ARTICLE 13 (REPRESENTATIONS, WARRANTIES, AND COVENANTS), THE INTELLECTUAL PROPERTY RIGHTS PROVIDED BY IONIS ARE PROVIDED "AS IS" AND WITHOUT WARRANTY. EXCEPT AS EXPRESSLY SET FORTH IN THIS ARTICLE 13 (REPRESENTATIONS, WARRANTIES, AND COVENANTS), EACH OF THE PARTIES EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, VALIDITY, OR ENFORCEABILITY OF THEIR RESPECTIVE INTELLECTUAL PROPERTY RIGHTS, AND NONINFRINGEMENT OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES, ARISING FROM A COURSE OF DEALING, USAGE, OR TRADE PRACTICES, IN ALL CASES WITH RESPECT THERETO.

13.6 **Limitation of Liability**. NEITHER OF THE PARTIES WILL BE ENTITLED TO RECOVER FROM THE OTHER PARTY ANY SPECIAL, INCIDENTAL, INDIRECT, CONSEQUENTIAL, OR PUNITIVE DAMAGES OR DAMAGES FOR LOSS OF PROFIT, LOSS OF REVENUE, OR LOST OPPORTUNITY IN CONNECTION WITH THIS AGREEMENT, ITS PERFORMANCE OR LACK OF PERFORMANCE HEREUNDER, OR ANY LICENSE GRANTED HEREUNDER, EXCEPT TO THE EXTENT THE DAMAGES RESULT FROM A BREACH OF THE OBLIGATIONS OF A PARTY UNDER ARTICLE 14 (CONFIDENTIALITY) OR ARTICLE 3 (EXCLUSIVITY), MISAPPROPRIATION OR INFRINGEMENT OF INTELLECTUAL PROPERTY OWNED OR CONTROLLED BY THE OTHER PARTY, OR AMOUNTS REQUIRED TO BE PAID TO A THIRD PARTY AS PART OF A CLAIM FOR WHICH A PARTY PROVIDES INDEMNIFICATION UNDER ARTICLE 15 (INDEMNIFICATION).

ARTICLE 14
CONFIDENTIALITY

14.1 **Duty of Confidence**. Subject to the other provisions of this Article 14 (Confidentiality):

14.1.1 except to the extent expressly authorized by this Agreement, all Confidential Information disclosed by a Party or its Affiliates (the "***Disclosing Party***") will be maintained in confidence and otherwise safeguarded, and not published or otherwise disclosed, by the Party (and its Affiliates) receiving such information (the "***Receiving Party***");

14.1.2 the Receiving Party will treat all Confidential Information provided by the Disclosing Party, at a minimum, with the same degree of care as the Receiving Party uses for its own similar information, but in no event less than a reasonable degree of care;

14.1.3 the Receiving Party may only use any Confidential Information of the Disclosing Party for the purposes of performing its obligations or exercising its rights under this Agreement;

14.1.4 a Receiving Party may only disclose Confidential Information of the Disclosing Party to: (a) such Receiving Party's Affiliates, and potential and actual licensees and Sublicensees; and (b) employees, directors, officers, agents, contractors, consultants, attorneys, accountants, banks, investors, and advisors of the Receiving Party and its Affiliates, licensees, and Sublicensees, in each case ((a) and (b)), to the extent reasonably necessary for the purposes of, and for those matters undertaken pursuant to, this Agreement; *provided* that such Persons are bound by legally enforceable obligations of confidentiality and non-use with respect to the Disclosing Party's Confidential Information, or subject to professional ethical obligations of confidentiality, no less stringent than the confidentiality and non-use obligations set forth in this Agreement, except that the term of such obligation will be customary for such recipient of Confidential Information. Each Party will remain responsible for any failure by its Affiliates, licensees, and Sublicensees, and its and its Affiliates', licensees', and Sublicensees' respective employees, directors, officers, agents, consultants, attorneys, accountants, banks, investors, advisors, and contractors, in each case, to treat such Confidential Information as required under this Section 14.1 (Duty of Confidence) (as if such Persons were Parties directly bound to the requirements of this Section 14.1 (Duty of Confidence)); and

14.1.5 each Party will promptly notify the other Party of any misuse or unauthorized disclosure of the other Party's Confidential Information.

14.1.6 The confidentiality, non-use, and non-disclosure obligations set forth in this Section 14.1 (Duty of Confidence) will be in full force and effect from the Effective Date until [***] after expiration or termination of this Agreement, *provided* that, with respect to any Know-How that is a trade secret and is identified as such by the Disclosing Party at the time of disclosure, the obligations of this Section 14.1 (Duty of Confidence) will continue for so long as such Know-How remains a trade secret.

14.2 **Confidential Information**. The Ionis Know-How will be the Confidential Information of Ionis. The Joint Collaboration Know-How and the terms of this Agreement will be the Confidential Information of both Parties, with each Party deemed to be the Receiving Party of such information. The Ono Know-How will be the Confidential Information of Ono. Except as provided in Section 14.4 (Authorized Disclosures) and Section 14.7 (Publicity; Use of Names), neither Party nor its Affiliates may disclose the existence or the terms of this Agreement.

14.3 **Exemptions**. Information of a Disclosing Party will not be the Confidential Information of such Disclosing Party to the extent that the Receiving Party can demonstrate through competent evidence that such information:

14.3.1 was already known by the Receiving Party or any of its Affiliates without an obligation of confidentiality at the time of its receipt from the Disclosing Party, and not through a prior disclosure by or on behalf of the Disclosing Party, as documented by the Receiving Party's business records;

14.3.2 was generally available to the public or otherwise part of the public domain before its receipt from the Disclosing Party;

14.3.3 became generally available to the public or otherwise part of the public domain after its disclosure by the Disclosing Party other than through any act or omission of the Receiving Party or any of its Affiliates or disclosees in breach of this Agreement;

14.3.4 is subsequently disclosed to the Receiving Party or any of its Affiliates without obligation of confidentiality by a Third Party who may rightfully do so and is not under a conflicting obligation of confidentiality to the Disclosing Party; or

14.3.5 is developed by the Receiving Party or any of its Affiliates independently and without use of or reference to any Confidential Information received from the Disclosing Party, as documented by the Receiving Party's business records.

No combination of features or disclosures will be deemed to fall within the foregoing exclusions merely because individual features are published or available to the general public or in the rightful possession of the Receiving Party unless the combination itself and principle of operation are published or available to the general public or in the rightful possession of the Receiving Party.

14.4 Authorized Disclosures.

14.4.1 **Permitted Circumstances**. Notwithstanding the obligations set forth in Section 14.1 (Duty of Confidence) and Section 14.6 (Publication and Listing of Clinical Trials), a Party may disclose the other Party's Confidential Information (including this Agreement and the terms herein) to the extent such disclosure is reasonably necessary in the following situations:

(a) the prosecution or enforcement of Ionis Patent Rights or Collaboration Patent Rights, in each case, as contemplated by this Agreement;

(b) Regulatory Submissions and other filings or communications with Governmental Authorities (including Regulatory Authorities), as necessary for the Exploitation of the Licensed Products in accordance with the rights and obligations of the applicable Party under this Agreement;

(c) disclosure of this Agreement, its terms, and the status and results of Exploitation of the Licensed Products to actual or *bona fide* potential investors, acquirors, (sub)licensees, lenders, and other financial or commercial partners (including in connection with any royalty financing transaction), and their respective attorneys, accountants, banks, investors, and advisors, solely for the purpose of evaluating or carrying out an actual or potential investment, acquisition, (sub)license, debt transaction, or collaboration; *provided* that, in each such case, (i) such Persons are bound by obligations of confidentiality and non-use, or subject to professional ethical obligations of confidentiality, at least as stringent as those set forth in Article 14 (Confidentiality), [***] and (ii) the scope of any such disclosure is limited to the maximum extent practicable for the particular context in which it is being disclosed;

(d) such disclosure is required to comply with Applicable Law (whether generally or in pursuit of an application for listing of securities) including the United States Securities and Exchange Commission or equivalent foreign agency or regulatory body, or otherwise required by judicial or administrative process, *provided* that in each such event, as promptly as reasonably practicable and to the extent not prohibited by Applicable Law or judicial or administrative process, such Party will notify the other Party of such required disclosure and provide a draft of the disclosure to the other Party reasonably in advance of such filing or disclosure for the other Party's review and comment. The non-disclosing Party will provide any comments as soon as practicable, and the disclosing Party will consider in good faith any timely comments provided by the non-disclosing Party; *provided* that the disclosing Party may or may not accept such comments in its sole discretion. Confidential Information that is disclosed in order to comply with Applicable Law or by judicial or administrative process pursuant to this Section 14.4.1(d), in each case, will remain otherwise subject to the confidentiality and non-use provisions of this Article 14 (Confidentiality) with respect to the Party disclosing such Confidential Information, and such Party will take all steps reasonably necessary, including seeking of confidential treatment or a protective order for a period of at least [***] (to the extent permitted by Applicable Law or Governmental Authority), to ensure the continued confidential treatment of such Confidential Information, and each Party will be responsible for its own legal and other External Costs in connection with any such filing or disclosure pursuant to this Section 14.4.1(d); or

(e) disclosure pursuant to Section 14.6 (Publication and Listing of Clinical Trials) and Section 14.7 (Publicity; Use of Name).

14.4.2 If and whenever any Confidential Information is disclosed in accordance with this Section 14.4 (Authorized Disclosures), such disclosure will not cause any such information to cease to be Confidential Information except to the extent that such disclosure results in a public disclosure of such information (other than by breach of this Agreement).

14.5 Publications.

14.5.1 **Ono's Right to Publish**. After the Effective Date, Ono will have the right to publicly present or publish any Clinical Trial data, non-clinical or preclinical data, or any associated results or conclusions generated by or on behalf of Ionis or Ono pursuant to this Agreement (each such proposed presentation or publication, an "***Ono Publication***"), [***], and solely to the extent such publication or presentation is, with respect to any data generated by or on behalf of Ionis, approved in advance by Ionis[***]. If Ono desires to publicly present or publish an Ono Publication in accordance with the foregoing sentence, then Ono will provide Ionis (including Ionis' Liaison and all Ionis members of the JSC) with a copy of such proposed Ono Publication at least [***] prior to the earlier of its presentation or intended submission for publication, and Ionis will have [***] after receiving such proposed Ono Publication to review and provide comments thereto (such applicable [***] period, the "***Ionis Review Period***"). [***]. Notwithstanding any provision to the contrary set forth in this Agreement, Ono will (i) [***], and (ii) [***]. Ono will provide Ionis a copy of any Ono Publication at the time of the submission or presentation thereof. Ono agrees to determine the authorship of all Ono Publications in accordance with all applicable International Committee of Medical Journal Editors (ICMJE) guidelines. Ono will require its Affiliates and Sublicensees to comply with the obligations of this Section 14.5 (Publications) as if they were Ono, and Ono will be liable for any non-compliance of such Persons.

14.5.2 **Ionis' Right to Publish**. Ionis will have the right to publicly present or publish any Clinical Trial data, non-clinical or preclinical data, or any associated results or conclusions generated by or on behalf of Ionis pursuant to this Agreement (each such proposed presentation or publication, an "***Ionis Publication***") [***]. If Ionis desires to publicly present or publish a Ionis Publication in accordance with the foregoing sentence, then Ionis will provide Ono (including Ono's Liaison and all Ono members of the JSC) with a copy of such proposed Ionis Publication [***] with respect to Ionis Publications to be made in 2025 after the Effective Date, and with respect to any Ionis Publication to be made after 2025, at least [***] prior to the earlier of its presentation or intended submission for publication. Ono will have [***] (or a shorter period of time, as may be specified by Ionis for Ionis Publications to be made in 2025, considering the deadlines for such Ionis Publications) after receiving such proposed Ionis Publication to review and provide comments thereto (such applicable period, the "***Ono Review Period***"). [***]. Notwithstanding any provision to the contrary set forth in this Agreement, Ionis will (i) [***], (ii) [***] and (iii) [***]. Ionis will provide Ono a copy of any Ionis Publication at the time of the submission or presentation thereof. Ionis agrees to determine the authorship of all Ionis Publications in accordance with all applicable International Committee of Medical Journal Editors (ICMJE) guidelines. Ionis will require its Affiliates and Sublicensees to comply with the obligations of this Section 14.5 (Publications) as if they were Ionis, and Ionis will be liable for any non-compliance of such Persons.

14.5.3 **Subsequent Publications**. After any Ono Publication or Ionis Publication has been published or publicly presented in accordance with Section 14.5.1 (Ono's Right to Publish) or Section 14.5.2 (Ionis' Right to Publish), as applicable, either Party may make subsequent publications or presentations of the content of such previously published Ono Publication or Ionis Publication without further approval or review by the other Party; *provided*, that such subsequent publication or presentation does not include any new data, information, or conclusions, or present the content in a form or matter that materially alters the conclusion or subject matter of the previous publication or public presentation.

14.6 Publication and Listing of Clinical Trials. With respect to the listing of Clinical Trials or the publication of Clinical Trial results for the Licensed Products and to the extent applicable to a Party's activities conducted under this Agreement, each Party will comply with (a) the Pharmaceutical Research and Manufacturers of America (PhRMA) Guidelines on the listing of Clinical Trials and the Publication of Clinical Trial results, and (b) any Applicable Law or applicable court order, stipulations, consent agreements, and settlements entered into by such Party. The Parties agree that any such listings or publications made pursuant to this Section 14.6 (Publication and Listing of Clinical Trials) will be considered a Publication for purposes of this Agreement and will be subject to Section 14.5 (Publications).

14.7 Publicity; Use of Names.

14.7.1 **Press Release**. Each Party may issue a press release announcing this Agreement, on such date and time and in such form, in each case, as may be agreed by the Parties. Other than such press release and the public disclosures permitted by this Section 14.7 (Publicity; Use of Names) and Section 14.4 (Authorized Disclosures), the Parties agree that the portions of any other news release or other public announcement relating to this Agreement or the performance hereunder that would disclose information other than that already in the public domain will require prior review and approval by both Parties (with such approval not to be unreasonably withheld, conditioned, or delayed). However, the Parties agree that after (a) a disclosure pursuant to Section 14.7 (Publicity; Use of Names) or Section 14.4 (Authorized Disclosures) or (b) the issuance of a press release (including the initial press release) or other public announcement pursuant to this Section 14.7.1 (Press Release) that has been reviewed and approved by the other Party, the disclosing Party may make subsequent public disclosures reiterating such information without having to obtain the other Party's prior consent and approval so long as the information in such press release or other public announcement remains true, correct, and the most current information with respect to the subject matters set forth therein. Similarly, after a Publication has been made available to the public, each Party may post such Publication or a link to it on its corporate website or social media platforms (or any website managed by such Party in connection with a Clinical Trial for the Licensed Products, as appropriate) without the prior written consent of the other Party, so long as the information in such Publication remains true, correct, and the most current information with respect to the subject matters set forth therein.

14.7.2 **Disclosures by Ionis**. Notwithstanding any provision to the contrary set forth in this Agreement, Ionis has the right to publicly disclose (in written, oral, or other form): (a) the achievement of any Milestone Event under this Agreement (including the amount, payment, and timing of any such Milestone Event); (b) the commencement, completion, material data, or key results of any Clinical Trials for the Licensed Products conducted by or on behalf of Ionis; and (c) the achievement of Regulatory Approval for any Licensed Product throughout the world.

14.7.3 **Use of Names**. Each Party will have the right to use the other Party's name and logo in presentations, its website, collateral materials, and corporate overviews to describe the collaboration relationship, as well as in taglines of press releases issued pursuant to this Section 14.7 (Publicity; Use of Names); *provided* that [***], and each Party will [***]. Except as permitted under this Section 14.7 (Publicity; Use of Names) or with the prior express written permission of the other Party, neither Party will use the name, trademark, trade name, or logo of the other Party or its Affiliates or their respective employees in any publicity, promotion, news release, or disclosure relating to this Agreement or its subject matter except as may be required by Applicable Law.

14.8 Acknowledgement.

14.8.1 Ono [***]. Ionis will [***].

14.8.2 [***]. As such, Ono agrees that it will [***].

ARTICLE 15
INDEMNIFICATION

15.1 Indemnification by Ionis. Ionis will indemnify, hold harmless, and defend Ono and its Affiliates and their respective directors, officers, employees, and agents (each, a "***Ono Indemnitee***") from and against any and all Third Party suits, claims, actions, or demands ("***Third Party Claims***") and all liabilities, expenses, or losses (including reasonable attorneys' fees, court costs, witness fees, damages, judgments, fines, and amounts paid in settlement) arising therefrom ("***Losses***") to the extent that the applicable Third Party Claims and such Losses arise out of (a) a breach of this Agreement by Ionis, (b) the Exploitation of the Licensed Products by or on behalf of Ionis or any of its Affiliates, licensees (not including Ono or its Affiliates, Sublicensees, or its subcontractors), Sublicensees, or subcontractors (i) prior to the Effective Date, (ii) in connection with the Ongoing Clinical Trial, or (iii) after any early termination of the Agreement in accordance with Article 16 (Term and Termination), or (c) the negligence or willful misconduct of any Ionis Indemnitee. Notwithstanding the foregoing, Ionis will not have any obligation to indemnify Ono Indemnitees to the extent that any Losses arise out of any Third Party Claim for which Ono is responsible for indemnifying Ionis pursuant to Section 15.2 (Indemnification by Ono).

15.2 **Indemnification by Ono**. Ono will indemnify, hold harmless, and defend Ionis and its Affiliates, and their respective directors, officers, employees, and agents (each, an "***Ionis Indemnitee***") from and against any and all Losses, to the extent that the applicable Third Party Claims and such Losses arise out of (a) a breach of this Agreement by Ono, (b) the Exploitation of the Licensed Products by or on behalf of Ono or any of its Affiliates, Sublicensees, or subcontractors, or (c) the negligence or willful misconduct of any Ono Indemnitee. Notwithstanding any provision to the contrary set forth in this Agreement, Ono will not have any obligation to indemnify the Ionis Indemnitees to the extent that any Losses arise out of any Third Party Claim for which Ionis is responsible for indemnifying Ono pursuant to Section 15.1 (Indemnification by Ionis).

15.3 **Indemnification Procedure**. If either Party is seeking indemnification under Section 15.1 (Indemnification by Ionis) or Section 15.2 (Indemnification by Ono) (the "***Indemnified Party***"), then it will inform the other Party (the "***Indemnifying Party***") of the Third Party Claim giving rise to such indemnification obligations within [***] after receiving written notice of the Third Party Claim (it being understood and agreed, however, that the failure or delay by an Indemnified Party to give such notice of a Third Party Claim will not affect the Indemnifying Party's indemnification obligations hereunder except to the extent the Indemnifying Party will have been actually and materially prejudiced as a result of such failure or delay to give notice). The Indemnifying Party will have the right to assume the defense of any such Third Party Claim for which it is obligated to indemnify the Indemnified Party. The Indemnified Party will cooperate with the Indemnifying Party and the Indemnifying Party's insurer as the Indemnifying Party may reasonably request, and at the Indemnifying Party's cost and expense. The Indemnified Party will have the right to participate, with counsel of its choice, in the defense of any Third Party Claim that has been assumed by the Indemnifying Party, which participation will be at the Indemnified Party's expense unless (a) the Indemnifying Party has agreed to pay such fees and expenses, (b) the Indemnifying Party has failed to employ counsel reasonably satisfactory to the Indemnified Party in a timely manner, or (c) the Indemnified Party has been advised by counsel that there are actual or potential conflicting interests between the Indemnifying Party and the Indemnified Party, including situations in which there are one or more legal defenses available to the Indemnified Party that are different from or additional to those available to the Indemnifying Party. Neither Party will have the obligation to indemnify the other Party in connection with any settlement made without the Indemnifying Party's written consent, which consent will not be unreasonably withheld, conditioned, or delayed. The Indemnifying Party will not admit any fault or negligence on the part of the Indemnified Party, or impose any obligation on, or otherwise materially adversely affect, the Indemnified Party, without the Indemnified Party's prior written consent, which consent will not be unreasonably withheld, conditioned, or delayed. If the Parties cannot agree as to the application of Section 15.1 (Indemnification by Ionis) or Section 15.2 (Indemnification by Ono) as to any Third Party Claim, then, pending resolution of the dispute pursuant to Article 17 (Dispute Resolution; Governing Law), the Parties may conduct separate defenses of such Third Party Claims, with each Party retaining the right to claim indemnification from the other Party in accordance with Section 15.1 (Indemnification by Ionis) or Section 15.2 (Indemnification by Ono), as applicable, upon resolution of the underlying Third Party Claim.

15.4 **Insurance**. Each Party will, at its own expense, procure and maintain insurance, including product liability insurance, adequate to cover its obligations hereunder and that is consistent with normal business practices of prudent companies similarly situated at all times during which any Licensed Product is being clinically tested in human subjects or commercially distributed or sold by such Party pursuant to this Agreement. It is understood that such insurance will not be construed to create a limit of either Party's liability with respect to its indemnification obligations under this Article 15 (Indemnification). Each Party will provide the other Party with written evidence of such insurance upon request. Each Party will provide the other Party with [***].

ARTICLE 16
TERM AND TERMINATION

16.1 **Term**. The term of this Agreement will begin on the Effective Date and, unless earlier terminated in accordance with this Article 16 (Term and Termination), will continue, on a Licensed Product-by-Licensed Product and country-by-country basis, until the expiration of the Royalty Term for such Licensed Product in such country (the "***Term***"). If the Effective Date has not occurred by the [***] following the Execution Date, then this Agreement may be terminated by either Party upon written notice to the other Party, *provided* that a Party shall not be entitled to terminate this Agreement pursuant to this sentence if such Party is in breach of this Agreement and such breach has caused the Effective Date not to occur by the [***] following the Execution Date.

16.2 **Termination for Material Breach**.

16.2.1 **Material Breach**. If either Party believes in good faith that the other is in material breach of this Agreement, then the non-breaching Party may deliver notice of such breach to the other Party stating the cause and proposed remedy ("***Breach Notification***"). For any breach arising from a failure to make a payment set forth in this Agreement, the allegedly breaching Party will have [***] from the receipt of the applicable Breach Notification to cure such breach. For all breaches other than a failure to make a payment as set forth in this Agreement, the allegedly breaching Party will have [***] from the date of the Breach Notification to cure such breach. If the allegedly breaching Party fails to cure the applicable breach within the applicable period set forth above, then the Party originally delivering the Breach Notification may terminate this Agreement effective on written notice of termination to such allegedly breaching Party. The Parties stipulate and agree, for purposes of this Section 16.2 (Termination for Material Breach), that a material breach by Ono, its Affiliates or Sublicensees of [***]. The Parties further stipulate and agree, for purposes of this Section 16.2 (Termination for Material Breach), that a material breach by Ionis, its Affiliates or Sublicensees of [***].

16.2.2 **Disagreement as to Material Breach**. Notwithstanding Section 16.2.1 (Material Breach), if the Parties, reasonably and in good faith, disagree as to whether there has been a material breach of this Agreement, then: (a) the Party that disputes whether there has been a material breach may contest the allegation by referring such matter, within the cure period applicable to such alleged material breach, for resolution in accordance with Article 17 (Dispute Resolution; Governing Law); (b) the relevant cure period with respect to such alleged material breach will be tolled from the date on which the Party that disputes whether there has been a material breach notifies the other Party of such dispute and through the resolution of such dispute in accordance with Article 17 (Dispute Resolution; Governing Law); and (c) during the pendency of such dispute, all of the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

16.3 **Termination by Ono for Convenience**. At any time after payment of the Upfront Payment and until [***], Ono will have the right to terminate the Agreement in its entirety upon [***] prior written notice. After [***], Ono will have the right to terminate the Agreement in its entirety upon [***] prior written notice.

16.4 [***].

16.5 **Termination for Patent Challenge**. Except to the extent unenforceable under Applicable Law, Ionis may terminate this Agreement in its entirety by providing written notice of termination to Ono if Ono or its Affiliates (individually or in association with any Person) contests or assists a Third Party in contesting the scope, validity, or enforceability of any Ionis Patent Right anywhere in the world in any court, tribunal, arbitration proceeding, or other proceeding, including the U.S. Patent and Trademark Office, the U.S. International Trade Commission, the European Patent Office, the European Patent Court, or any national court or patent office in Europe (a "***Patent Challenge***"). If there is a Patent Challenge, then Ionis will provide prompt written notice of such Patent Challenge to Ono, and Ionis may immediately terminate this Agreement by providing written notice of such termination to Ono. If termination of this Agreement pursuant to this Section 16.5 (Termination for Patent Challenge) is not an available remedy under Applicable Law, then [***]; *provided, however*, that nothing in this Section 16.5 (Termination for Patent Challenge) prevents Ono or its Affiliates from taking any of the actions referred to in this Section 16.5 (Termination for Patent Challenge), and *provided further* that [***]. If [***]. As used herein, a Patent Challenge includes: (i) filing an action under 28 U.S.C. §§ 2201-2202 seeking a declaration of invalidity or unenforceability of any such Patent Right; (ii) filing, or joining in, a petition under 35 U.S.C. § 311 to institute *inter partes* review of any such Patent Right; (iii) filing, or joining in, a petition under 35 U.S.C. § 321 to institute post-grant review of any such Patent Right or any portion thereof; (iv) filing or commencing any opposition, nullity, or similar proceedings challenging the validity of any such Patent Right in the Territory; or (v) any foreign equivalent of clauses (i), (ii), (iii), or (iv). [***]. It is understood and agreed by the Parties that [***].

16.6 **Termination for Insolvency**.

16.6.1 Each Party will have the right to terminate this Agreement upon delivery of written notice to the other Party if (a) such other Party files in any court or agency pursuant to any statute or regulation of any jurisdiction a petition in bankruptcy or insolvency or for reorganization or similar arrangement for the benefit of creditors or for the appointment of a receiver or trustee of such other Party or its assets, (b) such other Party is served with an involuntary petition against it in any insolvency proceeding and such involuntary petition has not been stayed or dismissed within [***] of its filing, or (c) such other Party makes an assignment of substantially all of its assets for the benefit of its creditors.

16.6.2 All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") licenses of rights to "intellectual property" as defined in Section 101(35A) of the Bankruptcy Code. The Parties will retain and may fully exercise all their respective rights and elections under the Bankruptcy Code. Upon the bankruptcy of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and such, if not already in its possession, will be promptly delivered to the non-bankrupt Party, unless the bankrupt Party elects in writing to continue, and continues, to perform all its obligations under this Agreement.

16.7 **Full Force and Effect During Notice Period**. This Agreement will remain in full force and effect until the expiration of the applicable termination notice period. For clarity, if Ono or any of its Affiliates or Sublicensees achieve any Milestone Events during the termination notice period, then the corresponding Milestone Payment is accrued and Ono will remain responsible for the payment of such Milestone Payment even if the due date of such Milestone Payment occurs after the effective date of the termination.

16.8 **Effects of Termination**. Upon any expiration or termination of this Agreement, each Party will destroy (at the other Party's election) all Confidential Information of the other Party in its possession upon termination of this Agreement, and, if applicable, the Receiving Party will provide a written confirmation of such destruction within [***] of such request. Notwithstanding the foregoing or any provision to the contrary set forth in this Agreement, (a) the foregoing terms of this Section 16.8 (Effects of Termination) will not apply to any Confidential Information that is necessary to allow the Receiving Party to perform its obligations or exercise any of its rights that expressly survive the applicable termination of this Agreement, and the Receiving Party may retain one copy of such Confidential Information for its legal archives; and (b) the Receiving Party will not be required to destroy electronic files containing such Confidential Information that are made in the ordinary course of its business information back-up procedures pursuant to its electronic record retention and destruction practices that apply to its own general electronic files and information. Further, if this Agreement is terminated by either Party pursuant to Section 16.2 (Termination for Material Breach) or Section 16.6 (Termination for Insolvency), by Ono pursuant to Section 16.3 (Termination by Ono for Convenience), or by Ionis pursuant to Section 16.4 (Cessation of Development and Commercialization), or Section 16.5 (Termination for Patent Challenge), then all rights in the Licensed Products will revert to Ionis, and the following will apply with respect to the Licensed Products:

16.8.1 **Termination of Licenses**. As of the effective date of termination of this Agreement, all rights licensed to Ono under Section 2.1 (Grant of Licenses to Ono) or otherwise under this Agreement (except for the licenses granted under Section 2.5 (Improvement Enabling License)), in each case, will each terminate, but each Party will retain its joint ownership interests in the Joint Collaboration Technology. Subject to Section 16.8.7 (Appointment as Exclusive Distributor) and Section 16.8.2 (Effects of Termination on Sublicenses), Ono and its Affiliates and Sublicensees will cease selling Licensed Products that are the subject of such termination.

16.8.2 **Effects of Termination on Sublicenses**. If this Agreement is terminated for any reason, then any sublicense granted hereunder by Ono, will, at the Sublicensee's request within [***] of such termination, survive such termination; *provided* that (a) the relevant Sublicensee is not in breach of any of its obligations under such sublicense, (b) Ionis is not required to assume any obligations or liabilities (contingent or otherwise) not set forth in this Agreement, (c) such Sublicensee agrees in writing to comply with all of the terms and conditions of this Agreement to the extent applicable to the rights originally sublicensed to it by Ono, and (d) such Sublicensee agrees to assume all of Ono's financial obligations under this Agreement to the extent applicable to the rights.

16.8.3 **Reversion License**.

(a) **License Grant**. Ionis will have, and Ono hereby grants to Ionis, effective upon such termination, a worldwide, exclusive, perpetual, irrevocable, and sublicensable (through multiple tiers) license under any Patent Rights and Know-How Controlled by Ono as of the effective date of such termination, other than any Ono Technology, that are necessary or actually used to Exploit the Licensed Products, solely to Exploit the Licensed Products in the Territory (the "***Reversion License***"), which license will be (a) royalty-bearing if [***] and (b) [***]. Except as otherwise provided in Section 16.8.7 (Appointment as Exclusive Distributor), Ono will not Commercialize any Licensed Product in the Territory upon and following the effective date of termination of this Agreement.

(b) **Reversion Royalty**. If this Agreement is terminated by Ono under Section 16.2 (Termination for Material Breach), then, promptly following notice of termination, the Parties will negotiate in good faith and agree on a reasonable royalty to be paid by Ionis to Ono in consideration of the Reversion License, taking into account, among other things, [***]. If the Parties are unable to agree on the royalty rate for the Reversion License within [***] after the effective date of termination, then either Party may refer such matter for resolution pursuant to SCHEDULE 16.8.3(b) (Reversion Royalties Dispute Resolution). The terms of Section 11.3.2 (Royalty Adjustments) and Section 11.3.4 (Royalty Payments and Reports) will apply to the payment and reporting of any royalties described in this Section 16.8.3(b) (Reversion Royalties), *mutatis mutandis*.

16.8.4 **Transition Services**.

(a) **Scope**. Ionis may request that Ono perform transition activities with respect to any Licensed Products that are necessary or reasonably useful to (i) provide patients with continued access to the Licensed Products, (ii) transition the responsibilities under all Regulatory Approvals and ongoing Clinical Trials for Licensed Products to Ionis or its designee, or (iii) transition the then-current supply process and responsibilities for the Licensed Products to Ionis or its designee. If Ionis requests that Ono perform any such transition activities, then the Parties will enter into a transition agreement for Ono to perform transition services[***] and such activities, the "***Transition Services***").

(b) **Transition Plan**. Ionis may elect to have Ono perform the Transition Services by providing written notice to Ono no later than the later of (i) [***] following the effective date of the termination and (ii) [***] following [***]. If Ionis requests that Ono perform the Transition Services, then Ionis will propose a transition plan setting forth the Transition Services to be performed by Ono, and promptly after such request, the Parties will negotiate and enter into a transition plan [***]. While Ono is providing Transition Services, Ono and Ionis will mutually agree on talking points and a communication plan to key stakeholders, including customers, specialty pharmacies, physicians, Regulatory Authorities, patient advocacy groups, payors, and clinical study investigators, and Ono will make all such communication to such entities and individuals in accordance with the mutually agreed talking points.

(c) **Costs**. Ionis will pay Ono for the Transition Services [***]. In addition, Ionis will reimburse [***].

16.8.5 **Assignment and Disclosure**. To the extent requested by Ionis following the date that a Party provides notice of termination of this Agreement, Ono will promptly (and in any event no later than [***] after the effective date of termination unless agreed otherwise in the Transition Plan):

(a) provide to Ionis for its review unredacted copies of all clinical trial agreements and distribution agreements (to the extent assignable and not cancelled), in each case, that are necessary or reasonably useful for the Exploitation of the Licensed Products, and, following such review, upon Ionis' request, assign and transfer to Ionis or its designee all of Ono's rights, title, and interests in and to any such agreements;

(b) assign or amend, as appropriate, any agreements or arrangements with Third Party vendors (including distributors) solely related to the Licensed Products or, to the extent any such Third Party agreement or arrangement is not assignable to Ionis, reasonably cooperate with Ionis to arrange to continue to provide such services for a reasonable time after termination of this Agreement to facilitate the orderly transition of all Commercialization and other activities then being performed by or on behalf of Ono or its Affiliates or Sublicensees for the Licensed Products to Ionis or its designee;

(c) assign and transfer to Ionis or its designee, as of the effective date of termination, all of Ono's rights, title, and interests in and to the trademarks used for the Licensed Products (other than any corporate trademarks of Ono) and any domain names associated with such trademarks (to the extent that Ono or its Affiliates has any), and promptly provide to Ionis all login and password information necessary to maintain such domain names;

(d) assign and transfer to Ionis or its designee all of Ono's rights, title, and interests in and to any promotional materials, training materials, medical education materials, and all other literature or other materials related to the Licensed Products used to support Commercialization of such Licensed Products, and copyrights and any registrations for the foregoing; and

(e) disclose to Ionis or its designee all documents, records, and materials that embody any of the foregoing and that are controlled by Ono or that Ono is able to obtain using reasonable efforts.

Subject to Section 16.8.11 (Termination by Ono for Breach), Ono will be responsible for [***] the assignments set forth in this Section 16.8.5 (Assignment and Disclosure). To the extent that any agreement or other asset described in this Section 16.8.5 (Assignment and Disclosure) is not assignable by Ono, then such agreement or other asset will not be assigned, and upon the request of Ionis, Ono will take such steps as may be necessary to allow Ionis to obtain and to enjoy the benefits of such agreement or other asset, in the form of a license or other right to the extent Ono has the right and ability to do so. For clarity, Ionis will have the right to request that Ono take any or all of the foregoing actions in whole or in part, or with respect to all or any portion of the assets set forth in the foregoing provisions.

16.8.6 **Regulatory Submissions and Regulatory Approvals**. Ono will and hereby does, and will cause its Affiliates and Sublicensees to, (a) no later than [***] after the effective date of termination of this Agreement, at Ionis' request either (i) assign and transfer to Ionis or its designee all of Ono's rights, title, and interests in and to all Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals, or (ii) withdraw all Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals, in each case ((i) or (ii)), solely for the Licensed Products that are the subject of termination, and (b) to the extent assignment pursuant to clause (a)(i) is delayed or is not permitted by the applicable Regulatory Authority, permit Ionis to cross-reference and rely upon any such Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals filed by Ono or any of its Affiliates or Sublicensees. Ono will execute and deliver, or will cause to be executed and delivered, to Ionis or its designee such endorsements, assignments, commitments, acknowledgements, and other documents as may be necessary to assign, convey, transfer, and deliver to Ionis or its designee all of Ono's or its applicable Affiliate's or designee's rights, title, and interests in and to all such assigned Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals, including submitting to each applicable Regulatory Authority or other Governmental Authority a letter or other necessary documentation (with copy to Ionis) notifying such Regulatory Authority or other Governmental Authority of, or otherwise giving effect to, the transfer of ownership to Ionis of all such assigned Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals. In addition, upon Ionis' written request, Ono will provide to Ionis copies of all material related documentation, including material non-clinical, preclinical, and clinical data related to the Licensed Products that are held by or reasonably available to Ono or its Affiliates or Sublicensees. Subject to Section 16.8.11 (Termination by Ono for Breach), Ono shall conduct the activities set forth in this Section 16.8.6 (Regulatory Submissions and Regulatory Approvals) [***].

16.8.7 **Appointment as Exclusive Distributor**. If Ono is Commercializing any Licensed Product as of the applicable effective date of termination, then, [***], either (a) Ono will appoint Ionis or its designee as its exclusive distributor of such Licensed Product in such country and grant Ionis or its designee the right to appoint sub-distributors, or (b) Ono will have the continued right to sell the Licensed Products from its inventory; *provided*, *however*, that Ono's obligations under this Agreement with respect to the Licensed Products that Ono sells, including the obligation to pay Royalties to Ionis hereunder, will continue in full force and effect during such period.

16.8.8 **Know-How Transfer Support**. In furtherance of the assignment of Know-How pursuant to Section 16.8.5 (Assignment and Disclosure), Ono will, for a period of [***] from the effective date of such termination, provide such consultation or other assistance, as Ionis may reasonably request to assist Ionis in becoming familiar with such Know-How in order for Ionis to undertake further Exploitation of the Licensed Products [***].

16.8.9 **Inventory**. At Ionis' election and request, unless Ionis elects to grant to Ono the continued right to sell the Licensed Products from its inventory pursuant to clause (b) of Section 16.8.7 (Appointment as Exclusive Distributor), Ono will transfer to Ionis or its designee some or all inventory of the Licensed Products (including all final product, bulk drug substance, intermediates, works-in-process, formulation materials, reference standards, drug product clinical reserve samples, packaged retention samples, and the like) then in the possession or Control of Ono, its Affiliates or Sublicensees; *provided* that [***].

16.8.10 **Wind Down and Transition**. Ono will be responsible, [***], for the wind-down of Ono's and its Affiliates' and its Sublicensees' activities with respect to the Licensed Products. In accordance with Ionis' election under Section 16.8.6(a)(i) (Regulatory Submissions and Regulatory Approvals), Ono will, and will cause its Affiliates and Sublicensees to, reasonably cooperate with Ionis to facilitate orderly transition to Ionis or its designee of all Commercialization and other activities then being performed by or on behalf of Ono or its Affiliates or Sublicensees for the Licensed Products, including reasonably cooperating with Ionis to transfer all Commercialization and other activities to Ionis or its designee and continuing to perform such activities on Ionis' behalf for a reasonable time after termination of this Agreement until such transfer is completed.

16.8.11 **Termination by Ono for Breach**. Notwithstanding any provision to the contrary in this Section 16.8 (Effects of Termination), if Ono terminates this Agreement pursuant to Section 16.2 (Termination for Material Breach), then [***].

16.8.12 **Other Assistance; Further Assurances**. Without limiting the assistance to be provided under Section 16.8.8 (Know-How Transfer Support), Ono will provide any other assistance reasonably requested by Ionis for the purpose of allowing Ionis or its designee to proceed expeditiously with the Exploitation of the Licensed Products for a period of [***] after the effective date of termination of this Agreement. Ono will execute all documents and take all such further actions as may be reasonably requested by Ionis in order to give effect to the requirements in this Section 16.8 (Effects of Termination).

16.9 **Survival; Accrued Rights**. Expiration or termination of this Agreement will not relieve the Parties of any liability that accrued hereunder prior to the effective date of such expiration or termination nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement, nor prejudice either Party's right to obtain performance of any obligation. Without limiting the foregoing, the following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 2.4 (Responsibility for Sublicensees and Subcontractors), Section 2.5 (Improvement Enabling License), Section 2.6 (No Other Rights and Retained Rights), Section 7.9 (Development Records), Section 8.2 (Correspondence with Regulatory Authorities), Section 8.10.1, Section 11.2.3 (Notice and Payment), Section 11.3.4(b) (Royalty Report) (solely with respect to the report covering the final Calendar Quarter prior to expiration or termination of the Agreement), Section 11.3.4(c) (Royalty Payments) (solely with respect to Royalties dur for the final Calendar Quarter prior to expiration or termination of the Agreement), Section 11.4 (Other Amounts Payable), Section 11.5 (Financial Records and Audits), Section 11.6 (No Refunds), Section 11.8 (Method of Payment; Exchange Rate), Section 11.9 (Blocked Payments), Section 11.10 (Taxes), Section 11.11 (Late Payments; Disputed Payments), Article 12 (Intellectual Property), Section 13.5 (Disclaimer), Section 13.6 (Limitation of Liability), Article 14 (Confidentiality), Article 15 (Indemnification), Article 16 (Term and Termination), Article 17 (Dispute Resolution; Governing Law), and Article 18 (Miscellaneous).

ARTICLE 17
DISPUTE RESOLUTION; GOVERNING LAW

17.1 **Executive Officers; Disputes**. Each Party will ensure that an Executive Officer is designated for such Party at all times during the Term for dispute resolution purposes and will promptly notify the other Party of any change in its designated Executive Officer. Except as expressly set forth in this Agreement, if a dispute arises under, in relation to, or in connection with, this Agreement (except for disputes arising at the JSC, which will be resolved in accordance with Section 4.3 (Decision-Making)), then the Parties will refer such dispute to their Executive Officers, and such Executive Officers or designees will attempt in good faith to resolve such dispute. If the Parties are unable to resolve any such dispute within [***] after referring such dispute to the designated Executive Officers pursuant to this Section 17.1 (Executive Officers; Disputes), then either Party will have the right to pursue any and all remedies available at law or equity, as set forth in Section 17.2 (Arbitration) or Section 17.3 (Intellectual Property Disputes), as applicable.

17.2 **Arbitration**. Except as otherwise expressly set forth in this Agreement, if the Executive Officers do not resolve a dispute within [***] after such dispute is referred to them in accordance with Section 17.1 (Executive Officers Disputes), then, either Party may at any time after such [***] period submit such dispute to be finally settled by arbitration administered by the International Chamber of Commerce (the "***ICC***") in accordance with its Rules of Arbitration in effect at the time of the arbitration, except as modified by this Section 17.2 (Arbitration) (the "***Arbitration***"). The Arbitration will be governed by the Applicable Law of the State of New York. The language of the arbitration will be English. The Arbitration will be heard and determined by three arbitrators who are retired judges or attorneys with at least 20 years of relevant experience in the pharmaceutical and biotechnology industry, each of whom will be impartial and independent and will not have worked for or on behalf of either Party for at least [***]. Each Party will appoint one arbitrator and the third arbitrator will be selected by the two Party-appointed arbitrators, or, failing agreement within [***] following appointment of the second arbitrator, by the ICC. Such Arbitration will take place in New York, NY. The Arbitration award so given will, absent manifest error, be a final and binding determination of the dispute, will be fully enforceable in any court of competent jurisdiction, and will not include any damages expressly prohibited by Section 13.6 (Limitation of Liability). Ionis will pay the fees, costs, and expenses for the arbitrator it chooses, Ono will pay the fees, costs, and expenses for the arbitrator it chooses, and the Parties will share payment for the third arbitrator. Except in a proceeding to enforce the results of the Arbitration or as otherwise required by Applicable Law or securities exchange, neither Party nor any arbitrator may disclose the existence, content, or results of any Arbitration hereunder without the prior written consent of both Parties.

17.3 **Intellectual Property Disputes**. Notwithstanding any provision to the contrary set forth in this Agreement, if a dispute arises under this Agreement with respect to the validity, scope, enforceability, or ownership of any Patent Right or other intellectual property rights, and such dispute is not resolved in accordance with Section 17.1 (Executive Officers; Disputes), then such dispute will be [***].

17.4 **Equitable Remedies**. Notwithstanding any provision to the contrary set forth in this Agreement, the Parties each stipulate and agree that (a) the other Party's Confidential Information includes highly sensitive trade secret information such that a breach of Article 14 (Confidentiality) by a Party will cause irrevocable harm for which monetary damages would not provide a sufficient remedy; and (b) in such case of such breach of Article 14 (Confidentiality), the non-breaching Party will be entitled to seek equitable relief, including specific performance, temporary or permanent restraining orders, preliminary injunction, permanent injunction, or other equitable relief without the posting of any bond or other security, from any court of competent jurisdiction. In addition, and notwithstanding any provision to the contrary set forth in this Agreement, if there is any other actual or threatened breach hereunder, then the aggrieved Party may seek equitable relief (including specific performance, temporary or permanent restraining orders, or other equitable relief) from any court of competent jurisdiction without first submitting to the dispute resolution procedures set forth in Article 17 (Dispute Resolution; Governing Law).

17.5 **Governing Law; English Language**. This Agreement and all amendments, modifications, alterations, or supplements hereto, and the rights of the Parties, will be construed under and governed by the laws of [***], exclusive of its conflicts of laws principles. This Agreement has been prepared in the English language and the English language will control its interpretation. All consents, notices, reports, and other written documents to be delivered or provided by a Party under this Agreement will be in the English language (and the Party delivering or providing such consent, notice, report, or other written document shall bear the cost of translating such consent, notice, report, or other written document into English if not originally prepared in English), and if there is any conflict between the provisions of any document and the English language translation thereof, then the terms of the English language translation will control.

ARTICLE 18
MISCELLANEOUS

18.1 **Assignment**. This Agreement may not be assigned or otherwise transferred, nor may any right or obligation hereunder be assigned or transferred, by either Party without the prior written consent of the other Party. Notwithstanding the foregoing, (a) Ionis may assign its rights to receive payments under this Agreement to one or more Persons without consent of Ono (including as part of a royalty monetization transaction) with prior notice to Ono, and (b) either Party may, without consent of the other Party, assign this Agreement and its rights and obligations hereunder (i) in whole or in part to an Affiliate of such Party (for so long as such Affiliate remains an Affiliate), or (ii) in whole to its successor-in-interest in connection with the sale of all or substantially all of its assets, whether in a merger, acquisition, or similar transaction or series of related transactions. If there is an assignment pursuant to the foregoing clauses (b)(i) or (b)(ii), then such assignment will only be effective if the Person to whom this Agreement is assigned agrees in writing to assume all of the assigning Party's obligations under this Agreement and the assigning Party provides written notice of such assignment to the non-assigning Party within [***] after the effective date of such assignment. Any attempted assignment of this Agreement in violation of this Section 18.1 (Assignment) will be null, void, and of no legal effect. Any permitted assignee will assume all assigned obligations of its assignor under this Agreement. This Agreement will be binding on and will inure to the benefit of the permitted successors and assigns of the Parties.

18.2 **Entire Agreement; Amendment**. This Agreement, together with all exhibits and schedules attached hereto, constitutes the entire agreement between the Parties with respect to the subject matter hereof, and supersedes and merges all prior and contemporaneous negotiations, representations, and understandings regarding the same, (including that certain mutual confidential disclosure agreement between the Parties dated [***] ("***Confidential Disclosure Agreement***")). All information shared by the Parties pursuant to the Confidential Disclosure Agreement will be Confidential Information under this Agreement from and after the Effective Date, and the use and disclosure thereof will be governed by Article 14 (Confidentiality). This Agreement may not be modified or amended, except by another agreement in writing executed by duly authorized signatories of each Party.

18.3 **No Strict Construction; Interpretation**. This Agreement has been prepared jointly and will not be strictly construed against either Party. Ambiguities, if any, in this Agreement will not be construed against any Party, irrespective of which Party may be deemed to have authored the ambiguous provision. Except where the context expressly requires otherwise, (a) whenever any provision of this Agreement uses the term "including" (or "includes"), such term will be deemed to mean "including without limitation" and "including but not limited to" (or "includes without limitations" and "includes but is not limited to") regardless of whether the words "without limitation" or "but not limited to" actually follow the term "including" (or "includes"); (b) "herein," "hereby," "hereunder," "hereof," and other equivalent words will refer to this Agreement in its entirety and not solely to the particular portion of this Agreement in which any such word is used; (c) all definitions set forth herein will be deemed applicable whether the words defined are used herein in the singular or the plural; (d) wherever used herein, any pronoun or pronouns will be deemed to include both the singular and plural and to cover all genders; (e) the recitals set forth at the start of this Agreement, along with the schedules and exhibits to this Agreement, and the terms and conditions incorporated in such recitals and schedules and exhibits will be deemed integral parts of this Agreement and all references in this Agreement to this Agreement will encompass such recitals and schedules and exhibits and the terms and conditions incorporated in such recitals and schedules and exhibits; *provided* that if there is any conflict between the terms and conditions of this Agreement and any terms and conditions set forth in the recitals, schedules, or exhibits, then the terms and conditions of this Agreement will control; (f) if there is any conflict between the terms and conditions of this Agreement and any terms and conditions that may be set forth on any order, invoice, verbal agreement, or otherwise, then the terms and conditions of this Agreement will govern; (g) unless otherwise provided, all references to Sections, Articles, and Schedules in this Agreement are to Sections, Articles, and Schedules of and to this Agreement; (h) any reference to any federal, national, state, local, or foreign statute or law will be deemed to also refer to all rules and regulations promulgated thereunder, and any reference to any law, rule, or regulation will be deemed to include the then-current amendments thereto or any replacement or successor law, rule, or regulation thereof; (i) wherever used, the word "shall" and the word "will" are each understood to be imperative or mandatory in nature and are interchangeable with one another; (j) the term "or" will be interpreted in the inclusive sense commonly associated with the term "and/or"; (k) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement; (l) the section headings and captions used herein are inserted for convenience of reference only and will not be construed to create obligations, benefits, or limitations; (m) any definition of or reference to any agreement, instrument, or other document herein will be construed as referring to such agreement, instrument, or other document as from time to time amended, supplemented, or otherwise modified (subject to any restrictions on such amendments, supplements, or modifications set forth herein); (n) the word "notice" means notice in writing (whether or not specifically stated) and will include notices, consents, approvals, and other written communications contemplated under this Agreement; and (o) provisions that require that a Party, the Parties, or any committee hereunder "agree," "consent," or "approve" or the like will require that such agreement, consent, or approval be specific and in writing, whether by written agreement, letter, approved minutes, or otherwise (but excluding e-mail and instant messaging).

18.4 **Severability**. If any provision of this Agreement is declared invalid by a court of last resort or by any court or other governmental body, the decision of which is not appealed within the time provided by law, then this Agreement will be deemed to have been terminated only as to the portion thereof that relates to the provision invalidated by that decision and only in the relevant jurisdiction, and this Agreement will remain in force in all other respects and all other jurisdictions; *provided, however*, that if the provision so invalidated is essential to the Agreement as a whole, then the Parties will negotiate in good faith to amend the terms hereof as nearly as practical to carry out the original intent of the Parties, and, failing such amendment, either Party may submit the matter for resolution pursuant to Article 17 (Dispute Resolution; Governing Law).

18.5 **Force Majeure**. Neither Party will be held liable or responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in fulfilling or performing any obligation (other than a payment obligation) of this Agreement when such failure or delay is due to force majeure. For purposes of this Agreement, "***Force Majeure***" is defined as any cause beyond the control of the affected Party and without the fault or negligence of such Party, which may include acts of God; material changes in Applicable Law; war; civil commotion; destruction of production facilities or materials by fire, flood, earthquake, explosion or storm; labor disturbances; epidemic; pandemic; quarantine; and failure of public utilities or common carriers. Notwithstanding the foregoing, a Party will not be excused from making payments owed hereunder due to any such Force Majeure circumstances affecting such Party. In such event the Party affected by such force majeure will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will thereupon be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of [***], after which time the Parties will promptly meet to discuss in good faith how to best proceed in a manner that maintains and abides by the Agreement. To the extent possible, each Party will use reasonable efforts to minimize the duration of any Force Majeure.

18.6 **Notices**. All notices that are required or permitted hereunder will be in writing and sufficient if delivered by internationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, and in each case, addressed as follows (with a courtesy copy sent by email, which will not constitute notice):

If to Ionis:

Ionis Pharmaceuticals, Inc.
[***]

With a copy (which will not constitute notice for purposes of this Agreement) to:

[***]

If to Ono:

Ono Pharmaceutical Co., Ltd.
[***]

With a copy (which will not constitute notice for purposes of this Agreement) to:

[***]

[***]

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance with this Section 18.6 (Notices). Any such notice will be deemed to have been given: (a) on the [***] after dispatch if sent by internationally-recognized overnight courier; or (b) on the [***] after dispatch if sent by registered or certified mail, postage prepaid, return receipt requested.

18.7 **Further Assurances**. The Parties agree to reasonably cooperate with each other in connection with any actions required to be taken as part of their respective obligations under this Agreement, and will (a) furnish to each other such further information; (b) execute and deliver to each other such other documents; and (c) do such other acts and things (including working collaboratively to correct any clerical, typographical, or other similar errors in this Agreement), all as the other Party may reasonably request for the purpose of carrying out the intent of this Agreement.

18.8 **Performance by Affiliates**. If Ono or Ionis performs any or all of its obligations or exercises any or all of its rights under this Agreement through any Affiliate, then Ono and Ionis each hereby guarantees the performance by its Affiliates of its obligations under this Agreement and will cause its Affiliates to comply with the provisions of this Agreement in connection with such performance.

18.9 **Agency**. Neither Party is, nor will be deemed to be an employee, agent, or representative of the other Party for any purpose. Each Party is an independent contractor, not an employee or partner of the other Party. Neither Party will have the authority to speak for, represent, or obligate the other Party in any way without prior written authority from the other Party.

18.10 **Binding Effect; No Third-Party Beneficiaries or Obligors**. As of the Effective Date, this Agreement will be binding upon and inure to the benefit of the Parties and their respective permitted successors and assigns. Except as set forth in Article 15 (Indemnification), no Person other than Ionis, Ono, and their respective permitted successors and assigns hereunder will be deemed an intended beneficiary hereunder, nor have any right to enforce any obligation of any Party to this Agreement, nor will any Person other than Ionis and Ono and their respective permitted successors and assigns have any obligations to any Party under this Agreement.

18.11 **No Waiver**. Any omission or delay by either Party at any time to enforce any right or remedy reserved to it, or to require performance of any of the terms, covenants, or provisions hereof, by the other Party, will not constitute a waiver of such Party's rights to the future enforcement of its rights under this Agreement. Any waiver by a Party of a particular breach or default by the other Party will not operate or be construed as a waiver of any subsequent breach or default by the other Party.

18.12 **Cumulative Remedies**. No remedy referred to in this Agreement, including termination of this Agreement, is intended to be exclusive, but each will be cumulative and in addition to any other remedy referred to in this Agreement or otherwise available under law. Without limiting the foregoing, neither Party will be entitled to recover any liabilities, expenses, or losses (including reasonable attorneys' fees, court costs, witness fees, damages, judgments, fines, and amounts paid in settlement) to the extent that such Party has already recovered such liabilities, expenses, or losses pursuant to other provisions of this Agreement, including recoveries under Section 15.1 (Indemnification by Ionis) or Section 15.2 (Indemnification by Ono).

18.13 **Counterparts**. This Agreement may be executed in one or more counterparts, all of which taken together will be regarded as one and the same instrument. Each Party may execute this Agreement in Adobe™ Portable Document Format (PDF) sent by electronic mail. PDF signatures of authorized signatories of the Parties will be deemed to be original signatures, will be valid and binding upon the Parties, and, upon delivery, will constitute due execution of this Agreement.

[Remainder of page intentionally left blank. Signature page follows.]

IN WITNESS WHEREOF, the Parties have executed this Agreement through their duly authorized representatives to be effective as of the Effective Date.

IONIS PHARMACEUTICALS, INC.

By: */s/ Brett Monia*

Name: Brett Monia

Title: Chief Executive Officer

ONO PHARMACEUTICAL CO., LTD.

By: */s/ Toichi Takino*

Name: Toichi Takino

Title: Representative Director, President and Chief Operating Officer

Appendix 1

Definitions

For purposes of this Agreement, whether used in the singular or plural, the following terms will have the meanings set forth below:

1.1 "***Accounting Standards***" means, with respect to a Party or its Affiliate or Sublicensee, GAAP or IFRS, as such Person uses for its financial reporting standards from time to time, in each case, as consistently applied.

1.2 "***Additional Know-How Transfer***" has the meaning set forth in Section 6.2 (Additional Know-How Transfer).

1.3 "***Affiliate***" means, with respect to a Person, any corporation or other business entity controlled by, controlling, or under common control with such Person, with "control" meaning (a) direct or indirect beneficial ownership of more than 50% of the voting stock or other ownership interest of, or more than 50% interest in the income of, the applicable entity, or (b) the possession, directly or indirectly, of the power to direct the management or policies of the applicable entity, whether through the ownership of voting securities or other equity rights, by contract relating to voting rights or corporate governance, or otherwise. Notwithstanding the foregoing, "Affiliates" will not include, with respect to an entity, *bona fide* venture capital investors in such entity or *bona fide* institutional investors in such entity, in each case, that routinely make venture capital investments for the potential financial return on such investments and not with any view to acquisition or for other strategic purpose, or Affiliates of such venture capital or institutional investors.

1.4 "[***]" means [***].

1.5 "***Annual Net Sales***" means the Net Sales for a Fiscal Year.

1.6 "***Antitrust Authorities***" has the meaning set forth in Section 5.2.1.

1.7 "***Antitrust Filings***" has the meaning set forth in Section 5.2.1.

1.8 "***Applicable Law***" means applicable (with respect to the particular activity, task, or obligation under this Agreement to which such term applies) laws, statutes, rules, regulations, and other pronouncements having the effect of law of any Governmental Authority that may be in effect from time to time, including for clarity any applicable rules, regulations, guidelines, or other requirements of data protection, privacy, or any Regulatory Authority that may be in effect from time to time.

1.9 "***Approved Labeling***" means, with respect to a Licensed Product and a jurisdiction: (a) the applicable Regulatory Authority-approved full prescribing information for such Licensed Product in such jurisdiction; and (b) the applicable Regulatory Authority-approved labels and other written, printed, or graphic materials on any container, wrapper, or any package insert that is used with or for such Licensed Product in such jurisdiction.

1.10 "***Arbitration***" has the meaning set forth in Section 17.2 (Arbitration).

1.11 "***ASO***" means a [***] oligonucleotide compound, or analog or variant thereof that is at least [***] bases long and is designed to inhibit expression of a gene target via the binding, partially or wholly, of such compound to the RNA transcript of such gene target.

1.12 "***Bankruptcy Code***" has the meaning set forth in Section 16.6.2.

1.13 "***Business Day***" means a day other than a Saturday, Sunday, or a day on which banking institutions in California or Japan are required by Applicable Law to remain closed, a day that is a legal holiday in California or Japan, or any day within Ionis' corporate holidays (for Ionis' obligations and response times) or Ono's corporate holidays (for Ono's obligations and response times).

1.14 "***Calendar Quarter***" means, with respect to the first Calendar Quarter during the Term, the period beginning on the Effective Date and ending on the last day of the Calendar Quarter within which the Effective Date falls, and thereafter each successive period of three calendar months ending on (and including) each of March 31, June 30, September 30, and December 31; except that the last Calendar Quarter during the Term will end upon the expiration of the Term.

1.15 "***Calendar Year***" means the period of 12 consecutive calendar months beginning on January 1 and ending on December 31; except that (a) the first Calendar Year during the Term will begin on the Effective Date and end on December 31 of the Calendar Year within which the Effective Date falls, and (b) the last Calendar Year during the Term will end upon expiration of the Term.

1.16 "***Change of Control***" means, with respect to a Party, that: (a) any Third Party acquires directly or indirectly the beneficial ownership of any voting security of such Party, or if the percentage ownership of such Third Party in the voting securities of such Party is increased through stock redemption, cancellation, or other recapitalization, and immediately after such acquisition or increase such Third Party is, directly or indirectly, the beneficial owner of voting securities representing more than 50% of the total voting power of all of the then outstanding voting securities of such Party; (b) a merger, consolidation, recapitalization, or reorganization of such Party is consummated that would result in shareholders or equity holders of such Party immediately prior to such transaction owning 50% or less of the outstanding voting securities of the surviving entity (or its parent entity) immediately following such transaction; or (c) the sale or transfer to a Third Party, in one or more related transactions, of all or substantially all of such Party's consolidated assets taken as a whole.

1.17 "***Clinical Trial***" means any clinical trial in humans.

1.18 "***CMC***" means chemistry, manufacturing, and controls.

1.19 "***Collaboration Know-How***" means all Know-How developed or invented by a Party's or its Affiliates', [***] either alone or jointly with the other Party's or its Affiliates', [***] in each case, in the performance of activities under this Agreement during the Term.

1.20 "***Collaboration Patent Rights***" means any Patent Right that (a) has a priority date after the Effective Date and (b) Covers any Invention included in the Collaboration Know-How.

1.21 "***Commercialization***" means any and all activities directed to the marketing, promotion, distribution, pricing, reimbursement, offering for sale, and sale of a pharmaceutical or biologic product and interacting with Regulatory Authorities following receipt of Regulatory Approval in the applicable country for such pharmaceutical or biologic product regarding the foregoing, including [***], but excluding activities directed to [***]. "***Commercialize***," "***Commercializing***," and "***Commercialized***" will be construed accordingly.

1.22 "***Commercially Reasonable Efforts***" means, with respect to the Exploitation of a Licensed Product by a Party, [***].

1.23 "***Competitive Infringement***" means any actual or alleged infringement, unauthorized use, misappropriation or threatened infringement or misappropriation by a Third Party with respect to any Ionis Technology, Ono Technology, or Joint Collaboration Technology by reason of the [***] of an [***] designed to bind to the RNA encoded by TMPRSS6.

1.24 "***Confidential Disclosure Agreement***" has the meaning set forth in Section 18.2 (Entire Agreement; Amendment).

1.25 "***Confidential Information***" means, subject to Section 14.3 (Exemptions), (a) the terms of this Agreement, and (b) Know-How and any technical, scientific, trade, research, Manufacturing, business, financial, marketing, product, supplier, intellectual property, and other non-public or proprietary data or information (including unpublished patent applications) that may be disclosed by the Disclosing Party to the Receiving Party pursuant to this Agreement (including information disclosed prior to the Effective Date pursuant to the Confidential Disclosure Agreement), that is specifically marked or designated as confidential or, if disclosed orally, confirmed by a written summary thereof (which may consist of a copy of slides used in an oral presentation) sent to the Receiving Party promptly after such oral disclosure; *provided, however*, that the failure to so mark or summarize Confidential Information will not compromise or alter its confidential status if a reasonable person in the industry would recognize, based on its content or the context of its disclosure, that such disclosure was intended as confidential.

1.26 "***Control***" or "***Controlled***" means the possession by a Party (whether by ownership, license, or otherwise other than pursuant to this Agreement) of, (a) with respect to any materials or other tangible Know-How, the legal authority or right to physical possession of such materials or tangible Know-How, with the right to provide such materials or tangible Know-How to the other Party on the terms set forth herein, (b) with respect to Patent Rights, Regulatory Approvals, Regulatory Submissions, intangible Know-How, or other intellectual property, the legal authority or right to grant a license, sublicense, access, or right to use (as applicable) to the other Party under such Patent Rights, Regulatory Approvals, Regulatory Submissions, intangible Know-How, or other intellectual property on the terms set forth herein, in each case ((a) and (b)), without breaching or otherwise violating the terms of any arrangement or agreement with a Third Party in existence as of the time such Party or its Affiliates would first be required hereunder to grant the other Party such access, right to use, license, or sublicense or incurring any additional payment obligations to a Third Party as a result of such access, right to use, license, or sublicense, other than payment obligations incurred under an agreement entered into in accordance with Section 2.8 (Future Third-Party IP Agreements), and (c) with respect to any product, the possession by a Party of the ability (whether by sole or joint ownership, license, or otherwise, other than pursuant to the licenses granted under this Agreement) to grant an exclusive license or sublicense of Patent Rights that Cover such product or proprietary Know-How that is used in connection with the Exploitation of such product. Notwithstanding the foregoing, [***].

1.27 "***Cost Overrun***" has the meaning set forth in Section 7.6.3 (Cost Overruns).

1.28 "***Cover***" means, with respect to a particular subject matter at issue and a relevant Patent Right or individual claim in such Patent Right, as applicable, that the manufacture, use, sale, offer for sale, or importation of such subject matter would fall within the scope of one or more claims in such Patent Right.

1.29 "***Debarred/Excluded***" has the meaning set forth in Section 13.1.5 (Mutual Representations and Warranties**)**.

1.30 "***Development***" means all internal and external research, development and regulatory activities regarding pharmaceutical or biologic products, including (a) [***], and (b) [***] for the purpose of submission to a Regulatory Authority to obtain authorization to conduct Clinical Trials and to obtain, support, or maintain Regulatory Approval of a pharmaceutical or biologic product, but excluding activities [***]. "***Develop***," "***Developing***," and "***Developed***" will be construed accordingly.

1.31 "***Development Milestone Event***" has the meaning set forth in Section 11.2.1 (Development Milestone Payments).

1.32 "***Development Milestone Payment***" has the meaning set forth in Section 11.2.1 (Development Milestone Payments).

1.33 "***Disclosing Party***" has the meaning set forth in Section 14.1 (Duty of Confidence**)**.

1.34 "***Effective Date***" has the meaning set forth in Section 5.1 (Closing).

1.35 "***EMA***" means the European Medicines Agency or any successor agency thereto.

1.36 "[***]" means [***].

1.37 "***European Union***" or "***E.U.***" means the economic, scientific, and political organization of member states of the European Union as it may be constituted from time to time.

1.38 "***Execution Date***" has the meaning set forth in the Preamble to this Agreement.

1.39 "***Executive Officer***" means (a) with respect to Ono, [***] and (b) with respect to Ionis, [***]**.**

1.40 "***Existing Third-Party IP Agreement***" means any agreement between Ionis (or any of its Affiliates) and any Third Party entered into prior to the Effective Date under which such Third Party grants Ionis (or any of its Affiliates) a license to any of the Ionis Technology that is sublicensed to Ono hereunder as of the Effective Date or during the Term.

1.41 "***Exploit***" means to make, have made, use, offer to sell, sell, Develop, Manufacture, Commercialize, or otherwise exploit. "***Exploitation***" will be construed accordingly.

1.42 "***External Costs***" means, with respect to a Party, expenses paid to Third Parties (or payable to Third Parties and accrued in accordance with such Party's Accounting Standards) by such Party (or its Affiliate) in consideration of the performance of activities under this Agreement, and excluding any Internal Costs.

1.43 "***FD&C Act***" means the United States Federal Food, Drug and Cosmetic Act, as amended from time-to-time, together with any rules, regulations, and requirements promulgated thereunder (including all additions, supplements, extensions, and modifications thereto).

1.44 "***FDA***" means the U.S. Food and Drug Administration or any successor agency thereto.

1.45 "***Field***" means the treatment, prevention, or diagnosis of any diseases and conditions in humans.

1.46 "***Fill***" means the process of adding the Licensed Compound to a container, such as a vial, syringe, or cartridge, prior to Packaging and Labeling such Licensed Compound for distribution.

1.47 "***First Commercial Sale***" means, with respect to a Licensed Product in a country, the first sale for end use or consumption to a Third Party of such Licensed Product in such country by Ono, or its Affiliates or Sublicensees after the receipt of Regulatory Approval in the Field for such Licensed Product by the relevant Regulatory Authority in such country. First Commercial Sale excludes any sale or other distribution for use in a [***].

1.48 "***Fiscal Year***" means a twelve-month accounting period that begins on April 1 and ends on March 31.

1.49 "***Flash Report***" has the meaning set forth in Section 11.3.4(a) (Flash Reports).

1.50 "***Follow-On Compound***" has the meaning set forth in Section 2.9.1.

1.51 "***FTE***" means the equivalent of the work of one duly qualified employee of a Party full time for one year (consisting of a total of [***] hours per year) carrying out [***] under this Agreement. Overtime, and work on weekends, holidays and the like will not be counted with any multiplier (*e.g.*, time-and-a-half or double time) toward the number of hours that are used to calculate the FTE contribution, and no individual may be charged at greater than one FTE, regardless of that individual's hours worked during that year. The portion of an FTE billable by a Party for one employee during a given accounting period will be determined by dividing the number of hours worked directly by such employee on the work to be conducted under this Agreement during such accounting period by the number of FTE hours applicable for such accounting period based on [***] working hours per Calendar Year.

1.52 "***FTE Rate***" means, for a given Calendar Year, the rate that a Party charges for an FTE with the appropriate technical skill for such Calendar Year. For the avoidance of doubt, such FTE Rate will [***].

1.53 "***Full Royalty Rate***" has the meaning set forth in Section 11.3.1 (Royalty Rate).

1.54 "***Future Third Party IP***" has the meaning set forth in Section 2.8.1 (Identification of Future Third Party Patent Rights).

1.55 "***GAAP***" means the generally accepted accounting principles in the United States.

1.56 "***Generic Product***" means, with respect to a Licensed Product in a country, a pharmaceutical product (other than such Licensed Product) that (a) is sold by a Third Party other than a Sublicensee under license from Ono in such country, (b) is authorized for use in such country in one or more of the indications for which such Licensed Product has Regulatory Approval in such country; and (c) contains the same active pharmaceutical ingredient(s) as such Licensed Product. A product will not be considered to be a Generic Product if (i) Ono or any of its Affiliates was involved in or authorized the Development or Commercialization of such product, (ii) Ono or any of its Affiliates has granted a license to such Third Party in respect of such product, or (iii) such product is Commercialized in a country by any Person who obtained such product in such country in a chain of distribution that is initiated by Ono or any of its Affiliates or Sublicensees under this Agreement.

1.57 "[***]" has the meaning set forth in Section [***].

1.58 "***Global Trade Control Laws***" means the U.S. Export Administration Regulations, the U.S. International Traffic in Arms Regulations, the economic sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Control, E.U. Council Regulations on export controls, including Nos. 428/2009, 267/2012, other E.U. Council sanctions regulations, as implemented in the E.U. member states, United Nations sanctions policies, and all relevant regulations made under any of the foregoing.

1.59 "***Good Clinical Practices***" or "***GCP***" means the then-current good clinical practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.60 "***Good Laboratory Practices***" or "***GLP***" means the then-current good laboratory practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.61 "***Good Manufacturing Practices***" or "***GMP***" means the then-current good manufacturing practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.62 "***Government Official***" means any official, officer, employee, or representative of: (a) any federal, state, provincial, administrative division, county, or municipal government or any department or agency thereof; (b) any public international organization or any department or agency thereof; or (c) any company or other entity owned or controlled by any government or Governmental Authority.

1.63 "***Governmental Authority***" means any court, agency, department, authority, tribunal, or other instrumentality of any supra-national, national, state, provincial, county, city, or other political subdivision. For clarity, Governmental Authorities include all Regulatory Authorities.

1.64 "***HSR Act***" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the rules and regulations promulgated thereunder.

1.65 "***HSR Clearance***" has the meaning set forth in Section 5.1 (Closing).

1.66 "***ICC***" has the meaning set forth in Section 17.2 (Arbitration).

1.67 "***IFRS***" means International Financial Reporting Standards, consistently applied.

1.68 "***IND***" means an Investigational New Drug application required pursuant to 21 C.F.R. Part 312 or any comparable filings outside of the U.S. required to commence human clinical trials in such country, and all supplements or amendments that may be filed with respect to the foregoing.

1.69 "***Indemnified Party***" has the meaning set forth in Section 15.3 (Indemnification Procedure).

1.70 "***Indemnifying Party***" has the meaning set forth in Section 15.3 (Indemnification Procedure).

1.71 "***Initial Know-How Transfer***" has the meaning set forth in Section 6.1 (Initial Know-How Transfer).

1.72 "***Initiation***" means dosing of the first patient in a Clinical Trial.

1.73 "***Internal Costs***" means, for any period of time, the product obtained by multiplying (a) the total FTEs (or portion thereof) devoted to the performance of activity under this Agreement during such period, by (b) the applicable FTE Rate for such period; *provided* that in determining the total number of FTEs, the applicable Party may rely on estimates as long as the method of calculating such estimates is consistently applied.

1.74 "***Invention***" means any new process, method, composition of matter, article of manufacture that is conceived or first reduced to practice (whether or not patentable).

1.75 "***Ionis Collaboration Know-How***" has the meaning set forth in Section 12.1.2(a).

1.76 "***Ionis Collaboration Patent Rights***" has the meaning set forth in Section 12.1.2(a).

1.77 "***Ionis Core Technology***" means Ionis Core Technology Know-How and the Ionis Core Technology Patents.

1.78 "***Ionis Core Technology Know-How***" means all Know-How, excluding Ionis Product-Specific Know-How, Ionis Manufacturing and Analytical Know-How, and Ionis' interest in any Joint Collaboration Know-How, that (a) is Controlled by Ionis or its Affiliates on the Execution Date or at any time during the Term, (b) is necessary or reasonably useful to Exploit a Licensed Product, and (c) relates generally to oligonucleotides, but *excluding* any Know-How to the extent solely related to any active pharmaceutical ingredient that is not a Licensed Compound.

1.79 "***Ionis Core Technology Patents***" means any Patent Rights, excluding Ionis Product-Specific Patents, Ionis Manufacturing and Analytical Patents, and Ionis' interest in any Joint Collaboration Patent Rights, that (a) are Controlled by Ionis or its Affiliates on the Execution Date or at any time during the Term, (b) are necessary or reasonably useful to Exploit a Licensed Product and (c) claim subject matter generally applicable to oligonucleotides, but *excluding* any Patent Rights to the extent solely related to any active pharmaceutical ingredient that is not a Licensed Compound. A list of the Ionis Core Technology Patents as of the Execution Date is set forth on Appendix 2 (Ionis Core Technology Patents); *provided* that, any Patent Right existing as of the Effective Date that otherwise would be included in the definition of Ionis Core Technology Patents but is not included on Appendix 2 (Ionis Core Technology Patents) will still be considered an Ionis Core Technology Patent.

1.80 "***Ionis Indemnitees***" has the meaning set forth in Section 15.2 (Indemnification by Ono).

1.81 "***Ionis Internal Oligonucleotide Safety Database***" has the meaning set forth in Section 8.10.1.

1.82 "***Ionis Know-How***" means the Ionis Core Technology Know-How, Ionis Manufacturing and Analytical Know-How, and Ionis Product-Specific Know-How.

1.83 "***Ionis Manufacturing and Analytical Know-How***" means Know-How, excluding Ionis' interest in any Joint Collaboration Know-How, that (a) is Controlled by Ionis or its Affiliates on the Execution Date or at any time during the Term, (b) is necessary or reasonably useful to Exploit a Licensed Compound or Licensed Product, and (c) relates to the synthesis or analysis of oligonucleotides generally, including a Licensed Product, but *excluding* any Know-How to the extent solely related to any active pharmaceutical ingredient that is not a Licensed Compound.

1.84 "***Ionis Manufacturing and Analytical Patents***" means Patent Rights, excluding Ionis' interest in any Joint Collaboration Patent Rights, that (a) are Controlled by Ionis or its Affiliates on the Execution Date or at any time during the Term, (b) are necessary or reasonably useful to Manufacture a Licensed Product, and (c) claim (i) methods and materials used in the synthesis or analysis of an oligonucleotide regardless of sequence or chemical modification, (ii) methods of manufacturing components of an oligonucleotide, and (iii) methods and materials used in Manufacturing a Licensed Product, but *excluding* any Patent Rights to the extent solely related to any active pharmaceutical ingredient that is not a Licensed Compound. A list of Ionis Manufacturing and Analytical Patents as of the Execution Date is set forth on Appendix 3 (Ionis Manufacturing and Analytical Patents); *provided* that, any Patent Right existing as of the Execution Date that otherwise would be included in the definition of Ionis Manufacturing and Analytical Patent but is not included on Appendix 3 (Ionis Manufacturing and Analytical Patents) will still be considered an Ionis Manufacturing and Analytical Patent.

1.85 "***Ionis Manufacturing and Analytical Technology***" means Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patents.

1.86 "***Ionis Patent Rights***" means the Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents, and Ionis Product-Specific Patents.

1.87 "***Ionis Product-Specific Know-How***" means all Know-How, excluding Ionis' interest in any Joint Collaboration Know-How, that is (a) Controlled by Ionis or its Affiliates on the Execution Date or at any time during the Term, (b) necessary or reasonably useful to Exploit a Licensed Product in the Field, and (c) specifically relating to (i) the composition of matter of a Licensed Product or (ii) methods of using a Licensed Product for the Field, but *excluding* any Know-How to the extent solely related to any active pharmaceutical ingredient that is not a Licensed Compound; *provided* however, such Know-How that (x) consists of subject matter applicable to oligonucleotide compounds or products in general or (y) relates to an [***] compound that does not specifically modulate expression of TMPRSS6 via the binding, partially or wholly, of such compound to RNA encoded by TMPRSS6, will not be considered Ionis Product-Specific Know-How, and in each case of (x) and (y), such Know-How will be considered Ionis Core Technology Know-How.

1.88 "***Ionis Product-Specific Patents***" means all Product-Specific Patents, excluding Ionis' interest in any Joint Collaboration Patent Rights, that are (a) Controlled by Ionis or its Affiliates on the Execution Date or at any time during the Term and (b) necessary or reasonably useful to Exploit a Licensed Product, but *excluding* any Patent Rights to the extent solely related to any active pharmaceutical ingredient that is not a Licensed Compound; *provided*, however, that such Patent Rights that include only claims that are directed to (i) subject matter applicable to oligonucleotide compounds or products in general or (ii) an [***] compound that does not specifically modulate expression of TMPRSS6 via the binding, partially or wholly, of such compound to RNA encoded by TMPRSS6, will not be considered Ionis Product-Specific Patents, and in each case of (i) and (ii), such Patent Rights will be considered Ionis Core Technology Patents. A list of Ionis Product-Specific Patents as of the Execution Date is set forth on Appendix 4 (Ionis Product-Specific Patents); *provided* that, any Patent Right existing as of the Execution Date that otherwise would be included in the definition of Ionis Product-Specific Patent but is not included on Appendix 4 (Ionis Product-Specific Patents) will still be considered an Ionis Product-Specific Patent.

1.89 "***Ionis Product-Specific Technology***" means Ionis Product-Specific Know-How and Ionis Product-Specific Patents.

1.90 "***Ionis Publication***" has the meaning set forth in Section 14.5.2 (Ionis' Right to Publish).

1.91 "***Ionis Review Period***" has the meaning set forth in Section 14.5.1 (Ono's Right to Publish).

1.92 "***Ionis Technology***" means the Ionis Know-How, the Ionis Patent Rights, and Ionis' interest in the Joint Collaboration Technology.

1.93 "***IRS***" has the meaning set forth in Section 11.10.3 (Tax Cooperation).

1.94 "***Joint Collaboration*** [***] ***Technology***" means Joint Collaboration [***] Technology Know-How and Joint Collaboration [***] Technology Patents.

1.95 "***Joint Collaboration*** [***] ***Technology Know-How***" means all Joint Collaboration Know-How, excluding Joint Collaboration [***] Know-How and Joint Collaboration [***] Know-How, that [***].

1.96 "***Joint Collaboration*** [***] ***Technology Patents***" means any Joint Collaboration Patent Rights, excluding Joint Collaboration [***] Patents and Joint Collaboration Manufacturing and Analytical Patents, that [***].

1.97 "***Joint Collaboration Know-How***" means all Collaboration Know-How that is developed or invented jointly by a Party's or its Affiliates', [***], on the one hand, and the other Party's or its Affiliates', [***], on the other hand.

1.98 "***Joint Collaboration*** [***] ***Know-How***" means Joint Collaboration Know-How that [***].

1.99 "***Joint Collaboration*** [***] ***Patents***" means Joint Collaboration Patent Rights that [***].

1.100 "***Joint Collaboration*** [***] ***Technology***" means Joint Collaboration [***] Know-How and Joint Collaboration [***] Patents.

1.101 "***Joint Collaboration Patent Rights***" means all Collaboration Patent Rights that Cover Joint Collaboration Know-How.

1.102 "***Joint Collaboration*** [***] ***Know-How***" means Joint Collaboration Know-How that [***].

1.103 "***Joint Collaboration*** [***] ***Patents***" means Joint Collaboration Patent Rights that [***].

1.104 "***Joint Collaboration*** [***] ***Technology***" means Joint Collaboration [***] Know-How and Joint Collaboration [***] Patents.

1.105 "***Joint Collaboration Technology***" means the Joint Collaboration Know-How and the Joint Collaboration Patent Rights.

1.106 "***JSC***" has the meaning set forth in Section 4.1.1 (Formation and Purpose of the JSC).

1.107 "***JSC Co-Chairperson***" has the meaning set forth in Section 4.1.2 (Membership**)**.

1.108 "***Know-How***" means proprietary Inventions, discoveries, trade secrets, materials, information, experience, data, formulas, procedures, technology, results, and other intellectual property (whether or not patentable), including practices, knowledge, know-how, experience and test data (including physical, chemical, biological, toxicological, pharmacological, clinical and veterinary data), correspondence, regulatory materials (including regulatory submissions, regulatory filings, and correspondence with Regulatory Authorities), dosage regimens, assays, diagnostics, product specifications, manufacturing techniques and costs, platform data, platform technology, analytical and quality control data and marketing, pricing and distribution costs, and sales practices, methods, data, and descriptions. Notwithstanding the foregoing, any Know-How that is Covered by Patent Rights shall not be deemed as Know-How.

1.109 "***Knowledge***" means the actual knowledge, without any inquiry or investigation, of (a) with respect to Ionis, its [***]; and (b) with respect to Ono, its [***].

1.110 "***Liaison***" has the meaning set forth in Section 4.6 (Liaisons).

1.111 "***Licensed CMO***" means a contract manufacturing organization to whom Ionis has granted a license under Ionis' manufacturing intellectual property to manufacture oligonucleotides. A list of the current Licensed CMOs as of the Execution Date is attached as SCHEDULE 10.4.

1.112 "***Licensed Compound***" means any ASO designed to bind to the RNA encoded by TMPRSS6 discovered by Ionis prior to the Effective Date of the Agreement, which for clarity includes the GalNAc-conjugated ASO known as sapablursen (the structure of which is set forth in APPENDIX 5), including any solvates, salts, esters, metabolites, acid forms, base forms, radioisomers, steroisomers, racemates, tautomers, polymorphs, hydrates and crystalline forms thereof; and any such ASOs designed to bind to the RNA encoded by TMPRSS6 discovered by Ionis prior to the Effective Date that are backups or derivatives or modifications of sapablursen.

1.113 "***Licensed Patent***" means (a) the Ionis Product-Specific Patents, (b) the Ionis Core Technology Patents, (c) the Ionis Manufacturing and Analytical Patents, and (d) Ionis' and its Affiliate's interest in any Joint Collaboration Patent Rights.

1.114 "***Licensed Product***" means any pharmaceutical product that contains, comprises, or incorporates a Licensed Compound as an active pharmaceutical ingredient, in all current and future formulations and in any dosage strengths, presentations, or package configuration, and for any mode of administration, whether alone or in combination with other active pharmaceutical ingredients, components, or devices. Any pharmaceutical product that contains the same active pharmaceutical ingredient within the scope of the Licensed Compound, whether alone or in combination with other active pharmaceutical ingredients shall be deemed as one and the same product regardless of the different formulation or route of administration.

1.115 "***Losses***" has the meaning set forth in Section 15.1 (Indemnification by Ionis).

1.116 "***MAA***" means any (a) New Drug Application as defined in the FD&C Act, (b) a marketing authorization application filed with (i) the EMA under the centralized EMA filing procedure to gain approval to market a biopharmaceutical in the E.U., or (ii) a Regulatory Authority in any country in the E.U. if the centralized EMA filing procedure is not used to gain approval to market a biopharmaceutical in the E.U., or (c) substantially similar application or submission to those set forth in clause (a) or clause (b) filed with a Regulatory Authority in a country or group of countries to obtain Regulatory Approval to Commercialize a biopharmaceutical or diagnostic product in that country or in that group of countries, in each case ((a) through (c)), including any amendments thereto, and supplemental applications, but excluding Reimbursement Approval applications.

1.117 "[***]" means[***].

1.118 "***Manufacture***" means activities directed to manufacturing, having manufactured, processing, packaging, labeling, filling, finishing, assembly, quality assurance, quality control, testing, and release, shipping, importing, exporting, or storage of any pharmaceutical or biologic product (or any components or process steps involving any product or any companion diagnostic), placebo, or comparator agent, as the case may be, including qualification, validation, and scale-up, pre-clinical, clinical, and commercial manufacture and analytic development, product characterization, and stability testing, but excluding activities directed to Development, or Commercialization. "***Manufacturing***" and "***Manufactured***" will be construed accordingly.

1.119 "[***]" means, with respect to a Licensed Product, [***].

1.120 "***Manufacturing Technology Transfer***" has the meaning set forth in Section 6.3 (Manufacturing Technology Transfer).

1.121 "***Milestone Event***" means a Development Milestone Event or a Sales Milestone Event, individually or collectively as the context requires.

1.122 "***Milestone Payment***" means a Development Milestone Payment or a Sales Milestone Payment, individually or collectively as the context requires.

1.123 "[***]" means [***].

1.124 "[***]" has the meaning set forth in Section [***].

1.125 "***Net Sales***" means, with respect to any Licensed Product, the amount billed by Ono or its Affiliates or Sublicensees (each a "***Selling Party***") for sales of such Licensed Product in arm's length transactions to Third Parties in the Territory, after deduction (if not already deducted in the amount invoiced) of the following items with respect to sales of such Licensed Product:

(a) Normal and customary trade, quantity, or cash discounts (including 340B drug pricing program) to non-affiliated brokers, agents or customers to the extent actually allowed and taken, *provided* that [***];

(b) Actual amounts repaid or credited by reason of rejections or returns ([***]);

(c) To the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes or other governmental charges paid and levied on the production, sale, transportation, delivery, or use of the Licensed Products;

(d) Rebates, fees, and chargeback payments required to sell products granted to managed health care organizations, group purchasing organizations, pharmacy benefit managers (or equivalent thereof), national, state/provincial, local, and other governments, their agencies/purchasers/reimbursement providers, or to trade customers;

(e) [***] lump sum of the gross amount invoiced for Net Sales of the Licensed Product to cover outbound transportation costs prepaid or allowed and costs of insurance in transit, with the exclusion of [***];

(f) Any invoiced amounts that are not collected, including bad debts; *provided* that the following deductions are not allowed in the calculation of Net Sales: [***]; and

(g) Any mandatory sales-based contributions actually made for [***].

If a Selling Party [***], then [***].

Net Sales will not include [***].

1.126 "***Non-Manufacturing Technology Transfer***" has the meaning set forth in Section 6.2 (Additional Know-How Transfer).

1.127 "***OFAC***" means the Office of Foreign Assets Control of the United States Department of the Treasury or any successor agency thereto.

1.128 "***Ongoing Clinical Trial***" has the meaning set forth in Section 7.1 (Ongoing Clinical Trial).

1.129 "***Ongoing Clinical Trial Development Plan***" has the meaning set forth in Section 7.1 (Ongoing Clinical Trial).

1.130 "***Ongoing Clinical Trial Extension***" has the meaning set forth in Section 7.2 (Extension of Ongoing Clinical Trial).

1.131 "***Ongoing Clinical Trial Extension Budget***" has the meaning set forth in Section 7.2 (Extension of Ongoing Clinical Trial).

1.132 "***Ono Collaboration Know-How"*** has the meaning set forth in Section 12.1.2(b).

1.133 "***Ono Collaboration Patent Rights***" has the meaning set forth in Section 12.1.2(b).

1.134 "***Ono Indemnitees***" has the meaning set forth in Section 15.1 (Indemnification by Ionis).

1.135 "***Ono Know-How***" means all Know-How (excluding the Ionis Know-How and Ono's interest in Joint Collaboration Know-How) that is (a) Controlled by Ono or any of its Affiliates as of the Effective Date or during the Term and (b) necessary or reasonably useful to Exploit a Licensed Product.

1.136 "***Ono Patent Rights***" means all Patent Rights (excluding the Ionis Patent Rights and Ono's interest in Joint Collaboration Patent Rights) that are (a) Controlled by Ono or any of its Affiliates as of the Effective Date or during the Term and (b) necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product.

1.137 "***Ono Publication***" has the meaning set forth in Section 14.5.1 (Ono's Right to Publish).

1.138 "***Ono Review Period***" has the meaning set forth in Section 14.5.2 (Ionis' Right to Publish).

1.139 "***Ono Technology***" means Ono Know-How, Ono Patent Rights, and Ono's interest in the Joint Collaboration Technology.

1.140 "[***]" means [***].

1.141 "[***]" means [***].

1.142 "***Other Covered Party***" means any political party or party official, or any candidate for political office.

1.143 "***Package and Label***" means primary, secondary, or tertiary packaging and labeling of a Licensed Product for sale or use in a country, including the Approved Labeling and insertion of materials such as patient inserts, patient medication guides, and professional inserts and any other written, printed, or graphic materials accompanying such Licensed Product and any brand security or anti-counterfeiting measures included in the packaging elements for such licensed Product considered to be part of the finished packaged Licensed Product, and all testing and release thereof.

1.144 "***Party Vote***" has the meaning set forth in Section 4.3.1 (General Decision-Making Process).

1.145 "***Patent Challenge***" has the meaning set forth in Section 16.5 (Termination for Patent Challenge).

1.146 "***Patent Prosecution***" means activities directed to (a) preparing, filing, and prosecuting applications (of all types) for any Patent Right, (b) maintaining any Patent Right, and (c) deciding whether to abandon or maintain any Patent Right.

1.147 "***Patent Rights***" means (a) all patents, patent applications, and utility models in any country or jurisdiction, including provisional applications, priority applications, and international applications, (b) any and all patents that have issued or in the future issue from the foregoing patent applications, (c) any and all substitutions, renewals, registrations, confirmations, revalidations, reissues, and re-examinations of the foregoing patents or patent applications, and (d) extensions, restorations, supplemental protection certificates, and the like based on any of the foregoing patents or patent applications.

1.148 "***Patent Term Extensions***" has the meaning set forth in Section 12.8 (Patent Term Extensions).

1.149 "***Permitted Licenses***" means (a) licenses granted by Ionis after the Effective Date to any Third Party under the Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents (but not under the Ionis Product-Specific Patents) solely to (i) conduct nonclinical research, or (ii) enable such Third Party to manufacture or formulate oligonucleotides, where such Third Party is primarily engaged in providing contract manufacturing services or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (b) material transfer agreements with academic collaborators or non-profit institutions solely to conduct non-commercial research.

1.150 "***Person***" means any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau, or agency, or any other entity or body, or an individual.

1.151 "***Pharmacovigilance Agreement***" means an agreement regarding receipt, investigation, and reporting of product complaints, adverse events, product recalls, and any other information related to the safety of the Licensed Products in the Territory.

1.152 "***Pivotal Clinical Trial***" means, with respect to a Licensed Product, (a) a Clinical Trial performed to gain evidence with statistical significance of the efficacy of such Licensed Product in a target population and to obtain expanded evidence of safety for such Licensed Product that is needed to evaluate the overall benefit-risk relationship of such Licensed Product, to form the basis for approval of an MAA by a Regulatory Authority and to provide an adequate basis for physician labeling, as described in 21 C.F.R. § 312.21(c), as amended from time to time, or the corresponding regulation in jurisdictions other than the United States; or (b) a Clinical Trial that satisfies the requirements of 21 C.F.R. § 312.21(c) and is a registration trial on a sufficient number of patients designed to establish statistically significant efficacy and safety of such Licensed Product for its target patient population, and to determine warnings, precautions, and adverse reactions that are associated with such Licensed Product in the dosage range to be prescribed, for the purpose of enabling the preparation and submission of application for an MAA to the competent Regulatory Authorities in a given country, as evidenced by (i) an agreement with or statement from the FDA on a Special Protocol Assessment or equivalent in another country, (ii) other guidance or minutes issued by the FDA for such registration trial or equivalent in another country, or (iii) Ono's public statements, in each case ((i)-(iii)), where the results of such Clinical Trial are intended (if supportive) to be used to establish both safety and efficacy of such Licensed Product in patients that are the subject of such trial and serve as the basis for obtaining initial or supplemental Regulatory Approval of such Licensed Product.

1.153 "***Prior Agreement***" means each agreement listed on Appendix 6 (Prior Agreements) attached hereto as it is in effect as of the Execution Date without giving effect to any amendments or modifications thereafter.

1.154 "***Product-Specific Know-How***" means, all Know-How that is (a) Controlled by a Party or its Affiliates on the Execution Date or at any time during the Term, (b) necessary or reasonably useful to Exploit a Licensed Product in the Field, and (c) specifically relating to (i) the composition of matter of a Licensed Product or (ii) methods of using a Licensed Product for the Field, but *excluding* any Know-How to the extent solely related to any active pharmaceutical ingredient that is not a Licensed Compound; *provided* however, such Know-How that is Controlled by Ionis and (x) consists of subject matter applicable to oligonucleotide compounds or products in general or (y) relates to an [***] compound that does not specifically modulate expression of TMPRSS6 via the binding, partially or wholly, of such compound to RNA encoded by TMPRSS6, will not be considered Product-Specific Know-How, and in each case of (x) and (y), such Know-How will be considered Ionis Core Technology Know-How.

1.155 "***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date claiming: (a) the specific composition of matter of a Licensed Product, or (b) methods of using such a Licensed Product.

1.156 "***Professional Requirements***" means (a) the codes and standards of the European Accreditation Council for Continuing Medical Education (EACCME) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), (b) the codes of the Prescription Medicines Code of Practice Authority (PMCPA) and the Association of the British Pharmaceutical Industry (ABPI), (c) FDA's regulations, guidance, and enforcement letters concerning the advertising of prescription drug products, (d) the American Medical Association's Guidelines on Gifts to Physicians from Industry, (e) the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support of Continuing Medical Education, (f) the Pharmaceutical Supply Chain Initiative (PSCI) and Pharmaceutical Industry Principles for Responsible Supply Chain Management, (g) the Code on Interactions with Healthcare Professionals promulgated by the Pharmaceutical Research and Manufacturers of America (PhRMA Code), (h) the Department of Health and Human Services Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers (OIG Compliance Guidance), and (i) all other accepted national and international pharmaceutical industry codes of practice in and for the relevant countries in the Territory, as any of the foregoing may be amended from time-to-time.

1.157 "***Publication***" has the meaning set forth in Section 14.5 (Publications).

1.158 "***Receiving Party***" has the meaning set forth in Section 14.1.1 (Duty of Confidence).

1.159 "***Reduction Circumstances***" has the meaning set forth in Section 11.3.3(c) ([***]).

1.160 "***Regulatory Approval***" means, with respect to a particular country or other regulatory jurisdiction, any approval of an MAA or other approval, product, or establishment license, registration, or authorization of any Regulatory Authority necessary for the commercial sale of a pharmaceutical, diagnostic, or biologic product in such country or other regulatory jurisdiction, excluding, in each case, [***].

1.161 "***Regulatory Authority***" means, in a particular country or jurisdiction, any applicable Governmental Authority involved in granting Regulatory Approval in such country or jurisdiction, including (a) in the U.S., the FDA and any other applicable Governmental Authority in the U.S. having jurisdiction over any pharmaceutical, diagnostic, or biologic product, (b) in the E.U., the EMA and any other applicable Governmental Authority in the E.U. having jurisdiction over any pharmaceutical, diagnostic, or biologic product, and (c) in other countries, other analogous Governmental Authorities having jurisdiction over any pharmaceutical, diagnostic, or biologic product.

1.162 "***Regulatory Exclusivity***" means, with respect to a Licensed Product in a country, the period of time during which: (a) Ono or its Affiliate or Sublicensee has been granted the exclusive legal right by a Regulatory Authority (or is otherwise entitled to the exclusive legal right by operation of Applicable Law) in such country to market and sell such Licensed Product, and such right precludes a Third Party from making such Licensed Product available for purchase for any indication; or (b) the data and information submitted by Ono or its Affiliate or Sublicensee to the relevant Regulatory Authority in such country for purposes of obtaining Regulatory Approval may not be referenced, or relied upon in any way by a Third Party or such Regulatory Authority to support the Regulatory Approval or marketing of any product by a Third Party in such country, or if such data and information is referenced, or relied upon to support a Regulatory Approval granted to a Third Party in such country, the product may not be placed on the market for any indication.

1.163 "***Regulatory Submission***" means any filing, application, or submission with any Regulatory Authority in support of the Development, Manufacture, Commercialization, or other Exploitation of a pharmaceutical, diagnostic, or biologic product (including to obtain, support, or maintain Regulatory Approval from that Regulatory Authority), and all written or electronic correspondence or communication with or from the relevant Regulatory Authority, as well as minutes of any material meetings, telephone conferences, or discussions with the relevant Regulatory Authority. Regulatory Submissions include all INDs, MAAs, and other applications for Regulatory Approval and their equivalents.

1.164 "***Reimbursement Approval***" means any approval, agreement, determination, or other decision by the applicable Governmental Authority in a given country that establishes prices charged to end-users for pharmaceutical, diagnostic, or biologic products at which such pharmaceutical, diagnostic, or biologic products will be reimbursed by the Regulatory Authorities or other applicable Governmental Authorities in such country or any other approvals related to pricing, reimbursement, or access to a pharmaceutical, diagnostic, or biologic product (including all activities related to tenders and contracts).

1.165 "***Restricted Party***" means any individual or entity on one or more of the Restricted Party Lists.

1.166 "***Restricted Party List***" means the list of sanctioned entities maintained by the United Nations; the Specially Designated Nationals and Blocked Persons List, the Foreign Sanctions Evaders List and the Sectoral Sanctions Identifications List, all administered by OFAC; the U.S. Denied Persons List, the U.S. Entity List, and the U.S. Unverified List, all administered by the U.S. Department of Commerce; and the entities subject to restrictive measures and the consolidated list of Persons, Groups, and Entities Subject to E.U. Financial Sanctions, as implemented by the E.U. Common Foreign & Security Policy.

1.167 "***Review Period***" has the meaning set forth in Section 14.5.1 (Ono's Right to Publish).

1.168 "[***]" has the meaning set forth in Section [***].

1.169 "[***]" has the meaning set forth in Section [***].

1.170 "***Royalties***" has the meaning set forth in Section 11.3.1 (Royalty Rate).

1.171 "***Royalty Report***" has the meaning set forth in Section 11.3.4(b) (Royalty Report).

1.172 "***Royalty Term***" has the meaning set forth in Section 11.3.2(a) (Royalty Term).

1.173 "***Sales Milestone Event***" has the meaning set forth in Section 11.2.2 (Sales Milestone Payments).

1.174 "***Sales Milestone Payment***" has the meaning set forth in Section 11.2.2 (Sales Milestone Payments).

1.175 "***Selling Party***" has the meaning set forth in Section 1.125 (Net Sales) of this Appendix 1.

1.176 "***Sublicensee***" means, with respect to a Party, any Affiliate or Third Party to which such Party or its Affiliate grants a sublicense under any of the rights licensed to the applicable Party under this Agreement.

1.177 "***Tax***" or "***Taxes***" means any present or future taxes, levies, imposts, duties, charges, assessments or fees of any nature (including any interest thereon), including value add, sales, excise or similar taxes.

1.178 "***Taxation Forms***" means Form 3 and Form 17 posted in the WEB of National Tax Agency in Japan and certification of residence issued by the IRS.

1.179 "***Technology Transfers***" has the meaning set forth in Section 6.4 (Technology Transfer Costs and Support).

1.180 "***Term***" has the meaning set forth in Section 16.1 (Term).

1.181 "***Territory***" means worldwide.

1.182 "***Third Party***" means any Person other than a Party or its Affiliates.

1.183 "***Third Party Claims***" has the meaning set forth in Section 15.1 (Indemnification by Ionis).

1.184 "***Third Party Challenge***" has the meaning set forth in Section 12.4 (Defense of Third Party Challenges).

1.185 "***Third Party Payment***" means, with respect to the Licensed Product, any (a) payments (including upfront payments, milestone payments, license fees, and royalties) made by Ono or its Affiliate to a Third Party (i) pursuant to an agreement between Ono or its Affiliate and such Third Party entered into following the Effective Date in accordance with Section 2.8.2 (Future Third Party [***]) or Section 2.8.4(b) (Ono Step-In Right) to obtain rights to Patent Rights or Know-How from such Third Party that are necessary to Develop or Commercialize the Licensed Product in the form the Licensed Product exists as of the Effective Date or (ii) pursuant to an agreement between Ono or its Affiliate and such Third Party, or otherwise, entered into after the Effective Date, as part of a settlement or to satisfy a judgement in accordance with Section 12.5.3 (Settlement), or (b) amounts for which Ono reimburses Ionis under an agreement entered into by Ionis following the Effective Date in accordance with Section 2.8.3(b) (Ionis Step-In Right) to obtain rights to Patent Rights or Know-How from such Third Party that are necessary to Develop or Commercialize the Licensed Product in the form the Licensed Product exists as of the Effective Date, in each case ((a) and (b)) that are directly in consideration for or reasonably allocable to a license or sublicense (as applicable) to Ono or its Affiliate under, or are paid in settlement or to satisfy a judgment of a claim relating to, Patent Rights or Know-How controlled by such Third Party that are necessary to Develop or Commercialize the Licensed Product in the form the Licensed Product exists as of the Effective Date.

1.186 "***TMPRSS6***" means the human transmembrane serine protease 6 gene (NCBI Gene ID: 164656; Ensembl Gene ID: ENSG00000187045), including all mutants, polymorphisms, and fragments thereof.

1.187 "***USA***" means the United States of America (including all possessions and territories thereof, including Puerto Rico).

1.188 "***U.S. Dollars***" or "**$**" means the legal tender of the USA.

1.189 "***Valid Claim***" means: (a) a claim of an issued and unexpired patent (as may be adjusted through a patent term adjustment or extended through supplementary protection certificate or patent term extension or the like) that has not been revoked, held invalid, or held unenforceable by a patent office or other Governmental Authority of competent jurisdiction in a final and non-appealable judgment (or judgment from which no appeal was taken within the allowable time period); or (b) a pending claim of an unissued, pending patent application, which claim has not been pending for more than [***] years, unless and until such claim becomes an issued claim of an issued patent in which case it will again be considered a Valid Claim under the foregoing clause (a), *provided* that such [***]-year period will be tolled for the duration of any adverse proceeding (e.g., appeals during examination or any appeal thereof) with respect to the patent application at issue.

1.190 "***Withheld Amount***" has the meaning set forth in Section 11.10.2 (Withholding Tax).

1.191 "***Working Group***" has the meaning set forth in Section 4.1.1 (Formation and Purpose of the JSC).

APPENDIX 2

Ionis Core Technology Patents

Ionis File No.	Country/Treaty	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]		[***]

APPENDIX 3

Ionis Manufacturing and Analytical Patents

Ionis File No.	Country	Status	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]		[***]
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[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]

Ionis File No.	Country	Status	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]		[***]
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[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
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[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]

APPENDIX 4

Ionis Product-Specific Patents

Ionis File No.	Country	Status	Application No./ Patent No.	Date Filed	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]

Ionis File No.	Country	Status	Application No./ Patent No.	Date Filed	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]

APPENDIX 5

Sapablursen Structure

[***]

APPENDIX 6

Prior Agreements

1. [***].
2. [***].
3. [***].
4. [***].
5. [***].
6. [***].
7. [***].
8. [***].
9. [***].
10. [***].
11. [***].

SCHEDULE 6.1

[***]

[***]

SCHEDULE 6.4

[***]

[***]

SCHEDULE 7.1

Ongoing Clinical Trial Development Plan

[***]

SCHEDULE 7.2

Extension of Ongoing Clinical Trial – Estimated Development Plan and Costs

[***]

SCHEDULE 10.1 (A)

MANUFACTURING HISTORY AND CURRENT INVENTORY

[***]

SCHEDULE 10.1 (B)

[***]

[***]

SCHEDULE 10.4

Licensed CMOs

1. [***].
2. [***].
3. [***].
4. [***].
5. [***].
6. [***].

SCHEDULE 13.1.6

[***]

[***]

SCHEDULE 13.2.5

Existing Third-Party IP Agreements

[***]

SCHEDULE 16.8.3(B)

Reversion Royalties Dispute Resolution

[***]

SCHEDULE 16.8.4

[***]

[***]

EXHIBIT 31.1

CERTIFICATION

I, Brett P. Monia, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: April 30, 2025

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

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: April 30, 2025

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

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Brett P. Monia, the Chief Executive Officer of Ionis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2025, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: April 30, 2025

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

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

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