UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended September 30, 2021

OR

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

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

760-931-9200

(Registrant's telephone number, including area code)

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

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

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

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

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

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

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

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

The number of shares of voting common stock outstanding as of October 27, 2021 was 141,210,015.

IONIS PHARMACEUTICALS, INC.
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TRADEMARKS

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

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

	September 30, 2021	December 31, 2020 (as revised*)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 632,953	$ 397,664
Short-term investments	1,354,146	1,494,711
Contracts receivable	9,068	76,204
Inventories	22,930	21,965
Other current assets	136,643	140,163
Total current assets	2,155,740	2,130,707
Property, plant and equipment, net	180,144	181,077
Patents, net	30,038	27,937
Deposits and other assets	48,971	50,034
Total assets	$ 2,414,893	$ 2,389,755
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 8,357	$ 17,199
Accrued compensation	32,320	65,728
Accrued liabilities	75,681	90,161
Income taxes payable	450	1,324
1 percent convertible senior notes, net	61,936	308,809
Current portion of long-term obligations	3,109	7,301
Current portion of deferred contract revenue	97,925	108,376
Total current liabilities	279,778	598,898
Long-term deferred contract revenue	362,887	424,046
0 percent convertible senior notes, net	618,341	—
0.125 percent convertible senior notes, net	541,768	540,136
Long-term obligations, less current portion	21,628	23,409
Long-term mortgage debt	59,955	59,984
Total liabilities	1,884,357	1,646,473
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 141,184,026 and 140,365,594 shares issued and outstanding at September 30, 2021 (unaudited) and December 31, 2020, respectively	141	140
Additional paid-in capital	1,942,348	1,895,519
Accumulated other comprehensive loss	(27,437)	(21,071)
Accumulated deficit	(1,384,516)	(1,131,306)
Total stockholders' equity	530,536	743,282
Total liabilities and stockholders' equity	$ 2,414,893	$ 2,389,755

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020 (as revised*)	2021	2020 (as revised*)
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 66,572	$ 74,171	$ 198,726	$ 211,925
TEGSEDI and WAYLIVRA revenue, net	15,519	19,040	46,901	50,562
Licensing and other royalty revenue	2,729	2,129	9,502	6,548
Total commercial revenue	84,820	95,340	255,129	269,035
Research and development revenue under collaborative agreements	48,273	64,739	115,321	169,948
Total revenue	133,093	160,079	370,450	438,983
Expenses:				
Cost of sales	3,079	3,086	8,616	8,646
Research, development and patent	184,770	125,083	463,878	364,298
Selling, general and administrative	31,093	68,447	148,747	215,455
Total operating expenses	218,942	196,616	621,241	588,399
Loss from operations	(85,849)	(36,537)	(250,791)	(149,416)
Other income (expense):				
Investment income	872	6,454	8,236	25,913
Interest expense	(2,340)	(2,428)	(7,111)	(7,076)
Gain on investments	4,013	835	4,885	10,722
Loss on early retirement of debt	—	—	(8,627)	—
Other income (expenses)	(469)	126	(656)	(122)
Loss before income tax benefit (expense)	(83,773)	(31,550)	(254,064)	(119,979)
Income tax benefit (expense)	1,307	(5,064)	854	(4,077)
Net loss	(82,466)	(36,614)	(253,210)	(124,056)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	12,147	—	34,325
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (82,466)	$ (24,467)	$ (253,210)	$ (89,731)
Basic and diluted net loss per share	$ (0.58)	$ (0.18)	$ (1.80)	$ (0.64)
Shares used in computing basic and diluted net loss per share	141,139	139,708	140,958	139,497

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020 (as revised*)	2021	2020 (as revised*)
Net loss	$ (82,466)	$ (36,614)	$ (253,210)	$ (124,056)
Unrealized gains (losses) on debt securities, net of tax	(1,618)	(3,448)	(6,321)	5,803
Currency translation adjustment	(23)	275	(45)	357
Comprehensive loss	(84,107)	(39,787)	(259,576)	(117,896)
Comprehensive loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	(12,188)	—	(33,883)
Comprehensive loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (84,107)	$ (27,599)	$ (259,576)	$ (84,013)

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Three Months Ended September 30, 2020 and 2021
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at June 30, 2020 (as revised*)	139,489	$ 139	$ 2,053,502	$ (16,440)	$ (752,308)	$ 1,284,893	$ 217,620	$ 1,502,513
Net loss	—	—	—	—	(24,467)	(24,467)	—	(24,467)
Change in unrealized losses, net of tax	—	—	—	(3,448)	—	(3,448)	—	(3,448)
Foreign currency translation	—	—	—	275	—	275	—	275
Issuance of common stock in connection with employee stock plans	321	1	12,997	—	—	12,998	—	12,998
Stock-based compensation expense	—	—	45,845	—	—	45,845	—	45,845
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(16)	—	(990)	—	—	(990)	—	(990)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(17,803)	41	—	(17,762)	5,615	(12,147)
Balance at September 30, 2020 (as revised*)	139,794	$ 140	$ 2,093,551	$ (19,572)	$ (776,775)	$ 1,297,344	$ 223,235	$ 1,520,579
Balance at June 30, 2021	141,022	$ 141	$ 1,910,379	$ (25,796)	$ (1,302,050)	$ 582,674	$ —	$ 582,674
Net loss	—	—	—	—	(82,466)	(82,466)	—	(82,466)
Change in unrealized losses, net of tax	—	—	—	(1,618)	—	(1,618)	—	(1,618)
Foreign currency translation	—	—	—	(23)	—	(23)	—	(23)
Issuance of common stock in connection with employee stock plans	176	—	1,922	—	—	1,922	—	1,922
Stock-based compensation expense	—	—	30,537	—	—	30,537	—	30,537
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(14)	—	(490)	—	—	(490)	—	(490)
Balance at September 30, 2021	141,184	$ 141	$ 1,942,348	$ (27,437)	$ (1,384,516)	$ 530,536	$ —	$ 530,536

* We revised our 2019 and 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Nine Months Ended September 30, 2020 and 2021
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2019 (as revised*)	140,340	$ 140	$ 1,985,650	$ (25,290)	$ (596,495)	$ 1,364,005	$ 213,453	$ 1,577,458
Net loss	—	—	—	—	(89,731)	(89,731)	—	(89,731)
Change in unrealized gains, net of tax	—	—	—	5,803	—	5,803	—	5,803
Foreign currency translation	—	—	—	357	—	357	—	357
Issuance of common stock in connection with employee stock plans	1,141	1	29,449	—	—	29,450	—	29,450
Repurchases and retirements of common stock	(1,478)	(1)	—	—	(90,549)	(90,550)	—	(90,550)
Stock-based compensation expense	—	—	135,077	—	—	135,077	—	135,077
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(209)	—	(12,960)	—	—	(12,960)	—	(12,960)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(43,665)	(442)	—	(44,107)	9,782	(34,325)
Balance at September 30, 2020 (as revised*)	139,794	$ 140	$ 2,093,551	$ (19,572)	$ (776,775)	$ 1,297,344	$ 223,235	$ 1,520,579
Balance at December 31, 2020 (as revised*)	140,366	$ 140	$ 1,895,519	$ (21,071)	$ (1,131,306)	$ 743,282	$ —	$ 743,282
Net loss	—	—	—	—	(253,210)	(253,210)	—	(253,210)
Change in unrealized losses, net of tax	—	—	—	(6,321)	—	(6,321)	—	(6,321)
Foreign currency translation	—	—	—	(45)	—	(45)	—	(45)
Issuance of common stock in connection with employee stock plans	1,094	1	11,563	—	—	11,564	—	11,564
Issuance of warrants	—	—	89,752	—	—	89,752	—	89,752
Purchase of note hedges	—	—	(136,620)	—	—	(136,620)	—	(136,620)
Stock-based compensation expense	—	—	98,419	—	—	98,419	—	98,419
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(276)	—	(16,285)	—	—	(16,285)	—	(16,285)
Balance at September 30, 2021	141,184	$ 141	$ 1,942,348	$ (27,437)	$ (1,384,516)	$ 530,536	$ —	$ 530,536

* We revised our 2019 and 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Nine Months Ended September 30,	
	2021	**2020 (as revised*)**
Operating activities:		
Net loss	$ (253,210)	$ (124,056)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	11,665	9,713
Amortization of right-of-use operating lease assets	1,171	1,356
Amortization of patents	1,740	1,526
Amortization of premium on investments, net	13,515	7,812
Amortization of debt issuance costs	3,586	2,388
Stock-based compensation expense	98,419	135,077
Gain on investments	(933)	(10,722)
Loss on early retirement of debt	8,627	—
Non-cash losses related to patents	1,150	616
Provision for deferred income taxes	—	1,649
Changes in operating assets and liabilities:		
Contracts receivable	67,136	24,057
Inventories	(965)	(1,468)
Other current and long-term assets	10,358	(5,647)
Income taxes (payable) receivable	134	(23,674)
Accounts payable	(10,737)	(10,970)
Accrued compensation	(33,408)	(8,967)
Accrued liabilities and other current liabilities	(19,526)	13,195
Deferred contract revenue	(71,610)	(73,970)
Net cash used in operating activities	(172,888)	(62,085)
Investing activities:		
Purchases of short-term investments	(930,963)	(1,376,631)
Proceeds from sale of short-term investments	1,051,857	1,497,433
Purchases of property, plant and equipment	(9,453)	(29,971)
Acquisition of patents, net	(4,459)	(4,203)
Purchase of Bicycle Therapeutics plc common stock	(7,185)	—
Net cash provided by investing activities	99,797	86,628
Financing activities:		
Proceeds from equity, net	11,564	29,450
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(16,285)	(12,960)
Proceeds from issuance of 0 percent convertible senior notes	632,500	—
0 percent convertible senior notes issuance costs	(15,525)	—
Repurchase of $247.9 million principal amount of 1 percent convertible senior notes	(256,963)	—
Proceeds from issuance of warrants	89,752	—
Purchase of note hedges	(136,620)	—
Repurchases and retirements of common stock	—	(90,548)
Payments of transaction costs for Akcea merger	—	(1,071)
Net cash provided by (used in) financing activities	308,423	(75,129)
Effects of exchange rates on cash	(43)	358
Net increase (decrease) in cash and cash equivalents	235,289	(50,228)
Cash and cash equivalents at beginning of period	397,664	683,287
Cash and cash equivalents at end of period	$ 632,953	$ 633,059
Supplemental disclosures of cash flow information:		
Interest paid	$ 3,527	$ 3,700
Income taxes paid	$ 3	$ 23,532
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,811	$ 6,576
Amounts accrued for Akcea merger transaction costs	$ —	$ 8,103

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and nine months ended September 30, 2021 and 2020 on the same basis as the audited financial statements for the year ended December 31, 2020, with the exception of our retrospective adoption of Accounting Standards Update, or ASU, 2020-06, which simplifies the accounting for convertible debt instruments. See Note 2, *Significant Accounting Polices*, *Convertible Debt*, for details of our adoption of this guidance. 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, 2020 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 formed Akcea in December 2014. In July 2017, Akcea completed an initial public offering, or IPO, which reduced our ownership of Akcea's common stock below 100 percent. In October 2020, we completed a merger transaction with Akcea such that following the completion of the merger, Akcea became our wholly owned subsidiary. We will refer to this transaction as the Akcea Merger throughout the remainder of this document. We reflected changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the changes occurred.

2. Significant Accounting Policies

Revenue Recognition

Our Revenue Sources

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our condensed consolidated balance sheet.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We earn commercial revenue primarily in the form of royalty payments on net sales of SPINRAZA. We will also recognize as commercial revenue sales milestone payments and royalties we earn under our other partnerships.

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

In April 2021, we began commercializing TEGSEDI in North America through a distribution agreement with Swedish Orphan Biovitrum AB, or Sobi. In January 2021, we began commercializing TEGSEDI and WAYLIVRA in Europe through a distribution agreement with Sobi. Under our agreements, we are responsible for supplying finished goods inventory to Sobi and Sobi is responsible for selling each medicine to the end customer. As a result of these agreements, we earn a distribution fee on net sales from Sobi for each medicine.

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

Under our collaboration agreement with PTC Therapeutics International Limited, or PTC, PTC is responsible for commercializing TEGSEDI and WAYLIVRA in Latin America and Caribbean countries. In the third quarter of 2021, we earned a $4 million milestone payment from PTC when WAYLIVRA was approved in Brazil, which we included in TEGSEDI and WAYLIVRA revenue in our condensed consolidated statement of operations.

Research and development revenue under collaborative agreements

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

See Note 5, *Collaborative Arrangements and Licensing Agreements*, for collaborations with substantive changes that occurred in 2021. Additionally, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2020 for a summary of each of our material collaborative agreements.

Steps to Recognize Revenue

We use a five-step process to determine the amount of revenue we should recognize and when we should recognize it. The five-step process is as follows:

1. Identify the contract

Accounting rules require us to first determine if we have a contract with our partner, including confirming that we have met each of the following criteria:

- We and our partner approved the contract and we are both committed to perform our obligations;
- We have identified our rights, our partner's rights and the payment terms;
- We have concluded that the contract has commercial substance, meaning that the risk, timing, or amount of our future cash flows is expected to change as a result of the contract; and
- We believe collectability of the consideration is probable.

2. Identify the performance obligations

We next identify our performance obligations, which represent the distinct goods and services we are required to provide under the contract. We typically have only one performance obligation at the inception of a contract, which is to perform R&D services.

Often we enter into a collaboration agreement in which we provide our partner with an option to license a medicine in the future. We may also provide our partner with an option to request that we provide additional goods or services in the future, such as active pharmaceutical ingredient, or API. We evaluate whether these options are material rights at the inception of the agreement. If we determine an option is a material right, we will consider the option a separate performance obligation. Historically, we have concluded that the options we grant to license a medicine in the future or to provide additional goods and services as requested by our partner are not material rights because these items are contingent upon future events that may not occur and are not priced at a significant discount. When a partner exercises its option to license a medicine or requests additional goods or services, then we identify a new performance obligation for that item.

In some cases, we deliver a license at the start of an agreement. If we determine that our partner has full use of the license and we do not have any additional material performance obligations related to the license after delivery, then we consider the license to be a separate performance obligation.

3. Determine the transaction price

We then determine the transaction price by reviewing the amount of consideration we are eligible to earn under the collaboration agreement, including any variable consideration. Under our collaboration agreements, consideration typically includes fixed consideration in the form of an upfront payment and variable consideration in the form of potential milestone payments, license fees and royalties. At the start of an agreement, our transaction price usually consists of only the upfront payment. We do not typically include any payments we may receive in the future in our initial transaction price because the payments are not probable and are contingent on certain future events. We reassess the total transaction price at each reporting period to determine if we should include additional payments in the transaction price.

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and/or are usually based on scientific progress which is inherently uncertain. For example, in the third quarter of 2021, we earned a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 cardiovascular outcome study of pelacarsen. We did not consider the milestone payment probable until Novartis achieved the milestone event because it was contingent on Novartis' enrollment of patients and was not within our control. We recognized the milestone payment in full in the period the milestone event was achieved because we did not have any remaining performance obligations related to the milestone payment.

4. Allocate the transaction price

Next, we allocate the transaction price to each of our performance obligations. When we have to allocate the transaction price to more than one performance obligation, we make estimates of the relative stand-alone selling price of each performance obligation because we do not typically sell our goods or services on a stand-alone basis. We then allocate the transaction price to each performance obligation based on the relative stand-alone selling price. We do not reallocate the transaction price after the start of an agreement to reflect subsequent changes in stand-alone selling prices.

We may engage a third party, independent valuation specialist to assist us with determining a stand-alone selling price for collaborations in which we deliver a license at the start of an agreement. We estimate the stand-alone selling price of these licenses using valuation methodologies, such as the relief from royalty method. Under this method, we estimate the amount of income, net of taxes, for the license. We then discount the projected income to present value. The significant inputs we use to determine the projected income of a license could include:

- Estimated future product sales;
- Estimated royalties we may receive from future product sales;
- Estimated contractual milestone payments we may receive;
- Estimated expenses we may incur;
- Estimated income taxes; and
- A discount rate.

We typically estimate the selling price of R&D services by using our internal estimates of the cost to perform the specific services. The significant inputs we use to determine the selling price of our R&D services include:

- The estimated number of internal hours we will spend performing these services;
- The estimated cost of work we will perform;
- The estimated cost of work that we will contract with third parties to perform; and
- The estimated cost of API we will use.

For purposes of determining the stand-alone selling price of the R&D services we perform and the API we will deliver, accounting guidance requires us to include a markup for a reasonable profit margin.

5. Recognize revenue

We recognize revenue in one of two ways, over time or at a point in time. We recognize revenue over time when we are executing on our performance obligation over time and our partner receives benefit over time. For example, we recognize revenue over time when we provide R&D services. We recognize revenue at a point in time when our partner receives full use of an item at a specific point in time. For example, we recognize revenue at a point in time when we deliver a license or API to a partner.

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

The following are examples of when we typically recognize revenue based on the types of payments we receive.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We recognize royalty revenue, including royalties from SPINRAZA sales, in the period in which the counterparty sells the related product and recognizes the related revenue, which in certain cases may require us to estimate our royalty revenue.

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

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

Prior to our distribution agreements with Sobi, we recognized TEGSEDI and WAYLIVRA commercial revenue in the period when our customer obtained control of our products, which occurred at a point in time upon transfer of title to the customer. We classified payments to customers or other parties in the distribution channel for services that were distinct and priced at fair value as selling, general and administrative, or SG&A, expenses in our condensed consolidated statements of operations. We classified payments to customers or other parties in the distribution channel that did not meet those criteria as a reduction of revenue, as discussed further below. We excluded from revenues taxes collected from customers relating to TEGSEDI and WAYLIVRA commercial revenue and remitted these amounts to governmental authorities.

Reserves for TEGSEDI and WAYLIVRA commercial revenue

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

Prior to our distribution agreements with Sobi, we recorded TEGSEDI and WAYLIVRA commercial revenue at our net sales price, or transaction price. We included in our transaction price estimated reserves for discounts, returns, chargebacks, rebates and other allowances that we offered within contracts between us and our customers, wholesalers, distributors, health care providers and other indirect customers. We estimated our reserves using the amounts we have earned or we could claim on the associated sales. We classified our reserves as a reduction of accounts receivable when we were not required to make a payment or as a current liability when we were required to make a payment. In certain cases, our estimates included a range of possible outcomes that were probability weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, our reserves reflected our best estimates under the terms of our respective contracts. When calculating our reserves and related TEGSEDI and WAYLIVRA commercial revenue, we only recognized amounts to the extent that we considered it probable that we would not have to reverse a significant amount of the cumulative sales we previously recognized in a future period. Under our agreements with Sobi, we transferred all reserves to Sobi. See our revenue recognition policy in Note 1, *Organization and Significant Accounting Policies*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2020 for additional details regarding how we accounted for the reserves related to TEDSEDI and WAYLIVIRA product sales prior to our agreements with Sobi.

Research and development revenue under collaboration agreements:

Upfront payments

When we enter into a collaboration agreement and receive an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services. For example, under our collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases, we received a $75 million upfront payment in the fourth quarter of 2018. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $75 million upfront payment using an input method over the estimated period of time we are providing R&D services.

Milestone payments

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

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the fourth quarter of 2020, we achieved a $7.5 million milestone payment from Biogen when we advanced a target under our 2018 strategic collaboration. We added this payment to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue related to this milestone payment over our estimated period of performance.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation. For example, in the third quarter of 2021, we recognized a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 cardiovascular outcome study of pelacarsen. We recognized the milestone payment in full in the third quarter of 2021 because we did not have any remaining performance obligations related to the milestone payment.

License fees

We generally recognize as revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery. For example, in the fourth quarter of 2020, we earned a $30 million license fee from AstraZeneca when AstraZeneca licensed ION455, an investigational medicine in development to treat nonalcoholic steatohepatitis, or NASH.

Sublicense fees

We recognize sublicense fee revenue in the period in which a party, who has already licensed our technology, further licenses the technology to another party because we do not have any performance obligations related to the sublicense.

Amendments to Agreements

From time to time we amend our collaboration agreements. When this occurs, we are required to assess the following items to determine the accounting for the amendment:

1) If the additional goods and/or services are distinct from the other performance obligations in the original agreement; and
2) If the goods and/or services are sold at a stand-alone selling price.

If we conclude the goods and/or services in the amendment are distinct from the performance obligations in the original agreement and at a stand-alone selling price, we account for the amendment as a separate agreement. If we conclude the goods and/or services are not distinct and are sold at a stand-alone selling price, we then assess whether the remaining goods or services are distinct from those already provided. If the goods and/or services are distinct from what we have already provided, then we allocate the remaining transaction price from the original agreement and the additional transaction price from the amendment to the remaining goods and/or services. If the goods and/or services are not distinct from what we have already provided, we update the transaction price for our single performance obligation and recognize any change in our estimated revenue as a cumulative adjustment.

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of fesomersen (IONIS-FXI-L$_{Rx}$), which Bayer licensed. As part of the 2017 amendment, Bayer paid us $75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and fesomersen. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of fesomersen, to provide R&D services and to deliver API. We allocated the $75 million transaction price to these performance obligations. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2020 for further discussion of the Bayer collaboration.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same partner. We evaluate such agreements to determine whether we should account for them individually as distinct arrangements or whether the separate agreements should be combined and accounted for together. We evaluate the following to determine the accounting for the agreements:

- Whether the agreements were negotiated together with a single objective;
- Whether the amount of consideration in one contract depends on the price or performance of the other agreement; or
- Whether the goods and/or services promised under the agreements are a single performance obligation.

Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that accounting guidance requires us to account for them as a combined arrangement.

For example, in the second quarter of 2018, we entered into two separate agreements with Biogen at the same time: a new strategic neurology collaboration agreement and a stock purchase agreement, or SPA. We evaluated the Biogen agreements to determine whether we should treat the agreements separately or combine them. We considered that the agreements were negotiated concurrently and in contemplation of one another. Based on these facts and circumstances, we concluded that we should evaluate the provisions of the agreements on a combined basis.

Contracts Receivable

Our contracts receivable balance represents the amounts we have billed our partners or customers and that are due to us unconditionally for goods we have delivered or services we have performed. When we bill our partners or customers with payment terms based on the passage of time, we consider the contracts receivable to be unconditional. We typically receive payment within one quarter of billing our partner or customer.

As of September 30, 2021, approximately 58.3 percent of our contracts receivables were from three significant customers. As of December 31, 2020, approximately 99.5 percent of our contracts receivables were from two significant customers.

Unbilled SPINRAZA Royalties

Our unbilled SPINRAZA royalties represent our right to receive consideration from Biogen in advance of when we are eligible to bill Biogen for SPINRAZA royalties. We include these unbilled amounts in other current assets on our condensed consolidated balance sheet.

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our condensed consolidated balance sheet. During the three months ended September 30, 2021 and 2020, we recognized $21.1 million and $22.5 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. During the nine months ended September 30, 2021 and 2020, we recognized $71.9 million and $84.1 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Sales

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

Cash, Cash Equivalents and Investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term debt investments as “available-for-sale” and carry them at fair market value based upon prices on the last day of the fiscal period for identical or similar items. We record unrealized gains and losses on debt securities as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments in our condensed consolidated statement of operations. We use the specific identification method to determine the cost of securities sold.

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At September 30, 2021, we held equity investments in three publicly held companies, Antisense Therapeutics Limited, or ATL, Bicycle Therapeutics plc, or Bicycle, and ProQR Therapeutics N.V., or ProQR. We also held equity investments in seven privately held companies, Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, YourBio Health, Inc. (formerly Seventh Sense Biosystems) and Suzhou-Ribo Life Science Co, Ltd.

We are required to measure and record our equity investments at fair value and to recognize the changes in fair value in our condensed consolidated statement of operations. We account for our equity investments in privately held companies at their cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer. For example, during the second and fourth quarters of 2020, we revalued our investments in three privately held companies, Dynacure, Suzhou-Ribo and Aro Biotherapeutics because the companies sold additional equity securities that were similar to the equity we own. These observable price changes resulted in us recognizing a $6.3 million gain on our investment in Dynacure, a $3.0 million gain on our investment in Suzhou-Ribo and a $5.5 million gain on our investment in Aro Biotherapeutics in our condensed consolidated statement of operations during 2020 because the sales were at higher prices compared to our recorded value.

Inventory Valuation

We reflect our inventory on our condensed consolidated balance sheet at the lower of cost or net realizable value under the first-in, first-out method, or FIFO. We capitalize the costs of raw materials that we purchase for use in producing our medicines because until we use these raw materials, they have alternative future uses, which we refer to as clinical raw materials. We include in inventory raw material costs for medicines that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single medicine. For example, if one of our medicines failed, we could use the raw materials for that medicine to manufacture our other medicines. We expense these costs as R&D expenses when we begin to manufacture API for a particular medicine if the medicine has not been approved for marketing by a regulatory agency. Our raw materials- commercial inventory includes API for our commercial medicines. We capitalize material, labor and overhead costs as part of our raw materials- commercial inventory.

We obtained the first regulatory approval for TEGSEDI in July 2018 and for WAYLIVRA in May 2019. At September 30, 2021, our physical inventory for TEGSEDI and WAYLIVRA included API that we produced prior to when we obtained regulatory approval. As such, this API has no cost basis as we had previously expensed the costs as R&D expenses.

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. For the nine months ended September 30, 2021 and 2020, we recorded an immaterial amount of inventory write-offs.

Our inventory consisted of the following (in thousands):

	September 30, 2021	December 31, 2020
Raw materials:		
Raw materials- clinical	$ 11,993	$ 9,206
Raw materials- commercial	4,147	7,502
Total raw materials	16,140	16,708
Work in process	6,183	2,252
Finished goods	607	3,005
Total inventory	$ 22,930	$ 21,965

Leases

We determine if an arrangement contains a lease at inception. We currently only have operating leases. We recognize a right-of-use operating lease asset and associated short- and long-term operating lease liability on our condensed consolidated balance sheet for operating leases greater than one year. Our right-of-use assets represent our right to use an underlying asset for the lease term and our lease liabilities represent our obligation to make lease payments arising from the lease arrangement. We recognize our right-of-use operating lease assets and lease liabilities based on the present value of the future minimum lease payments we will pay over the lease term. We determine the lease term at the inception of each lease, and in certain cases our lease term could include renewal options if we concluded we were reasonably certain that we will exercise the renewal option. When we exercise a lease option that was not previously included in the initial lease term, we reassess our right-of-use asset and lease liabilities for the new lease term.

As our current leases do not provide an interest rate implicit in the lease, we used our incremental borrowing rate, based on the information available on the date we adopted Topic 842 (January 2019), as of the lease inception date or at the lease option extension date in determining the present value of future payments. We recognize rent expense for our minimum lease payments on a straight-line basis over the expected term of our lease. We recognize period expenses, such as common area maintenance expenses, in the period we incur the expense.

In September 2021, we entered into an operating lease agreement for office space located in Boston, Massachusetts. We determined that the lease commencement date is the date in which the space is ready for our occupancy, which we expect will be in the fourth quarter of 2021. We are leasing this space under a non-cancelable operating lease with an initial term ending 91 months following the lease commencement date and an option to extend the lease for an additional five-year term. Under the lease agreement, we will receive a seven-month free rent period, which will commence on the lease commencement date. Our lease payments over the initial term total $6.8 million. We will recognize a right-of-use lease asset and lease liability in the fourth quarter of 2021 upon the lease commencement date. Since we did not have the right to occupy the premises as of September 30, 2021, there was no accounting impact in the third quarter.

Research, Development and Patent Expenses

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

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

Income Taxes

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

We evaluate our deferred tax assets regularly to determine whether adjustments to the valuation allowance are appropriate due to changes in facts or circumstances, such as changes in expected future pre-tax earnings, tax law, interactions with taxing authorities and developments in case law. In making this evaluation, we rely on our recent history of pre-tax earnings. Our material assumptions are our forecasts of future pre-tax earnings and the nature and timing of future deductions and income represented by the deferred tax assets and liabilities, all of which involve the exercise of significant judgment.

We assessed our valuation allowance requirements and recorded a valuation allowance against all of Ionis' U.S. federal net deferred tax assets in the fourth quarter of 2020, due to uncertainties related to our ability to realize the tax benefits associated with these assets. We based our determination largely on Akcea rejoining the Ionis U.S. consolidated federal tax group in the fourth quarter of 2020. Due to Akcea's historical and projected financial statement losses, and the negative impact we expect this to have on Ionis' consolidated taxable income, there is uncertainty of generating sufficient consolidated pre-tax income in future periods to realize the Ionis deferred tax benefits. We also expect that Ionis' pre-tax income in future periods may be lower due to increased research and development expenses associated with our pipeline of wholly owned medicines. We continue to maintain a valuation allowance against all our consolidated U.S. federal and state net deferred tax assets.

Long-lived Assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets.

Use of Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the U.S. that require us to make estimates and assumptions that affect the amounts reported in our condensed consolidated financial statements and accompanying notes. Actual results could differ from our estimates.

Basic and Diluted Net Loss Per Share

Basic net loss per share

We calculated our basic net loss per share for the three and nine months ended September 30, 2021 by dividing our net loss by our weighted-average number of common shares outstanding during the period. For the first nine months of 2021, we did not have to consider Akcea results separately in our calculation because we owned 100 percent of Akcea for the entire period. Our basic net loss per share for the three and nine months ended September 30, 2021 was $0.58 and $1.80, respectively.

In the third quarter of 2020, prior to the Akcea Merger, we calculated our basic net loss per share for the three and nine months ended September 30, 2020 by calculating our net loss for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period to determine our total net loss attributable to our common stockholders. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's net loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net loss available to Ionis common stockholders for the calculation of net loss per share is different than our net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders in the condensed consolidated statements of operations.

We calculated our basic net loss per share for the three months ended September 30, 2020 as follows (in thousands, except per share amounts):

Three months ended September 30, 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation (as revised*)
Ionis' portion of Akcea's net loss	77,095	$ (0.49)	$ (37,822)
Akcea's net loss attributable to our ownership			$ (37,822)
Ionis' stand-alone net income			13,251
Net loss available to Ionis common stockholders			$ (24,571)
Weighted average shares outstanding			139,708
Basic net loss per share			$ (0.18)

We calculated our basic net loss per share for the nine months ended September 30, 2020 as follows (in thousands, except per share amounts):

Nine months ended September 30, 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation (as revised*)
Ionis' portion of Akcea's net loss	77,095	$ (1.40)	$ (108,176)
Akcea's net loss attributable to our ownership			$ (108,176)
Ionis' stand-alone net income			18,235
Net loss available to Ionis common stockholders			$ (89,941)
Weighted average shares outstanding			139,497
Basic net loss per share			$ (0.64)

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

Diluted net loss per share

For the three and nine months ended September 30, 2021 and 2020, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 0.125 percent convertible senior notes, or 0.125% Notes;
- Note hedges related to the 0.125% Notes;
- 1 percent convertible senior notes, or 1% Notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

For the three and nine months ended September 30, 2021, common stock from the following would also have had an anti-dilutive effect on net loss per share:

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

Additionally as of September 30, 2021, we had warrants related to our 0% and 0.125% Notes outstanding. We will include the shares issuable under these warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

Convertible Debt

Adoption of ASU 2020-06

In August 2020, the FASB issued ASU 2020-06, which simplifies the accounting for convertible debt instruments, amends the guidance on derivative scope exceptions for contracts in an entity's own equity, and modifies the guidance on diluted earnings per share calculations. We adopted ASU 2020-06 on January 1, 2021 under the full retrospective approach, which required us to revise our prior period financial statements. This guidance impacted our accounting for outstanding convertible debt. At January 1, 2021, we had two outstanding convertible notes, our 0.125% Notes, which mature in December 2024, and our 1% Notes, which mature in November 2021. In April 2021, we completed a $632.5 million offering of 0% Notes primarily to repurchase a majority of our 1% Notes. We accounted for our 0% Notes under ASU 2020-06 at issuance. Refer to Note 6, *Convertible Debt*, for further information.

The updated guidance eliminates the cash conversion accounting model we previously followed in Accounting Standard Codification, or ASC, 470-20, which required us to separate each of our convertible debt instruments at issuance into two units of accounting, a liability component, based on our nonconvertible debt borrowing rate at issuance, and an equity component. Under ASU 2020-06, we now account for each of our convertible debt instruments as a single unit of accounting, a liability, because we concluded that the conversion features do not require bifurcation as a derivative under ASC 815-15 and our convertible debt instruments were not issued at a substantial premium. Since we adopted ASU 2020-06 using the full retrospective approach, we were required to apply the guidance to all convertible debt instruments we had outstanding as of January 1, 2019. We recomputed the basis of each convertible debt instrument as if we accounted for each as a single unit of accounting at issuance. This update included recalculating the amortization of debt issuance costs using an updated effective interest rate. As a result of adopting ASU 2020-06, we recorded a cumulative adjustment to decrease our additional paid in capital and our accumulated deficit at January 1, 2019. We have updated these financial statements to reflect the cumulative adjustment for the periods presented. We have labeled our prior period financial statements "as revised" to indicate the change required under the new accounting guidance. Below is a summary of the change in our balance sheet at December 31, 2020 and statement of operations from the three and nine months ended September 30, 2020 under the ASC 470-20 legacy guidance compared to the new ASU 2020-06 guidance we adopted:

The following table summarizes the adjustments we made to the condensed consolidated balance sheet we originally reported at December 31, 2020 to adopt ASU 2020-06 (in thousands):

	December 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
1 percent convertible senior notes	$ 293,161	$ 15,648	$ 308,809
0.125 percent convertible senior notes	$ 455,719	$ 84,417	$ 540,136
Additional paid-in-capital	$ 2,113,646	$ (218,127)	$ 1,895,519
Accumulated deficit	$ (1,249,368)	$ 118,062	$ (1,131,306)

Under ASU 2020-06, our revised ending balances for our 1% Notes and 0.125% Notes as of December 31, 2020 represent the principal balance of each convertible debt instrument less debt issuance costs. Additionally, because we have deferred tax assets related to our convertible debt instruments, we also adjusted these amounts as part of our adoption of ASU 2020-06. However, because we have a full valuation allowance on our deferred tax assets, there was no impact to our condensed consolidated balance sheet related to our deferred tax assets.

The following tables summarize the adjustments we made to the condensed consolidated statement of operations we originally reported for the three and nine months ended September 30, 2020 to adopt ASU 2020-06 (in thousands):

	Three Months Ended September 30, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Interest expense	$ (11,321)	$ 8,893	$ (2,428)
Loss before income tax expense	$ (40,443)	$ 8,893	$ (31,550)
Income tax expense	$ (2,648)	$ (2,416)	$ (5,064)
Net loss	$ (43,091)	$ 6,477	$ (36,614)
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (30,944)	$ 6,477	$ (24,467)
Basic and diluted net loss per share	$ (0.22)	$ 0.04	$ (0.18)

	Nine Months Ended September 30, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Interest expense	$ (33,484)	$ 26,408	$ (7,076)
Loss before income tax benefit (expense)	$ (146,387)	$ 26,408	$ (119,979)
Income tax benefit (expense)	$ 1,047	$ (5,124)	$ (4,077)
Net loss	$ (145,340)	$ 21,284	$ (124,056)
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (111,015)	$ 21,284	$ (89,731)
Basic and diluted net loss per share	$ (0.80)	$ 0.16	$ (0.64)

Under ASU 2020-06, our revised interest expense is lower because we are no longer recording non-cash interest expense related to a debt discount. This decrease was partially offset by the increase in interest expense related to the amortization of debt issuance costs because we no longer allocate a portion of our debt issuance costs to stockholders' equity at issuance. Instead, the entire debt issuance costs were recorded as a contra-liability on our condensed consolidated balance sheet at issuance and we are amortizing them over the contractual term using an updated effective interest rate. Our updated effective interest rates for our 1% Notes and 0.125% Notes were 1.4 percent and 0.5 percent, respectively.

The following tables summarize the adjustments we made to our condensed consolidated statements of stockholders' equity we originally reported at December 31, 2020 and 2019 to adopt ASU 2020-06 (in thousands):

	December 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Additional paid-in-capital	$ 2,113,646	$ (218,127)	$ 1,895,519
Accumulated deficit	$ (1,249,368)	$ 118,062	$ (1,131,306)
Total stockholders' equity	$ 843,347	$ (100,065)	$ 743,282

	December 31, 2019		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Additional paid-in-capital	$ 2,203,778	$ (218,128)	$ 1,985,650
Accumulated deficit	$ (707,534)	$ 111,039	$ (596,495)
Total stockholders' equity	$ 1,684,547	$ (107,089)	$ 1,577,458

Call Spread

In conjunction with the issuance of our 0% Notes and 0.125% Notes in April 2021 and December 2019, respectively, we entered into call spread transactions, which were comprised of purchasing note hedges and selling warrants. We account for the note hedges and warrants as separate freestanding financial instruments and treat each instrument as a separate unit of accounting. We determined that the note hedges and warrants do not meet the definition of a liability using the guidance contained in ASC Topic 480, therefore we account for the note hedges and warrants using the Derivatives and Hedging – Contracts in Entity's Own Equity accounting guidance contained in ASC Topic 815. We determined that the note hedges and warrants meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders' equity. We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants as additional paid-in capital in our condensed consolidated balance sheet. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Segment Information

In 2021, we began operating as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment. Previously, we had operated as two operating segments, Ionis Core and Akcea Therapeutics. We completed the Akcea Merger in October 2020 and fully integrated Akcea's operations into ours as of January 1, 2021.

Stock-based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, PRSUs and stock purchase rights under our ESPP based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our condensed consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates. We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP.

On the grant date, we use our stock price and assumptions regarding a number of variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors.

We recognize compensation expense for stock options granted, RSUs, PRSUs and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

In December 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. As a result, all employees are now under an Ionis stock plan and subject to the same Black-Scholes assumptions.

For the nine months ended September 30, 2021 and 2020, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2021	**2020**
Risk-free interest rate	0.5%	1.5%
Dividend yield	0.0%	0.0%
Volatility	54.3%	58.8%
Expected life	4.9 years	4.7 years

Ionis Board of Director Stock Options:

	Nine Months Ended September 30,	
	2021	**2020**
Risk-free interest rate	1.2%	0.5%
Dividend yield	0.0%	0.0%
Volatility	55.9%	57.6%
Expected life	7.3 years	6.7 years

ESPP:

	Nine Months Ended September 30,	
	2021	**2020**
Risk-free interest rate	0.1%	0.8%
Dividend yield	0.0%	0.0%
Volatility	42.4%	47.9%
Expected life	6 months	6 months

RSU's:

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted to employees vest annually over a four-year period. The RSUs we granted to our board of directors prior to June 2020 vest annually over a four-year period. RSUs granted after June 2020 to our board of directors fully vest after one year. The weighted-average grant date fair value of RSUs granted to employees and our board of directors for the nine months ended September 30, 2021 was $59.15 and $39.42 per share, respectively.

PRSU's:

Beginning in 2020, we added PRSU awards to the compensation for our Chief Executive Officer, Dr. Brett Monia. Under the terms of the grants, one third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (i.e., the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on our relative total shareholder return, or TSR, as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. Under the terms of the grants no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero percentto 150 percent of the target number depending on our relative TSR.

We determined the fair value of Dr. Monia's PRSUs using a Monte Carlo model because the performance target is based on our relative TSR, which represents a market condition. We are recognizing the grant date fair value of these awards as stock-based compensation expense using the accelerated multiple-option approach over the vesting period. The weighted-average grant date fair value of PRSUs granted to Dr. Monia for the nine months ended September 30, 2021 was $77.17 per share.

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2021 and 2020 (in thousands).

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Cost of sales	$ 111	$ 315	$ 293	$ 902
Research, development and patent expense	23,332	25,359	71,979	76,931
Selling, general and administrative expense	7,094	20,171	26,147	57,244
Total non-cash stock-based compensation expense	$ 30,537	$ 45,845	$ 98,419	$ 135,077

As of September 30, 2021, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $65.3 million, $72.2 million and $2.5 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized non-cash stock-based compensation expense for future forfeitures. We expect to recognize the cost of non-cash stock-based compensation expense related to our non-vested stock options, RSUs and PRSUs over a weighted average amortization period of 1.2 years, 1.4 years and 1.2 years, respectively.

Amendments to Equity Plans

2020 Equity Incentive Plan

In the second quarter of 2021, our Compensation Committee approved an amendment to the 2020 Plan. The amendment decreased the total number of shares of common stock authorized for issuance under the 2020 Plan from approximately 2.6 million to 1.6 million. We assumed the 2020 Plan in connection with Ionis' reacquisition of all of the outstanding shares of Akcea Therapeutics, Inc. as part of the Akcea Merger.

2011 Equity Incentive Plan

In the second quarter of 2021, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan, or 2011 Plan. The amendment increased the total number of shares of common stock authorized for issuance under the 2011 Plan from 23.0 million to 29.7 million and added a fungible share counting ratio whereby the share reserve will be reduced by 1.7 shares for each share of common stock issued pursuant to a full value award (i.e., RSU or PRSU) and increased by 1.7 shares for each share of common stock returning from a full value award.

Impact of Recently Issued Accounting Standards

As disclosed in the "Convertible Debt" policy above within this footnote, we adopted the simplified accounting for convertible debt instrument guidance (ASU 2020-06) on January 1, 2021. Refer to the section above for the impact of adoption. We do not expect any other recently issued accounting standards to have a material impact to our financial results.

3. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of September 30, 2021:

One year or less	58%
After one year but within two years	26%
After two years but within three and a half years	16%
Total	100%

As illustrated above, at September 30, 2021, 84 percent of our available-for-sale securities had a maturity of less than two years.

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

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

At September 30, 2021, we had an ownership interest of less than 20 percent in seven private companies and three public companies with which we conduct business. The privately held companies are Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, YourBio Health, Inc. and Suzhou-Ribo Life Science Co, Ltd. The publicly traded companies are Antisense Therapeutics Ltd., Bicycle and ProQR.

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

September 30, 2021	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 447,173	$ 1,338	$ (50)	$ 448,461
Debt securities issued by U.S. government agencies	83,630	96	(7)	83,719
Debt securities issued by the U.S. Treasury (2)	89,267	10	(2)	89,275
Debt securities issued by states of the U.S. and political subdivisions of the states	141,161	103	(30)	141,234
Other municipal debt securities	5,028	—	(2)	5,026
Total securities with a maturity of one year or less	766,259	1,547	(91)	767,715
Corporate debt securities	366,907	1,181	(475)	367,613
Debt securities issued by U.S. government agencies	73,028	1	(120)	72,909
Debt securities issued by the U.S. Treasury	98,499	245	(88)	98,656
Debt securities issued by states of the U.S. and political subdivisions of the states	41,167	8	(65)	41,110
Other municipal debt	6,169	—	(26)	6,143
Total securities with a maturity of more than one year	585,770	1,435	(774)	586,431
Total available-for-sale securities	$ 1,352,029	$ 2,982	$ (865)	$ 1,354,146
Equity securities:				
Total equity securities included in other current assets (3)	$ 11,897	$ 1,935	$ (663)	$ 13,169
Total equity securities included in deposits and other assets (4)	15,615	16,707	—	32,322
Total equity securities	27,512	18,642	(663)	45,491
Total available-for-sale and equity securities	$ 1,379,541	$ 21,624	$ (1,528)	$ 1,399,637

December 31, 2020	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 514,182	$ 2,194	$ (41)	$ 516,335
Debt securities issued by U.S. government agencies	94,234	354	(2)	94,586
Debt securities issued by the U.S. Treasury (2)	307,576	233	(9)	307,800
Debt securities issued by states of the U.S. and political subdivisions of the states	104,271	196	(12)	104,455
Other municipal debt securities	5,191	—	(7)	5,184
Total securities with a maturity of one year or less	1,025,454	2,977	(71)	1,028,360
Corporate debt securities	325,079	4,941	(40)	329,980
Debt securities issued by U.S. government agencies	80,099	185	(9)	80,275
Debt securities issued by the U.S. Treasury	50,318	383	(4)	50,697
Debt securities issued by states of the U.S. and political subdivisions of the states	31,779	91	(16)	31,854
Other municipal debt securities	1,041	—	—	1,041
Total securities with a maturity of more than one year	488,316	5,600	(69)	493,847
Total available-for-sale securities	$ 1,513,770	$ 8,577	$ (140)	$ 1,522,207
Equity securities:				
Total equity securities included in other current assets (3)	$ 4,712	$ —	$ (2,681)	$ 2,031
Total equity securities included in deposits and other assets (4)	15,062	15,938	—	31,000
Total equity securities	19,774	15,938	(2,681)	33,031
Total available-for-sale and equity securities	$ 1,533,544	$ 24,515	$ (2,821)	$ 1,555,238

(1) We hold our available-for-sale securities at amortized cost.

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

(3) Our equity securities included in other current assets consisted of our investments in two publicly traded companies, ProQR and Bicycle, which we classify as Level 1 and Level 3 investments, respectively. We recognize publicly traded equity securities at fair value. In the nine months ended September 30, 2021, we recognized a $1.9 million unrealized gain and a $0.7 million unrealized loss on our condensed consolidated statement of operations related to our investments in Bicycle and ProQR, respectively. In the nine months ended September 30, 2020, our equity securities included in other current assets only consisted of ProQR.

(4) Our equity securities included in deposits and other assets consisted of our investments in privately held companies. We recognize our private company equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer.

The following is a summary of our investments we consider to be temporarily impaired at September 30, 2021 (in thousands, except for number of investments). All of these investments have less than 12 months of temporary impairment. We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	158	$ 334,828	$ (525)
Debt securities issued by U.S. government agencies	13	103,460	(127)
Debt securities issued by the U.S. Treasury	10	75,009	(90)
Debt securities issued by states of the U.S. and political subdivisions of the states	432	123,489	(95)
Other municipal debt securities	3	11,168	(28)
Total temporarily impaired securities	616	$ 647,954	$ (865)

4. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We classify most of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

The following tables present the major security types we held at September 30, 2021 and December 31, 2020 that we regularly measure and carry at fair value. As of September 30, 2021, our Bicycle investment was subject to trading restrictions that extend to the third quarter of 2022; as a result, we included a lack of marketability discount in valuing this investment, which is a Level 3 input. As of December 31, 2020, we did not have any investments that we valued using Level 3 inputs. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At September 30, 2021	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 545,339	$ 545,339	$ —	$ —
Corporate debt securities (2)	816,074	—	816,074	—
Debt securities issued by U.S. government agencies (2)	156,628	—	156,628	—
Debt securities issued by the U.S. Treasury (2)	187,931	187,931	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states	182,344	—	182,344	—
Other municipal debt securities (2)	11,169	—	11,169	—
Investment in Bicycle Therapeutics plc (3)	9,120	—	—	9,120
Investment in ProQR Therapeutics N.V. (3)	4,049	4,049	—	—
Total	$ 1,912,654	$ 737,319	$ 1,166,215	$ 9,120

	At December 31, 2020	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 221,125	$ 221,125	$ —
Corporate debt securities (4)	846,315	—	846,315
Debt securities issued by U.S. government agencies (2)	174,861	—	174,861
Debt securities issued by the U.S. Treasury (5)	358,497	358,497	—
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	136,309	—	136,309
Other municipal debt securities (2)	6,225	—	6,225
Investment in ProQR Therapeutics N.V. (3)	2,031	2,031	—
Total	$ 1,745,363	$ 581,653	$ 1,163,710

The following footnotes reference lines on our condensed consolidated balance sheet:

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

(2) Included in short-term investments.

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

(4) $10.0 million was included in cash and cash equivalents, with the difference included in short-term investments.

(5) $17.5 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

Convertible Notes

Our 1% Notes, 0.125% Notes and 0% Notes had a fair value of $61.9 million, $504.3 million and $581.4 million at September 30, 2021, respectively. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

5. Collaborative Arrangements and Licensing Agreements

Below, we have included our Biogen and Novartis collaborations, which are our only collaborations with substantive changes during 2021 from those included in Note 6 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2020.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. We and Biogen are currently developing eight investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with ALS, Alzheimer's disease and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through September 30, 2021, we have received more than $3.0 billion from our Biogen collaborations.

During the three and nine months ended September 30, 2021 and 2020, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
SPINRAZA royalties (commercial revenue)	$ 66.6	$ 74.2	$ 198.7	$ 211.9
R&D revenue	17.4	51.2	63.4	98.6
Total revenue from our relationship with Biogen	$ 84.0	$ 125.4	$ 262.1	$ 310.5
Percentage of total revenue	63%	78%	71%	71%

Our condensed consolidated balance sheet at September 30, 2021 and December 31, 2020 included deferred revenue of $412.5 million and $465.8 million, respectively, related to our relationship with Biogen.

During the first nine months of 2021, we did not have any changes to our performance obligations, transaction price or the timing in which we expect to recognize revenue under our Biogen collaborations.

In April 2021, we earned a $10 million milestone payment from Biogen when Biogen advanced ION541, an investigational medicine targeting ATXN2 to treat patients with ALS. We recognized the milestone payment in full in the second quarter of 2021 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of $8 million if Biogen advances one of the medicines under our 2013 strategic neurology collaboration.

Research, Development and Commercialization Partner

Novartis

In January 2017, we initiated a collaboration with Novartis to develop and commercialize pelacarsen. In February 2019, Novartis licensed pelacarsen. Novartis is responsible for conducting and funding future development and regulatory activities for pelacarsen, including a global Phase 3 cardiovascular outcomes study that Novartis initiated in the fourth quarter 2019. In connection with Novartis' license of pelacarsen, we and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of pelacarsen in selected markets. Included in this framework is an option by which Novartis could solely commercialize pelacarsen in exchange for Novartis paying us increased sales milestone payments based on sales of pelacarsen. From inception through September 30, 2021, we have received $425 million from our Novartis collaboration.

In August 2021, we earned a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 cardiovascular outcome study of pelacarsen. We recognized the milestone payment in full in the third quarter of 2021 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of up to $75 million if Novartis advances regulatory activities for pelacarsen.

Technology Enhancement Collaboration

Bicycle License Agreement

In December 2020, we entered into a collaboration agreement with Bicycle and obtained an option to license its peptide technology to potentially increase the delivery capabilities of our LIgand Conjugated Antisense, or LICA, medicines. In July 2021, we paid $42 million when we exercised our option to license Bicycle's technology, which included an equity investment in Bicycle. As part of our stock purchase, we entered into a lockup agreement with Bicycle that restricts our ability to trade our Bicycle shares for one year. In the third quarter of 2021, we recorded a $7.2 million equity investment for the shares we received in Bicycle. We recognized the remaining $34.8 million as R&D expense in the third quarter of 2021. From inception through September 30, 2021, we have paid $45 million under our collaboration agreement with Bicycle.

6. Convertible Debt

0 Percent Convertible Senior Notes and Call Spread

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

At September 30, 2021, we had the following 0% Notes outstanding (amounts in millions except interest rate and price per share data):

	0% Notes
Outstanding principal balance	$ 632.5
Unamortized debt issuance costs	$ 14.2
Maturity date	April 2026
Interest rate	0 percent
Effective interest rate	0.5 percent
Conversion price per share	$ 57.84
Effective conversion price per share with call spread	$ 76.39
Total shares of common stock subject to conversion	10.9

In conjunction with the April 2021 offering, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0% Notes by increasing the effective conversion price on our 0% Notes. We increased our effective conversion price to $76.39 with the same number of underlying shares as our 0% Notes. The call spread cost us $46.9 million, of which $136.7 million was for the note hedge purchase, offset by $89.8 million we received for selling the warrants. Similar to our 0% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0% Notes. The note hedges will expire upon maturity of the 0% Notes, or April 2026. The note hedges and warrants are separate transactions and are not part of the terms of our 0% Notes. The holders of the 0% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our condensed consolidated balance sheet. See our Call Spread accounting policy in Note 2, *Significant Accounting Policies*, in the Notes to the Condensed Consolidated Financial Statements. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

0.125 Percent Convertible Senior Notes and Call Spread

At September 30, 2021, we had the following 0.125% Notes outstanding with interest payable semi-annually (amounts in millions except interest rate and price per share data):

	0.125% Notes
Outstanding principal balance	$ 548.8
Unamortized debt issuance costs	$ 7.1
Maturity date	December 2024
Interest rate	0.125 percent
Effective interest rate	0.5 percent
Conversion price per share	$ 83.28
Effective conversion price per share with call spread	$ 123.38
Total shares of common stock subject to conversion	6.6

In conjunction with the issuance of our 0.125% Notes in December 2019, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the effective conversion price on our 0.125% Notes. We increased our effective conversion price to $123.38 with the same number of underlying shares as our 0.125% Notes. The call spread cost us $52.6 million, of which $108.7 million was for the note hedge purchase, offset by $56.1 million we received for selling the warrants. Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of the 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our condensed consolidated balance sheet. See our Call Spread accounting policy in Note 2, *Significant Accounting Policies*, in the Notes to the Condensed Consolidated Financial Statements. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

1 Percent Convertible Senior Notes

At September 30, 2021, we had the following 1% Notes outstanding with interest payable semi-annually (amounts in millions except interest rate and price per share data):

	1% Notes
Outstanding principal balance	$ 62.0
Unamortized debt issuance costs	$ 0.03
Maturity date	November 2021
Interest rate	1 percent
Effective interest rate	1.4 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	0.9

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

Other Terms of Convertible Senior Notes

The 0%, 0.125% and 1% 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.

7. Severance and Retention Costs

Akcea Merger

As a result of the Akcea Merger in October 2020, we began recognizing severance and retention expenses in the fourth quarter of 2020. The following table summarizes our total estimated severance and retention expenses related to the Akcea Merger (in millions):

	Severance and Retention Expenses
Total estimated expenses	$ 27.2
Expenses incurred from inception to September 30, 2021	27.0
Remaining estimated expenses to be recognized through October 2021	$ 0.2

The following table summarizes our severance and retention expenses related to the Akcea Merger that we recognized during the three and nine months ended September 30, 2021 (in millions):

	Three Months Ended September 30, 2021	Nine Months Ended September 30, 2021
Research, development and patent expenses	$ 1.3	$ 5.1
Selling, general and administrative expenses	0.6	6.6
Total	$ 1.9	$ 11.7

The following table summarizes the severance and retention reserve amounts related to the Akcea Merger that we included in accrued compensation for the period indicated (in millions):

	Nine Months Ended September 30, 2021
Beginning balance as of January 1, 2021	$ 14.7
Amounts expensed during the period	13.5
Reserve adjustments during the period	(1.8)
Net amount expensed during the period	11.7
Amounts paid during the period	(20.6)
Ending balance as of September 30, 2021	$ 5.8

The reserve adjustments during the period primarily related to forfeitures of severance and retention payments as a result of employee terminations before they earned the amounts.

Restructured European Operations

In December 2020, we entered into a distribution agreement with Sobi for TEGSEDI and WAYLIVRA in Europe. As a result, we restructured our European Operations, or Restructured European Operations. In the fourth quarter of 2020, we began recognizing severance and retention expenses related to our Restructured European Operations. The following table summarizes our total severance and retention expenses related to our Restructured European Operations (in millions):

	Severance and Retention Expenses
Total estimated expenses	$ 14.2
Expenses incurred from inception to September 30, 2021	14.0
Remaining estimated expenses to be recognized through October 2021	$ 0.2

The following table summarizes the severance and retention expenses related to our Restructured European Operations that we recognized during the three and nine months ended September 30, 2021 (in millions):

	Three Months Ended September 30, 2021	Nine Months Ended September 30, 2021
Research, development and patent expenses	$ 0.5	$ 0.6
Selling, general and administrative expenses	0.1	1.1
Total	$ 0.6	$ 1.7

The following table summarizes the severance and retention reserve amounts related to our Restructured European Operations that we included in accrued compensation for the period indicated (in millions):

	Nine Months Ended September 30, 2021
Beginning balance as of January 1, 2021	$ 12.4
Amounts expensed during the period	2.5
Reserve adjustments during the period	(0.8)
Net amount expensed during the period	1.7
Amounts paid during the period	(13.4)
Ending balance as of September 30, 2021	$ 0.7

The reserve adjustments during the period primarily related to tax expense adjustments.

Restructured North American TEGSEDI Operations

In April 2021, we entered into a distribution agreement with Sobi for TEGSEDI in North America. Under the terms of the distribution agreement, we will retain the marketing authorizations for TEGSEDI in the U.S. and Canada. We will continue to supply commercial product to Sobi and manage regulatory and manufacturing processes, as well as relationships with key opinion leaders. We will also continue to lead the TEGSEDI global commercial strategy. Sobi will otherwise have responsibility for commercializing TEGSEDI in the U.S. and Canada.

In connection with restructuring our North American TEGSEDI operations, or Restructured North American TEGSEDI Operations, we enacted a plan to reorganize our Akcea workforce in North America to better align with the needs of our business and to focus on our wholly owned pipeline.

The following table summarizes the severance expenses related to our Restructured North American TEGSEDI Operations that we recognized during the second quarter of 2021 (in millions):

	Three Months Ended June 30, 2021
Research, development and patent expenses	$ 2.3
Selling, general and administrative expenses	7.1
Total	$ 9.4

We recognized all severance expenses related to our Restructured North American TEGSEDI Operations during the three months ended June 30, 2021.

The following table summarizes the severance reserve amounts related to our Restructured North American TEGSEDI Operations that we included in accrued compensation for the period indicated (in millions):

	Nine Months Ended September 30, 2021
Beginning balance as of January 1, 2021	$ —
Amounts expensed during the period	9.4
Amounts paid during the period	(9.2)
Ending balance as of September 30, 2021	$ 0.2

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In this Report on Form 10-Q, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us," means Ionis Pharmaceuticals, Inc. and its wholly owned subsidiary, Akcea Therapeutics, Inc.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, the Report includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report and described in additional detail in our annual report on Form 10-K for the year ended December 31, 2020, which is on file with the U.S. Securities and Exchange Commission and is available from us, and those identified within Part II Item 1A. Risk Factors of this Report. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

Overview

We are a leader in RNA-targeted therapy and believe our medicines are pioneering new markets, changing standards of care and transforming the lives of people with devastating diseases. Our clinical pipeline of potential first-in-class and/or best-in-class medicines address a broad range of diseases. We are primarily focused on two core franchises: neurology and cardiometabolic. Our commercial products SPINRAZA, TEGSEDI and WAYLIVRA, are approved in major markets around the world. Within our late-stage pipeline, we have seven Phase 3 programs ongoing with five medicines: tofersen for SOD1-ALS, eplontersen (IONIS-TTR-L_{Rx}) for transthyretin, or TTR, amyloidosis, olezarsen (IONIS-APOCIII-L_{Rx}) for familial chylomicronemia syndrome, or FCS, and severe hypertriglyceridemia, or sHTG, pelacarsen for lipoprotein(a), or Lp(a), driven cardiovascular disease and ION363 for amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or FUS.

Our multiple sources of revenue and strong balance sheet provide us with substantial financial strength. Our financial strength enables us to execute on our capital allocation strategy, which is focused on internal investment in three key areas: our wholly owned pipeline, building our commercial capabilities and broadening the reach of our technology. We believe investing in these areas moves us closer to our goal of 12 or more marketed products in 2026 and will drive the greatest value for patients and shareholders.

Commercial Medicines

SPINRAZA is the global market leader for the treatment of patients of all ages with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Biogen, our partner responsible for commercializing SPINRAZA worldwide, reported that as of September 30, 2021, more than 11,000 patients were on SPINRAZA therapy in markets around the world. Through September 30, 2021, we have earned more than $1.5 billion in revenues from our SPINRAZA collaboration, including more than $1.1 billion in royalties on sales of SPINRAZA.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis, or hATTR, a debilitating, progressive, and fatal disease. We launched TEGSEDI in the U.S. and the European Union, or EU, in late 2018. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Sobi. Additionally, in the second quarter of 2021, Sobi also began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC, through its exclusive license agreement with us, is commercializing TEGSEDI in Brazil and is working towards access in additional Latin American countries.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine that received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. Through our exclusive license agreement with PTC, we are working to expand access to WAYLIVRA across Latin America, beginning in Brazil. In the third quarter of 2021, the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária), or ANVISA, approved WAYLIVRA in Brazil. As a result of the approval, we earned a $4 million milestone payment from PTC.

Under our distribution agreements with Sobi, we retained the marketing authorizations for TEGSEDI and WAYLIVRA. We will continue to supply commercial product to Sobi and manage regulatory and manufacturing processes, as well as relationships with key opinion leaders. We will also continue to lead the TEGSEDI and WAYLIVRA global commercial strategy. In connection with the agreements, we restructured our European operations in the first quarter of 2021 and we restructured our North American TEGSEDI operations in the second quarter of 2021.

Medicines in Phase 3 Studies

We currently have seven Phase 3 programs, which include:

- Tofersen: In October 2021, Biogen reported that tofersen did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring tofersen were seen across multiple secondary and exploratory measures of disease activity and clinical function
  - Given the high unmet medical need, Biogen will expand its ongoing early access program, or EAP, to the broader SOD1-ALS population
  - Biogen is actively engaging with regulators, the medical community, patient advocacy groups and other key stakeholders around the world to determine potential next steps
  - The Phase 3 ATLAS study in patients with presymptomatic SOD1-ALS is ongoing
- Eplontersen: We achieved full enrollment in the NEURO-TTRansform Phase 3 study with data expected mid-2022 and enrollment is ongoing in the CARDIO-TTRansform Phase 3 study
- Pelacarsen: In August 2021, Novartis achieved 50 percent enrollment in Novartis' Lp(a) HORIZON Phase 3 cardiovascular outcome study
- ION363: In April 2021, we initiated a Phase 3 study in patients with FUS-ALS, the most common cause of juvenile-onset ALS
- Olezarsen: Enrollment is ongoing in the BALANCE Phase 3 study in patients with FCS and in October 2021, we initiated the Phase 3 CORE study in patients with sHTG

COVID-19

As a company focused on improving the health of people around the world, our priority during the COVID-19 pandemic is the safety of our employees, their families, the healthcare workers who work with us and the patients who rely on our medicines. We are also focused on maintaining the quality of our studies and minimizing the impact to timelines. While the COVID-19 pandemic has impacted some areas of our business, we believe our mitigation efforts and financial strength will enable us to continue to manage through the pandemic and execute on our strategic initiatives. Because the situation is extremely fluid, we are continuing to evaluate the impact COVID-19 could have on our business, including the impact on our commercial products and the medicines in our pipeline.

Financial Highlights

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020 (as revised*)	2021	2020 (as revised*)
Total revenue	$ 133.1	$ 160.1	$ 370.5	$ 439.0
Total operating expenses	$ 218.9	$ 196.6	$ 621.2	$ 588.4
Loss from operations	$ (85.8)	$ (36.5)	$ (250.8)	$ (149.4)
Net loss	$ (82.5)	$ (36.6)	$ (253.2)	$ (124.1)

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

Our commercial revenue for the first nine months of 2021 included SPINRAZA royalties, TEGSEDI and WAYLIVRA revenue and licensing and royalties. Our revenue from SPINRAZA royalties decreased during the first nine months of 2021 compared to the same period in 2020. As a result of our distribution agreements with Sobi for TEGSEDI and WAYLIVRA, our commercial revenue from product sales shifted to revenue from distribution fees based on net sales generated by Sobi. We completed the transition of our TEGSEDI and WAYLIVRA commercial operations in Europe and our TEGSEDI commercial operations in North America to Sobi in the first and second quarters of 2021, respectively.

We earn our R&D revenue from multiple sources that can fluctuate depending on the timing of events. Our R&D revenue decreased in the first nine months of 2021 compared to the same period in 2020 primarily because we earned more milestone payments in the first nine months of 2020 than in the same period in 2021. In the third quarter of 2021, we earned a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 study of pelacarsen. We expect our R&D revenue to increase in the fourth quarter of 2021 compared to the first three quarters of 2021 as several of our partnered programs advance.

Our operating expenses increased in the first nine months of 2021 over the same period last year, principally due to our investments in advancing our late-stage wholly owned pipeline, including advancing the Phase 3 program for eplontersen and start-up costs associated with the initiation of the Phase 3 study for a second indication for olezarsen. Additionally, we recognized $35 million in R&D expense in the third quarter of 2021 for licensing Bicycle's technology. These increases were partially offset by a decrease in our SG&A expenses, including non-cash compensation expense, primarily due to cost savings we realized from integrating Akcea and restructuring our commercial operations.

We expect our operating expenses to continue to increase during the fourth quarter of 2021 compared to the first three quarters of 2021 as we continue to advance our strategic priorities, including our wholly owned pipeline. For example, in the fourth quarter of 2021, we expect to incur additional R&D expenses related to the Phase 3 CORE study for olezarsen in patients with sHTG.

We ended the third quarter of 2021, with $2.0 billion in cash and short-term investments. In April 2021, we issued $632.5 million of 0% senior convertible notes due in April 2026 and repurchased $247.9 million of our 1% senior convertible notes. In conjunction with these transactions, we also executed a call spread to increase the effective conversion price of the 0% senior convertible notes to $76.39. We intend to pay the remaining principal balance of our 1% senior convertible notes with $62 million of cash at maturity in November 2021. We believe our strong financial position should enable us to continue to execute on our corporate goals throughout this year and beyond, including developing and commercializing medicines within our wholly owned pipeline.

Recent Business Updates

Third Quarter 2021 Marketed Products Highlights

- SPINRAZA®: the global market leader for the treatment of spinal muscular atrophy (SMA) patients of all ages
  - $444 million in worldwide sales in the third quarter
  - More than 11,000 patients worldwide on therapy at the end of the third quarter across commercial, expanded access and clinical trial settings
  - Biogen plans to initiate the Phase 3b ASCEND study evaluating the potential benefit of an investigational higher dose of nusinersen in children, teens and adults with later-onset SMA previously treated with Evrysdi® (risdiplam)

- TEGSEDI® and WAYLIVRA®: important medicines approved for the treatment of patients with severe rare diseases
  - TEGSEDI achieved innovative drug pricing in Brazil reflecting the significant unmet medical need and prevalence of TTR polyneuropathy in Brazil
  - WAYLIVRA was approved in Brazil as the first and only treatment for patients with familial chylomicronemia syndrome

Third Quarter 2021 and Recent Events

- Advancing Ionis' leading cardiovascular and metabolic disease pipeline
  - Initiated the Phase 3 CORE study of olezarsen (IONIS-APOCIII-L_{Rx}) in patients with severe hypertriglyceridemia (sHTG)
  - Reached 50 percent enrollment in the Phase 3 Lp(a) HORIZON outcome study of pelacarsen for patients with established cardiovascular disease and elevated Lp(a), resulting in a $25 million payment from Novartis
  - Achieved full enrollment in the Bayer Phase 2b RE-THINc ESRD study of fesomersen (IONIS-FXI-L_{Rx}), with data expected in the first half of 2022
  - Achieved proof-of-mechanism, a strong indication of proof-of-concept and good safety and tolerability in a Phase 2 study and a preliminary assessment from an open-label extension study of cimdelirsen (IONIS-GHR-L_{Rx}) in acromegaly patients uncontrolled on standard of care therapy, supporting continued development. Data from the ongoing open-label extension study and monotherapy study are expected in 2022. The results from the Phase 2 study of cimdelirsen are posted to Ionis' website

- Addressing substantial unmet medical need with Ionis' broad neurological disease pipeline
  - The Biogen Phase 3 VALOR study of tofersen in patients with SOD1-ALS did not meet the primary endpoint of change from baseline to week 28 in the ALS Functional Rating Scale-Revised (ALSFRS-R); however, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed
  - Achieved full enrollment in the Phase 3 NEURO-TTRansform study of eplontersen in patients with TTR polyneuropathy, with data expected in mid-2022
  - Reported data from the Biogen Phase 1/2 study of IONIS-$MAPT_{Rx}$ in patients with Alzheimer's disease, demonstrating durable, time and dose-dependent reductions in CSF tau protein; IONIS-$MAPT_{Rx}$ was generally well tolerated

- Investing in expanding the reach of Ionis' technology
  - Entered a license agreement with Bicycle Therapeutics for exclusive rights to Bicycle's peptide technology targeting transferrin receptor 1 to expand the capabilities of Ionis' LICA technology
  - Entered a license agreement with Flamingo Therapeutics for the development and commercialization of programs from Ionis' oncology pipeline

Business Segment

In 2021, we began operating as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment. Previously, we had operated as two operating segments, Ionis Core and Akcea Therapeutics. We completed the Akcea Merger in October 2020 and fully integrated Akcea's operations into ours as of January 1, 2021.

Critical Accounting Estimates

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

- Assessing the propriety of revenue recognition and associated deferred revenue; and
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities

In the first quarter of 2021, we determined the estimation of our income taxes was no longer a critical accounting estimate because we recorded a valuation allowance against the entirety of our net deferred tax assets in the fourth quarter of 2020. We recorded the expected impact from the valuation allowance on our tax provision for 2021.

There have been no other material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our Annual Report on Form 10-K for the year ended December 31, 2020.

Results of Operations

Revenue

Total revenues for the three and nine months ended September 30, 2021 were $133.1 million and $370.5 million, respectively, compared to $160.1 million and $439.0 million for the same periods in 2020 and were comprised of the following (amounts in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 66.6	$ 74.2	$ 198.7	$ 211.9
TEGSEDI and WAYLIVRA revenue, net	15.5	19.0	46.9	50.6
Licensing and other royalty revenue	2.7	2.1	9.5	6.5
Total commercial revenue	84.8	95.3	255.1	269.0
R&D revenue:				
Amortization from upfront payments	16.7	18.9	56.8	68.0
Milestone payments	28.4	43.5	48.5	73.4
License fees	—	—	—	14.7
Other services	3.2	2.4	10.1	13.9
Total R&D revenue	48.3	64.8	115.4	170.0
Total revenue	$ 133.1	$ 160.1	$ 370.5	$ 439.0

Our commercial revenue for the first nine months of 2021 included SPINRAZA royalties, TEGSEDI and WAYLIVRA revenue and licensing and royalties. Our revenue from SPINRAZA royalties decreased during the first nine months of 2021 compared to the same period in 2020. As a result of our distribution agreements with Sobi for TEGSEDI and WAYLIVRA, our commercial revenue from product sales shifted to revenue from distribution fees based on net sales generated by Sobi. We completed the transition of our TEGSEDI and WAYLIVRA commercial operations in Europe and our TEGSEDI commercial operations in North America to Sobi in the first and second quarters of 2021, respectively. Additionally, in the third quarter of 2021, we earned a $4 million milestone payment from PTC when WAYLIVRA was approved in Brazil.

We earn our R&D revenue from multiple sources that can fluctuate depending on the timing of events. Our R&D revenue decreased in the first nine months of 2021 compared to the same period in 2020 primarily because we earned more milestone payments in the first nine months of 2020 than in the same period in 2021. In the third quarter of 2021, we earned a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 study of pelacarsen. We expect our R&D revenue to increase in the fourth quarter of 2021 compared to the first three quarters of 2021 as several of our partnered programs advance.

Operating Expenses

Our operating expenses were as follows (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 185.5	$ 150.8	$ 498.3	$ 453.3
Restructuring expenses	2.8	—	24.4	—
Total operating expenses, excluding non-cash compensation expense related to equity awards	188.3	150.8	522.7	453.3
Non-cash compensation expense related to equity awards	30.6	45.8	98.5	135.1
Total operating expenses	$ 218.9	$ 196.6	$ 621.2	$ 588.4

Operating expenses, excluding non-cash compensation expense related to equity awards, for the first nine months of 2021 increased compared to the same period in 2020. The increase was principally due to our investments in advancing our late-stage wholly owned pipeline, including advancing the Phase 3 program for eplontersen and start-up costs associated with the initiation of the Phase 3 study for a second indication for olezarsen. Additionally, in the third quarter of 2021, we recognized $35 million in R&D expense for licensing Bicycle's technology as discussed above. We also incurred approximately $24 million in costs related to the Akcea Merger and restructuring our commercial operations, primarily comprised of severance and retention costs. These increases were partially offset by a decrease in our SG&A expenses, primarily due to cost savings we realized from integrating Akcea and restructuring our commercial operations.

We expect our operating expenses to increase during the fourth quarter of 2021 compared to the first three quarters of 2021 as we continue to advance our strategic priorities, including our wholly owned pipeline. For example, in the fourth quarter of 2021, we expect to incur additional R&D expenses related to the Phase 3 CORE study for olezarsen in patients with sHTG.

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

Cost of Sales

Our cost of sales consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA and certain associated period costs. Prior to the regulatory approval of TEGSEDI and WAYLIVRA, we expensed as R&D expense a significant portion of the cost of producing TEGSEDI and WAYLIVRA that we are using in the commercial launches. We expect cost of sales to increase as we deplete these inventories.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 3.0	$ 2.8	$ 8.3	$ 7.7
Non-cash compensation expense related to equity awards	0.1	0.3	0.3	0.9
Total cost of sales	$ 3.1	$ 3.1	$ 8.6	$ 8.6

Our cost of sales, excluding non-cash compensation expense related to equity awards, for the first nine months of 2021 were consistent with the same period in 2020.

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for antisense drug discovery, antisense drug development, manufacturing and development chemistry and R&D support expenses.

The following table sets forth information on research, development and patent expenses (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 159.6	$ 99.7	$ 383.9	$ 287.4
Restructuring expenses	1.8	—	8.0	—
Total research, development and patent expenses, excluding non-cash compensation expense related to equity awards	161.4	99.7	391.9	287.4
Non-cash compensation expense related to equity awards	23.4	25.4	72.0	76.9
Total research, development and patent expenses	$ 184.8	$ 125.1	$ 463.9	$ 364.3

Antisense Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our partners. Antisense drug discovery is also the function that is responsible for advancing our antisense core technology. This function is also responsible for making investments in complementary technologies to expand the reach of our technology.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our pipeline.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 55.9	$ 20.0	$ 105.7	$ 57.1
Non-cash compensation expense related to equity awards	5.9	6.2	17.5	18.6
Total antisense drug discovery expenses	$ 61.8	$ 26.2	$ 123.2	$ 75.7

Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased for the first nine months of 2021 compared to the same period in 2020. In the third quarter of 2021, we recognized $35 million in R&D expense for licensing Bicycle's technology as discussed above. This increase was also due to expenses we incurred related to advancing our research programs and investments we made to enhance our antisense technology.

Antisense Drug Development

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
TEGSEDI	$ 2.2	$ 3.5	$ 5.3	$ 11.4
WAYLIVRA	1.3	1.3	2.1	4.6
Eplontersen	23.0	9.0	52.2	21.4
Olezarsen	4.9	0.9	10.4	4.0
ION363	2.0	0.2	5.7	0.2
Other antisense development projects	26.9	23.2	75.3	65.6
Development overhead expenses	20.9	18.2	61.3	54.0
Restructuring expenses	1.5	—	7.2	—
Total antisense drug development, excluding non-cash compensation expense related to equity awards	82.7	56.3	219.5	161.2
Non-cash compensation expense related to equity awards	10.2	12.4	32.4	38.2
Total antisense drug development expenses	$ 92.9	$ 68.7	$ 251.9	$ 199.4

Our development expenses, excluding non-cash compensation expense related to equity awards, increased for the first nine months of 2021 compared to the same period in 2020 primarily due to our broad Phase 3 program for eplontersen, which we initiated in late 2019. Additionally, we advanced other medicines in our wholly owned pipeline, including olezarsen, for which we initiated a Phase 3 program in patients with FCS in the fourth quarter of 2020 and incurred start-up costs associated with the initiation of a Phase 3 program in patients with sHTG in the fourth quarter of 2021 and ION363, for which we initiated a Phase 3 program in patients with FUS-ALS in the second quarter of 2021. In addition, our development overhead expenses increased year-over-year to support the growth of our Phase 3 programs and other mid-stage pipeline activities.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials, we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our medicines are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we may adjust the development strategy for each medicine. Although we may characterize a medicine as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous medicines based on each medicine’s particular needs at that time. This means we are constantly shifting resources among medicines. Therefore, what we spend on each medicine during a particular period is usually a function of what is required to keep the medicines progressing in clinical development, not what medicines we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one medicine to another and cannot be used to accurately predict future costs for each medicine. And, because we always have numerous medicines in preclinical and early stage clinical research, the fluctuations in expenses from medicine to medicine, in large part, offset one another. If we partner a medicine, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Manufacturing and Development Chemistry

Expenditures in our manufacturing and development chemistry function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. Our manufacturing and development chemistry function is responsible for providing drug supplies to antisense drug development and our collaboration partners. Our manufacturing procedures include testing to satisfy good laboratory and good manufacturing practice requirements.

Our manufacturing and development chemistry expenses were as follows (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 10.9	$ 13.0	$ 31.3	$ 38.8
Restructuring expenses	0.2	—	0.8	—
Total manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	11.1	13.0	32.1	38.8
Non-cash compensation expense related to equity awards	2.9	2.5	9.1	8.2
Total manufacturing and development chemistry expenses	$ 14.0	$ 15.5	$ 41.2	$ 47.0

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, decreased for the first nine months of 2021 compared to the same period in 2020. In the first nine months of 2020, we manufactured API for olezarsen and eplontersen.

R&D Support

In our research, development and patent expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, informatics costs, procurement costs and waste disposal costs. We call these costs R&D support expenses.

The following table sets forth information on R&D support expenses (in millions):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Personnel costs	$ 4.7	$ 3.4	$ 13.2	$ 10.8
Occupancy	3.2	2.5	9.6	7.4
Patent expenses	1.0	1.0	3.1	2.2
Insurance	0.8	0.6	2.4	1.8
Computer software and licenses	0.3	0.8	1.4	2.1
Other	1.6	2.1	4.8	5.9
Restructuring expenses	0.1	—	0.1	—
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	11.7	10.4	34.6	30.2
Non-cash compensation expense related to equity awards	4.4	4.3	13.0	12.0
Total R&D support expenses	$ 16.1	$ 14.7	$ 47.6	$ 42.2

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased for the first nine months of 2021 compared to the same period in 2020. The increase was primarily related to increased personnel and occupancy costs to support investments in our technology and advancing our pipeline.

Selling, General and Administrative Expenses

Selling, general and administrative, or SG&A, expenses include personnel and outside costs associated with the pre-commercialization and commercialization activities for our medicines and costs to support our company, our employees and our stockholders including, legal, human resources, investor relations, and finance. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above. We also include fees we owe under our in-licensing agreements related to SPINRAZA.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 23.0	$ 48.2	$ 106.1	$ 158.3
Restructuring expenses	1.0	—	16.4	—
Total selling, general and administrative expenses, excluding non-cash compensation related to equity awards	24.0	48.2	122.5	158.3
Non-cash compensation expense related to equity awards	7.1	20.2	26.2	57.2
Total selling, general and administrative expenses	$ 31.1	$ 68.4	$ 148.7	$ 215.5

SG&A expenses, excluding non-cash compensation expense related to equity awards, decreased for the first nine months of 2021 compared to the same period in 2020 due to operating efficiencies achieved from the Akcea integration and restructuring our commercial operations. Non-cash compensation expense related to equity awards decreased for the first nine months of 2021 compared to the same period in 2020 due to reduced headcount as a result of the Akcea Merger and restructuring our commercial operations.

Investment Income

Investment income for the three and nine months ended September 30, 2021 was $0.9 million and $8.2 million, respectively, compared to $6.5 million and $25.9 million for the same periods in 2020. The decrease in investment income was primarily due to a decline in interest rates during the three and nine months ended September 30, 2021 compared to the same periods in 2020.

Interest Expense

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Convertible notes:		(as revised*)		(as revised*)
Non-cash amortization of the debt discount and debt issuance costs	$ 1.4	$ 0.9	$ 3.5	$ 2.4
Interest expense payable in cash	0.3	0.9	1.7	2.8
Interest on mortgages for primary R&D and manufacturing facilities	0.6	0.6	1.8	1.8
Other	—	—	0.1	0.1
Total interest expense	$ 2.3	$ 2.4	$ 7.1	$ 7.1

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 2, *Significant Accounting Policies*, for further information.

Gain on Investments

We recorded a gain on investments of $4.9 million for the nine months ended September 30, 2021 compared to $10.7 million for the same period in 2020. During the nine months ended September 30, 2021, we revalued our investments in Bicycle and ProQR and recognized gains of $1.9 million and $2.0 million on our investments, respectively. During the nine months ended September 30, 2020, we revalued our investments in Dynacure and Suzhou-Ribo because the companies sold additional equity securities that were similar to those we own. These observable price changes resulted in us recognizing a $6.3 million gain on our investment in Dynacure and a $3 million gain on our investment in Suzhou-Ribo in our condensed consolidated statement of operations during the nine months ended September 30, 2020.

Early Retirement of Debt

As a result of the debt offering and debt repurchase completed in April 2021, we recorded an $8.6 million non-cash loss on early retirement of debt, reflecting the early retirement of a significant portion of our 1% Notes. The non-cash loss on the early retirement of our debt is the difference between the amount we paid to retire our 1% Notes and the net carrying balance of the liability at the time that we retired the debt.

Income Tax Expense (Benefit)

We recorded an income tax benefit of $1.3 million and $0.9 million for the three and nine months ended September 30, 2021, respectively. The income tax benefit recorded for the three months ended September 30, 2021 relates primarily to a reduction in our estimated state income tax liability. We recorded income tax expense of $5.1 million and $4.1 million for the three and nine months ended September 30, 2020, respectively. The income tax expense recorded for the first nine months of 2020 relates primarily to Ionis' standalone income for the period.

Net Loss

We had a net loss of $82.5 million and $253.2 million for the three and nine months ended September 30, 2021, respectively, compared to $36.6 million and $124.1 million for the same periods in 2020. Our net loss increased for the nine months ended September 30, 2021, compared to the same period in 2020 primarily due to decreased revenue and increased expenses year-over-year, as discussed above in the revenue and expenses sections, respectively.

Net Loss Attributable to Noncontrolling Interest in Akcea Therapeutics, Inc.

During the first nine months of 2020, we owned approximately 76 percent of Akcea. The shares of Akcea third parties owned represented an interest in Akcea's equity that we did not control. However, because we maintained overall control of Akcea through our voting interest, we reflected Akcea's results of operations in our condensed consolidated financial statements. We reflected the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line called "Net loss attributable to noncontrolling interest in Akcea" on our statement of operations. Our noncontrolling interest in Akcea on our statement of operations for the three and nine months ended September 30, 2020, was a loss of $12.1 million and $34.3 million, respectively. After we completed the Akcea Merger in October 2020, we no longer recorded any adjustment related to noncontrolling interest for Akcea's net loss.

Net Loss Attributable to Our Common Stockholders and Net Loss per Share

We had a net loss attributable to our common stockholders of $82.5 million and $253.2 million for the three and nine months ended September 30, 2021, respectively. We had a net loss attributable to our common stockholders of $24.5 million and $89.7 million for the same periods in 2020. Basic and diluted net loss per share for the three and nine months ended September 30, 2021 were $0.58 and $1.80, respectively, compared to $0.18 and $0.64 for the same periods in 2020.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and TEGSEDI and WAYLIVRA commercial revenue. From our inception through September 30, 2021, we have earned approximately $5.4 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through September 30, 2021, we have raised net proceeds of approximately $2.0 billion from the sale of our equity securities. Additionally, from our inception through September 30, 2021, we have borrowed approximately $2.1 billion under long-term debt arrangements to finance a portion of our operations.

Our cash, cash equivalents and short-term investments, debt obligations and working capital increased from December 31, 2020 to September 30, 2021, primarily as a result of issuing $632.5 million of 0% Notes (due in April 2026) and repurchasing $247.9 million of our 1% Notes in April 2021.

The following table summarizes our contractual obligations as of September 30, 2021. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

Contractual Obligations	**Payments Due by Period (in millions)**		
(selected balances described below)	**Total**	**Less than 1 year**	**More than 1 year**
0% Notes (principal payable)	$ 632.5	$ —	$ 632.5
0.125% Notes (principal and interest payable)	$ 551.2	$ 0.7	$ 550.5
1% Notes (principal and interest payable)	$ 62.3	$ 62.3	$ —
Building mortgage payments (principal and interest payable)	$ 74.0	$ 2.5	$ 71.5
Operating leases	$ 27.6	$ 3.7	$ 23.9
Other obligations (principal and interest payable)	$ 1.0	$ 0.1	$ 0.9
Total	$ 1,348.6	$ 69.3	$ 1,279.3

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility mortgages, facility leases, equipment financing arrangements and other obligations. Due to the uncertainty with respect to the timing of future cash flows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded our gross unrecognized tax benefits from our contractual obligations table above. We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

Convertible Debt and Call Spread

Refer to our Convertible Debt and Call Spread accounting policies in Note 2, *Significant Accounting Policies*, and Note 6, *Convertible Debt*, in the Notes to our condensed consolidated financial statements for the significant terms of each convertible debt instrument.

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million and our manufacturing facility for $14.0 million. We financed the purchase of these two facilities with mortgage debt of $60.4 million in total. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages, we are only required to make interest payments. Both mortgages mature in August 2027.

Operating Leases

In September 2021, we entered into an operating lease agreement for office space located in Boston, Massachusetts with an initial term ending 91 months following the lease commencement date. We included our contractual obligations related to this operating lease agreement in the table above. Refer to the Note 2, *Significant Accounting Policies* in the Notes of our condensed consolidated financial statements for the significant terms of the operating lease agreement.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2021 for the purchase of services, capital equipment and materials as part of our normal course of business.

We may enter into additional collaborations with partners which could provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

We are also exposed to changes in foreign currency exchange rates as we have foreign subsidiaries with functional currencies other than the U.S. dollar. We translate our subsidiaries' functional currencies into our reporting currency, the U.S. dollar. As a result, our financial position, results of operations and cash flows can be affected by market fluctuations in the foreign currencies to U.S. dollar exchange rate, which are difficult to predict. A hypothetical 10 percent change in foreign exchange rates during any of the periods presented would not have had a material impact on our condensed consolidated financial statements.

ITEM 4. CONTROLS AND PROCEDURES

We maintain disclosure controls and procedures that are designed to ensure that information we are required to disclose in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We design and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2021. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2021.

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

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

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

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

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, 2020.

Summary of Risk Factors

There are a number of risks related to our business and our securities. Some of the principal risks related to our business include the following:

- the impact on our operations and financial condition from the effects of the current COVID-19 pandemic;
- our ability to generate substantial revenue from the sale of our medicines;
- our and our partners' ability to compete effectively;
- the availability of adequate coverage and payment rates for our medicines;
- our ability to successfully manufacture our medicines;
- our ability to successfully develop and obtain marketing approvals for our medicines;
- our ability to secure and maintain effective corporate partnerships;
- our ability to sustain cash flows and achieve consistent profitability;
- our ability to protect our intellectual property;
- our ability to maintain the effectiveness of our personnel; and
- the other factors set forth below.

Risks Related to the COVID-19 Pandemic

Our business could be materially adversely affected by the effects of health epidemics. To date, we believe the impacts of the recent COVID-19 pandemic on our business are limited and manageable.*

Our business could be materially adversely affected by health epidemics in regions where we or our partners are commercializing our medicines, have concentrations of clinical trial sites or other business operations, and could cause significant disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, since December 2019, a novel strain of coronavirus, SARS-CoV-2, causing a disease referred to as COVID-19, has spread worldwide. In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic, or the COVID-19 Pandemic, and the U.S. government-imposed restrictions on travel between the U.S., Europe and certain other countries. In addition, the Governor of the State of California and the Governor of the Commonwealth of Massachusetts, the states in which our offices are located, each declared a state of emergency related to the spread of COVID-19 and issued executive orders that directed residents to stay at home.

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

These public health directives and orders have impacted our and our partners' sales efforts. For example, some physician and hospital policies that have been put in place as a result of the COVID-19 Pandemic restrict in-person access by third parties, which has in some cases impacted our commercialization efforts for TEGSEDI and WAYLIVRA. Additionally, Biogen has reported that as a result of the COVID-19 Pandemic, SPINRAZA sales revenues have decreased in part because SPINRAZA doses have been delayed due, directly or indirectly, to the COVID-19 Pandemic, and that future SPINRAZA sales revenues may be adversely affected by continued dosing delays. These and similar, and perhaps more severe, disruptions in our or our partner's commercial operations could materially impact our business, operating results and financial condition in the future.

Quarantines, shelter-in-place, executive and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, could impact personnel at third-party manufacturing facilities in the U.S. and other countries, or the availability or cost of materials, which would disrupt our supply chain.

We have experienced impacts to our clinical trial operations due to the COVID-19 Pandemic; however, we believe such impacts are limited and manageable. Some examples of these impacts include:

- we have experienced some impact on clinical site initiation and patient enrollment due to restrictions imposed as a result of the COVID-19 Pandemic;
  - For example, in March 2020, we instituted a temporary suspension of enrollment for new subjects in our Phase 3 studies of eplontersen based on advice from our trial advisory committee; however, enrollment has resumed.
- some patients have not been able to meet protocol requirements, as quarantines have impeded patient movement and interrupted healthcare services;
- we have experienced some delays in site initiations due to principle investigators and site staff focusing on and prioritizing COVID-19 patient care; and
- we have experienced some delays in necessary interactions with regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government or contractor personnel.

The spread of COVID-19 has caused a broad impact globally. While the potential economic impact brought by, and the duration of, the COVID-19 Pandemic may be difficult to assess or predict, it could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and has and could continue to affect the value of our securities.

The global COVID-19 Pandemic continues to rapidly evolve. While we have not yet experienced material adverse effects to our business as a result of the COVID-19 Pandemic, the ultimate impact of the COVID-19 Pandemic or a similar health epidemic is highly uncertain and subject to change. As such, we do not yet know the full extent of delays or impacts on our business, our clinical trials, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID-19 Pandemic closely.

Risks Related to the Commercialization of our Medicines

We have limited experience as a company in commercializing medicines, and we may have to invest significant resources to develop these capabilities. If we are unable to establish effective marketing, sales and distribution capabilities or enter into agreements with third parties to market, sell and distribute our medicines, we may not be able to generate revenue from our medicines.

We have limited experience as a company in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure to effectively manage our internal sales, marketing and distribution capabilities would adversely impact the commercialization of our medicines. In addition, we may not be able to enter into collaborations or hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms, or at all. Even if we are able to engage third parties to market, sell and distribute our medicines, our product revenues and profitability may be lower if we rely on such third parties for these functions than if we were to perform them on our own. We also will likely have little control over such third parties, and any of them may fail to devote the necessary resources and attention to market, sell and distribute our medicines effectively. If we are not successful in commercializing our medicines, either on our own or through arrangements with one or more third parties, we may not be able to generate revenue from our medicines.

If the market does not accept our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, we are not likely to generate substantial revenues or become consistently profitable.

Even if our medicines are authorized for marketing, including SPINRAZA, TEGSEDI and WAYLIVRA, our success will depend upon the medical community, patients and third-party payers accepting our medicines as medically useful, cost-effective, safe and convenient. Even when the FDA or foreign regulatory authorities authorize our or our partners' medicines for commercialization, doctors may not prescribe our medicines to treat patients. Furthermore, we and our partners may not successfully commercialize additional medicines.

Additionally, in many of the markets where we or our partners may sell our medicines in the future, if we or our partners cannot agree with the government or other third-party payers regarding the price we can charge for our medicines, then we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third-party payers could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, economically unviable.

The degree of market acceptance for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, depends upon a number of factors, including the:

- receipt and scope of marketing authorizations;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our medicines and their potential advantages over competing products;
- cost and effectiveness of our medicines compared to other available therapies;
- patient convenience of the dosing regimen for our medicines; and
- reimbursement policies of government and third-party payers.

Based on the profile of our medicines, physicians, patients, patient advocates, payers or the medical community in general may not accept or use any medicines that we may develop.

For example, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI is only available through a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is patisiran, marketed by Alnylam Pharmaceuticals, Inc. Although patisiran requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. Additionally, the product label for WAYLIVRA in the EU requires regular blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these medicines. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help mitigate safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we can better maintain patients on TEGSEDI and WAYLIVRA through our patient-centric commercial approach where we or our partner plan to have greater involvement with physicians and patients, if we or our partner cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on the ability to conduct periodic blood and urine monitoring of our patients as a result of the current COVID-19 Pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If we or our partners fail to compete effectively, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, will not contribute significant revenues.*

Our competitors engage in drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology. Our competitors may succeed in developing medicines that are:

- priced lower than our medicines;
- reimbursed more favorably by government and other third-party payers than our medicines;
- safer than our medicines;
- more effective than our medicines; or
- more convenient to use than our medicines.

These competitive developments could make our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other medicines either on their own or in collaboration with others, including our competitors, to treat the same diseases our own collaborative programs target. Competition may negatively impact a partner's focus on and commitment to our medicines and, as a result, could delay or otherwise negatively affect the commercialization of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products, in obtaining FDA and other regulatory authorizations of such products and in commercializing such products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization in certain geographic markets of products against targets that are also targets of products in our development pipeline. For example:

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Patisiran, tafamidis and tafamidis meglumine compete with TEGSEDI;
- Vutrisiran and acoramidis could compete with TEGSEDI and eplontersen;
- ARO-APOC3, lomitapide and gemcabene could compete with WAYLIVRA and olezarsen; and
- Arimoclomol, ultomiris, mastinib and trehalose could compete with tofersen and ION363.

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. Biogen has disclosed that SPINRAZA revenue has decreased due in part to lower sales volumes as a result of increased competition and that future sales of SPINRAZA may be adversely affected by the commercialization of competing products. SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries.

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.

Certain of our medicines may compete with our other medicines, which could reduce our expected revenues.

Certain of our medicines inhibit the production of the same protein. For example, WAYLIVRA inhibits the production of the same protein as olezarsen and TEGSEDI inhibits the production of the same protein as eplontersen. We believe the enhancements we incorporated into olezarsen and eplontersen can provide greater patient convenience by allowing for significantly lower doses and less frequent administration compared to WAYLIVRA and TEGSEDI, respectively. As such, to the extent physicians and patients elect to use olezarsen or eplontersen instead of WAYLIVRA or TEGSEDI, respectively, it will reduce the revenue we derive from those medicines. In addition, while vupanorsen, olezarsen and WAYLIVRA use different mechanisms of action, if vupanorsen and olezarsen can effectively lower triglyceride levels in patients, including patients with FCS, WAYLIVRA, vupanorsen and olezarsen may compete with each other.

Our medicines could be subject to regulatory limitations following approval.*

Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of medicines. Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development.

The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine through the product label and on advertising, promotional and distribution activities. For example:

- in the U.S., TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis;
- TEGSEDI requires periodic blood and urine monitoring; and
- in the U.S., TEGSEDI is available only through a REMS program.

Prescription medicines may be promoted only for the approved indications in accordance with the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the EU, we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA, EC or other foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and time consuming to fulfill.

If we or others identify side effects after any of our medicines are on the market, or if manufacturing problems occur subsequent to regulatory approval, or if we, our manufacturers or our partners fail to comply with regulatory requirements, we or our partners may, among other things, lose regulatory approval and be forced to withdraw products from the market, need to conduct additional clinical studies, incur restrictions on the marketing, distribution or manufacturing of the product, and/or change the labeling of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

We depend on our collaboration with Biogen for the development and commercialization of SPINRAZA.

We have entered into a collaborative arrangement with Biogen to develop and commercialize SPINRAZA. We entered into this collaboration primarily to:

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

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA, manufacture and successfully commercialize SPINRAZA. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaboration. If Biogen fails to further develop SPINRAZA, obtain additional regulatory approvals for SPINRAZA, manufacture or commercialize SPINRAZA, or if Biogen's efforts are not effective, our business may be negatively affected.

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

Our collaboration with Biogen may not result in the continued successful commercialization of SPINRAZA. If Biogen does not continue to successfully commercialize SPINRAZA, we will receive limited revenues for SPINRAZA.

We are relying on third parties to market, sell and distribute TEGSEDI and WAYLIVRA.*

We have entered into agreements with third parties to commercialize TEGSEDI and WAYLIVRA as follows:

- In April 2021, we entered into a distribution agreement with Sobi to commercialize TEGSEDI in the U.S. and Canada;
- In December 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe; and
- In August 2018, we granted PTC the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries.

We are relying on Sobi and PTC to effectively market, sell and distribute TEGSEDI and WAYLIVRA and have less control over sales efforts and may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. If Sobi or PTC does not successfully commercialize TEGSEDI or WAYLIVRA, including as a result of delays or disruption caused by the current COVID-19 Pandemic, we may receive limited revenue for TEGSEDI or WAYLIVRA in the U.S., Canada, Europe, Latin America or certain Caribbean countries, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

Our operations are subject to additional healthcare laws.

Our operations are subject to additional healthcare laws, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws, which are subject to change at any time. For example, in November 2020, the U.S. Department of Health and Human Services issued a final rule modifying the anti-kickback law safe harbors for Medicare Part D plans, pharmacies, and pharmaceutical benefit managers. Efforts to ensure that our operations comply with current applicable healthcare laws and regulations involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings.

If government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, our revenue will be limited.*

In both domestic and foreign markets, sales of our current and future products will depend in part upon the availability of coverage and reimbursement from third-party payers. The majority of patients in the U.S. who would fit within our target patient populations for our medicines have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new medicines when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our medicines affordable. Accordingly, SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, will face competition from other therapies and medicines for limited financial resources. We or our partners may need to conduct post-marketing studies to demonstrate the cost-effectiveness of any future products to satisfy third-party payers. These studies might require us to commit a significant amount of management time and financial and other resources. Third-party payers may never consider our future products as cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U.S., no uniform policy of coverage and reimbursement for medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act, was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers, and continues to significantly impact the U.S. pharmaceutical industry. There have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as efforts to repeal or replace certain aspects of the Affordable Care Act. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the Affordable Care Act are invalid as well. However, in March 2020, before the District Court could rule on the remaining provisions of the Affordable Care Act, the U.S. Supreme Court agreed to review the case. In June 2021, the Supreme Court dismissed the case on the basis that the states and individuals that brought the lawsuit did not have standing to challenge the law. It is unclear how future litigation and healthcare reform measures will impact the Affordable Care Act and our business.

Further, we believe that future coverage, reimbursement and pricing will likely be subject to increased restrictions both in the U.S. and in international markets. In the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries, legislation and executive orders designed to, among other things, reduce drug prices (e.g., by supporting drug price negotiation in Medicare Parts B and D, with those negotiated prices also available to commercial plans, and progressing legislation to slow price increases over time on existing drugs), increase competition (e.g., by supporting legislation to speed the entry of biosimilar and generic drugs, including shortening the period of exclusivity, policies in Medicare Part B to increase the prescribing of biosimilars by physicians, and a prohibition on “pay-for-delay” agreements and anti-competitive practices by drug manufacturers), lower out-of-pocket drug costs for patients (e.g., by capping Medicare Part D beneficiary out-of-pocket pharmacy expenses), and foster scientific innovation to promote better health care and improved health (e.g., by investing in public and private research and incentivizing the market to promote discovery of valuable and accessible new treatments). At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, and third-party payers, whether foreign or domestic, or governmental or commercial, may allocate their resources to address the current COVID-19 Pandemic or experience delays or disruptions in their ability to devote resources to coverage and reimbursement matters related to our products or medicines as a result of the COVID-19 Pandemic, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If we cannot manufacture our medicines or contract with a third party to manufacture our medicines at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.*

To successfully commercialize any of our medicines, we would need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities, including any interruption to our supply chain as a result of the current COVID-19 Pandemic, could limit the commercial success of our medicines. In addition, as our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. For example, we have plans to expand our manufacturing infrastructure to support our wholly owned pipeline. If we are not successful in executing this expansion, it could limit our ability to meet our manufacturing requirements and commercial objectives in the future.

Additionally, we have limited experience manufacturing pharmaceutical products of the chemical class represented by our medicines, called oligonucleotides, on a commercial scale for the systemic administration of a medicine. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our medicines, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We or our partners may not be able to manufacture our medicines at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's cGMP regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We, our partners and our contract manufacturers may not comply or maintain compliance with cGMP, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorizations for our medicines, including authorizations for SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, or result in enforcement action after authorization that could limit the commercial success of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development.

Risks Related to the Development and Regulatory Approval of our Medicines

If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for SPINRAZA, TEGSEDI and WAYLIVRA, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our medicines will be considered safe and effective or will be approved for commercialization. In addition, it is possible that SPINRAZA, TEGSEDI and WAYLIVRA may not be approved in additional markets or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our medicines before they can be approved or receive additional approvals for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our medicines. It is possible that regulatory agencies will not approve our medicines for marketing or SPINRAZA, TEGSEDI or WAYLIVRA in additional markets or for additional indications. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or our medicines in development, the agency will not approve the specific medicine or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the medicine. For example, in August 2018 we received a complete response letter from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018.

The FDA or other comparable foreign regulatory authorities can delay, limit or deny approval of a medicine for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical studies;
- we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a medicine is safe and effective for any indication;
- such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the U.S.;
- we or our partners may be unable to demonstrate that our medicine's clinical and other benefits outweigh its safety risks to support approval;
- such authorities may disagree with the interpretation of data from preclinical or clinical studies;
- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers who manufacture clinical and commercial supplies for our medicines, or may delay the inspection of such facilities due to restrictions related to the COVID-19 Pandemic; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

Failure to receive marketing authorization for our medicines, or failure to receive additional marketing authorizations for SPINRAZA, TEGSEDI or WAYLIVRA, or delays in these authorizations, could prevent or delay commercial introduction of the medicine, and, as a result, could negatively impact our ability to generate revenue from product sales.

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

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense medicines are a relatively new approach to therapeutics. If we cannot demonstrate that our medicines are safe and effective for human use in the intended indication, we may need to abandon one or more of our drug development programs.

Even if our medicines are successful in preclinical and human clinical studies, the medicines may not be successful in late-stage clinical studies.*

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies. If any of our medicines in Phase 3 clinical studies, including the studies of tofersen, pelacarsen, eplontersen, olezarsen and ION363, do not show sufficient efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

In the past, we have invested in clinical studies of medicines that have not met the primary clinical endpoints in their Phase 3 studies or have been discontinued for other reasons. For example, in October 2021, Biogen reported that tofersen did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring tofersen were seen across multiple secondary and exploratory measures of disease activity and clinical function. In addition, in March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington's disease based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. Similar results could occur in clinical studies for our other medicines, including the studies of pelacarsen, eplontersen, olezarsen and ION363.

There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a medicine on subjects or lack of efficacy in the trial;
- we, or our partners, may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- we or our partners, including our independent clinical investigators, contract research organizations and other third-party service providers on which we rely, may not identify, recruit and train suitable clinical investigators at a sufficient number of study sites or timely enroll a sufficient number of study subjects in the clinical study;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- enrollment in our clinical studies may be slower than we anticipate;
- people who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;
- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our medicines; and
- the supply or quality of our medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

The current COVID-19 Pandemic could make some of these factors more likely to occur.

In addition, our current medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our medicines or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our medicines: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. This happened in connection with the conditional marketing approval for WAYLIVRA in the EU, as the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. We have an ongoing open label extension, or OLE, study of WAYLIVRA in patients with FCS and an OLE study of TEGSEDI in patients with hATTR, and an EAP for WAYLIVRA. Adverse events or results from these studies or the EAPs could negatively impact our pending or future marketing approval applications for WAYLIVRA and TEGSEDI in patients with FCS or hATTR amyloidosis or the commercial opportunity for WAYLIVRA or TEGSEDI.

Any failure or delay in our clinical studies, including the studies of tofersen, pelacarsen, eplontersen, olezarsen and ION363, could reduce the commercial potential or viability of our medicines.

We depend on third parties to conduct our clinical studies for our medicines and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.*

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Pharmaceutical Research Associates, Inc., Icon Clinical Research Limited, Syneos Health, Inc., PPD and Medpace for the clinical studies for our medicines, including tofersen, pelacarsen, eplontersen, olezarsen and ION363. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations, including as a result of delays or disruption caused by the current COVID-19 Pandemic that may affect the third party's ability to conduct the clinical studies for our medicines, or a termination of our relationship with these third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines or additional marketing authorizations for TEGSEDI and WAYLIVRA.

Since corporate partnering is a significant part of our strategy to fund the advancement and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

To date, corporate partnering has played a significant role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize many of our unpartnered medicines. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our medicines could suffer.

Our corporate partners are developing and/or funding many of the medicines in our development pipeline. For example, we are relying on:

- Roche for development and funding of tominersen;
- Novartis for development and funding of pelacarsen; and
- Biogen for development and funding of tofersen.

If any of these pharmaceutical companies stops developing and/or funding these medicines, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these medicines on our own. Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, as part of a reprioritization of its pipeline and strategic review of its rare disease business, GSK declined its option to license TEGSEDI and IONIS-FB-L_{Rx}.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our drug development and commercial programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical studies;
- seek and obtain marketing authorizations; and
- manufacture, market and sell our medicines.

Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis, Pfizer and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we first anticipated.

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

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

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

If we do not progress in our programs as anticipated, the price of our securities could decrease.*

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain medicine will enter clinical trials, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization, or when we or our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions, many of which are outside of our control, including the current COVID-19 Pandemic. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to SPINRAZA, TEGSEDI, WAYLIVRA, tominersen, tofersen, pelacarsen, eplontersen, olezarsen and ION363, the price of our securities could decrease.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of September 30, 2021, we had an accumulated deficit of approximately $1.4 billion and stockholders' equity of approximately $0.5 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. If we do not continue to earn substantial revenue, we may incur additional operating losses in the future. We may not successfully develop any additional medicines or achieve or sustain future profitability.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorizations, preclinical activities and commitment of significant additional resources prior to their successful commercialization. These activities will require significant cash. As of September 30, 2021, we had cash, cash equivalents and short-term investments equal to $2.0 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- successful commercialization of SPINRAZA, TEGSEDI and WAYLIVRA;
- additional marketing approvals for WAYLIVRA and TEGSEDI;
- the profile and launch timing of our medicines, including TEGSEDI and WAYLIVRA;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- our manufacturing requirements and capacity to fulfill such requirements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or medicines.

Risks related to our intellectual property

If we cannot protect our patent rights or our other proprietary rights, others may compete more effectively against us.

Our success depends to a significant degree upon whether we can continue to develop, secure and maintain intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the U.S. or in other countries and we may not be able to obtain, maintain or enforce our patents and other intellectual property rights which could impact our ability to compete effectively. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

We cannot be certain that the U.S. Patent and Trademark Office, or U.S. PTO, and courts in the U.S. or the patent offices and courts in foreign countries will consider the claims in our patents and applications covering SPINRAZA, TEGSEDI, WAYLIVRA, or any of our medicines in development as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, including through legal action.

If we or any licensor partner loses or cannot obtain patent protection for SPINRAZA, TEGSEDI, WAYLIVRA, or any of our other medicines in development, it could have a material adverse impact on our business.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

From time to time we have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

If a third party claims that our medicines or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the U.S. are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain.

Risks related to our business strategy and personnel

If we fail to successfully integrate Akcea's business and operations, it may adversely affect our future results.

We believe our Akcea Merger will result in certain benefits, including a single vision and set of strategic priorities, led by one team, accelerating our next phase of growth and positioning us to more effectively deliver our medicines to patients. Following this transaction, Ionis now retains more value from Akcea's pipeline and commercial medicines, further strengthening our financial position and supporting continued investments in our future. The success of the transaction will depend on our ability to realize these anticipated benefits. We may fail to realize the anticipated benefits of the Akcea Merger for a variety of reasons, including the following:

- failure to successfully manage relationships with partners, customers, distributors and suppliers;
- disruptions to Akcea's commercial operations;
- potential incompatibility of technologies and systems;
- failure to leverage the capabilities of the combined company quickly and effectively;
- potential difficulties integrating and harmonizing business systems and processes;
- tax benefits of the combined structure may not be available or in the expected amounts; and
- the loss of key employees.

If our management transition is not successful our business could suffer.

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, transitioned from Chief Executive Officer to Executive Chairman of our Board of Directors, and Dr. Monia, who was our Chief Operating Officer and a member of our team since our founding over 30 years ago, began serving as our Chief Executive Officer. Following the 2021 Annual Meeting of Stockholders, Dr. Crooke stepped down from the Board and now serves as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. If this transition is not successful, our business could suffer.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel. Similarly, we are dependent on the principal members of our staff responsible for marketing, sales and distribution activities. If we are not able to recruit and retain qualified marketing and sales personnel, the sales of TEGSEDI and WAYLIVRA may be adversely affected.

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 that provision, we can carryforward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits.

Under the Tax Cut and Jobs Act of 2017, or the Tax Act, as modified by the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such U.S. federal net operating losses is limited to 80 percent of taxable income beginning in 2021. It is uncertain if and to what extent various states will conform to the federal Tax Act or the CARES Act. The CARES Act also reinstated the net operating loss carryback provisions whereby net operating losses incurred in calendar tax years 2018, 2019 and 2020 may be carried back to offset taxable income of the five tax years preceding the year of the loss.

In June 2020, California enacted Assembly Bill 85 (AB 85), which suspends NOLs and limits credit utilization to $5 million per year for the 2020, 2021 and 2022 tax years. AB 85 did not have a material impact on our 2020 tax provision, and we do not expect that it will materially impact our 2021 tax provision, but it is possible that it may in future years.

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 percent change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss 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 net operating loss carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. As a result of the Akcea Merger, we are subject to the Separate Return Limitation Year, or SRLY, rules. Under SRLY, our utilization of Akcea's pre-merger net operating loss and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-merger tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

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

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

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and sales taxes in the U.S. and foreign income taxes, withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value-added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.

General Risk Factors

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding September 30, 2021, the market price of our common stock ranged from $64.37 to $33.52 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

The current COVID-19 Pandemic has caused a significant disruption of global financial markets and has resulted in increased volatility in the trading price of our common stock. Additionally, broad market and industry factors may also materially harm the market price of our common stock irrespective of our operating performance. The stock market in general, and NASDAQ and the market for biotechnology companies in particular, have 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 which investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

Provisions in our certificate of incorporation, convertible notes documents, call spread hedge transaction documents and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 2/3 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

In April 2021, we completed a $632.5 million offering of 0% Notes and used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million of our 1% Notes for $257.0 million. In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0% Notes and 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 18.4 million shares of our common stock upon conversion of our 0% Notes, 0.125% Notes, and 1% Notes, up to 10.9 million shares in connection with the warrant transactions we entered into in connection with the issuance of our 0% Notes, and up to 6.6 million shares in connection with the warrant transactions we entered into in connection with the issuance of our 0.125% Notes, in each case subject to customary anti-dilution adjustments. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

In addition, pursuant to the call spread transactions we entered into in connection with the pricing of our 0% Notes and 0.125% Notes, the counterparties are likely to modify their hedge positions from time to time at or prior to the conversion or maturity of the notes by purchasing and selling shares of our common stock, other of our securities, or other instruments, including over-the-counter derivative instruments, that they may wish to use in connection with such hedging, which may have a negative effect on the conversion value of those notes and an adverse impact on the trading price of our common stock. The call spread transactions are expected generally to reduce potential dilution to holders of our common stock upon any conversion of our 0% Notes or 0.125% Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0% Notes or 0.125% Notes, as the case may be. However, the warrant transactions could separately have a dilutive effect to the extent that the market value per share of our common stock exceeds the applicable strike price of the warrants.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, product liability claims may result in decreased demand for our medicines, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

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

We are dependent upon our own and third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, with third-party phishing and social engineering attacks in particular increasing in connection with the COVID-19 Pandemic. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, our efforts may not prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store most of these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

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

In recent years, extreme weather events and changing weather patterns have become more common. As a result, we are potentially exposed to varying natural disaster or extreme weather risks such as hurricanes, tornadoes, fires, droughts, floods, or other events that may result from the impact of climate change on the environment. The potential impacts of climate change may also include increased operating costs associated with additional regulatory requirements and investments in reducing energy, water use and greenhouse gas emissions. In addition, we manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA. The facilities and the equipment we, our partners and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or those of our partners or contract manufacturers may be harmed by natural disasters or other events outside our control, such as earthquakes, pandemics, war, civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption insurance coverage, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

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

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole are currently experiencing substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government in response to the COVID-19 Pandemic. In the past, the failure, bankruptcy, or sale of various financial and other institutions created similar turmoil and uncertainty in such markets and industries. It is possible that a crisis in the global credit markets, the U.S. capital markets, the financial services industry or the U.S. economy may adversely affect our business, vendors and prospects, as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all. A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business.

In addition to our U.S. operations, we are commercializing TEGSEDI in the EU, Canada, Latin America and certain Caribbean countries, and WAYLIVRA in the EU, Latin America and certain Caribbean countries. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations, we are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines and foreign employees;
- complexities associated with managing multiple payer reimbursement regimes, government payers or patient self-pay systems;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions;
- economic weakness, including inflation, natural disasters, war, events of terrorism, political instability or public health issues or pandemics, such as the current COVID-19 Pandemic, in particular foreign countries or globally;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country;
- compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.; and
- changes in diplomatic and trade relationships.

The United Kingdom’s exit from the E.U. could increase these risks.

Our business activities outside of the U.S. are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom’s Bribery Act 2010. In many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have an adverse impact on our business and financial condition.

The impact on us of the vote by the United Kingdom to leave the European Union cannot be predicted.

The withdrawal of the UK from the EU, commonly referred to as "Brexit," may adversely impact our ability to obtain regulatory approvals of our medicines in the EU, result in restrictions or imposition of taxes and duties for importing our medicines into the EU, and may require us to incur additional expenses in order to develop, manufacture and commercialize our medicines in the EU.

Following the result of a referendum in 2016, the UK left the EU on January 31, 2020. Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period that ended December 31, 2020, or the Transition Period, during which EU rules continued to apply. A trade and cooperation agreement, or the Trade and Cooperation Agreement, that outlines the future trading relationship between the UK and the EU was agreed in December 2020.

Since a significant proportion of the regulatory framework in the UK applicable to our business and our medicines is derived from EU directives and regulations, Brexit has had, and may continue to have, a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our medicines in the UK or the EU. For example, Great Britain is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our medicines in Great Britain. It is currently unclear whether the Medicines & Healthcare products Regulatory Agency in the UK is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would delay or prevent us from commercializing our medicines in the UK or the EU.

While the Trade and Cooperation Agreement provides for the tariff-free trade of medicinal products between the UK and the EU, there may be additional non-tariff costs to such trade which did not exist prior to the end of the Transition Period. Further, should the UK diverge from the EU from a regulatory perspective in relation to medicinal products, tariffs could be put into place in the future. We could therefore, both now and in the future, face significant additional expenses (when compared to the position prior to the end of the Transition Period) to operate our business.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Amended and Restated Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated July 12, 2021. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.2	Collaboration and License Agreement by and between the Registrant and BicycleTX Limited dated July 9, 2021. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, formatted in Inline Extensible Business Reporting Language (iXBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of stockholders' equity, (v) condensed consolidated statements of cash flows and (vi) notes to condensed consolidated financial statements (detail tagged).
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101).

* This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ BRETT P. MONIA Brett P. Monia, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	November 3, 2021
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	November 3, 2021

Exhibit 10.1

CONFIDENTIAL
EXECUTION VERSION

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

AMENDED AND RESTATED

NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

IONIS PHARMACEUTICALS, INC.,

AND

BIOGEN MA INC.

Dated July 12, 2021

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AMENDED AND RESTATED NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

This AMENDED AND RESTATED NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 12th day of July, 2021 (the "***Amendment Date***") by and between **IONIS PHARMACEUTICALS, INC.** (formerly known as Isis Pharmaceuticals, Inc.), a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Ionis***"), and **BIOGEN MA INC.** (formerly known as Biogen Idec MA Inc.), a Massachusetts corporation, having its principal place of business at 225 Binney Street, Cambridge, MA 02142 ("***Biogen***"). Biogen and Ionis each may be referred to herein individually as a "***Party***" or 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 a part of this Agreement.

RECITALS

WHEREAS, Ionis possesses certain Patent Rights, Know-How, technology and expertise with respect to antisense therapeutics, and has novel and valuable capabilities for the research, discovery, identification, synthesis and development of antisense therapeutics;

WHEREAS, Biogen has expertise in developing and commercializing human therapeutics, and Biogen is interested in developing and commercializing antisense therapeutics for up to three gene targets;

WHEREAS, Biogen desires Ionis to (a) identify a development candidate for each of the three gene targets, (b) develop the development candidates through completion of the first clinical trial designed to demonstrate proof of mechanism or proof of therapeutic benefit and (c) provide Biogen an option to obtain an exclusive license under this Agreement to develop, manufacture and commercialize Products in the Field;

WHEREAS, Biogen and Ionis entered into that certain Neurology Drug Discovery and Development Collaboration, Option and License Agreement, as amended (the "***Original Agreement***") dated December 10, 2012 (the "***Effective Date***"); and

WHEREAS, Biogen and Ionis seek to amend and restate the Original Agreement in its entirety as set forth herein.

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1
RESEARCH AND DEVELOPMENT

1.1. **Collaboration Overview**. The intent of the collaboration is for Ionis to (a) conduct Collaboration Programs for each of the three Collaboration Targets, (b) generate at least one Development Candidate for each Collaboration Program; (c) advance each Development Candidate through the completion of the first PoC Trial under the applicable Collaboration Program; and (d) allow Biogen the opportunity to exercise an Option to further Develop and ultimately Commercialize Compounds and Products under such Collaboration Program under an exclusive license from Ionis. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **Collaboration Programs**. Subject to and in accordance with the terms of this Agreement, Ionis and Biogen will be responsible for conducting three programs to discover, Develop, Manufacture and Commercialize Products (each, a "***Collaboration Program***"), each to be focused on a different Collaboration Target, pursuant to which:

1.2.1. Ionis will use its Commercially Reasonable Efforts to (a) conduct drug discovery activities including drug screening, identification, characterization, optimization and other necessary activities according to the applicable Collaboration Program Research Plans to achieve Target Sanction status, (b) identify a Development Candidate for the applicable Collaboration Program, and (c) conduct drug development activities for each Development Candidate through completion of the first PoC Trial under a Collaboration Program in accordance with the applicable Development Plan; *provided* that Ionis will not be required to commence work on more than [***] Collaboration Programs in any rolling [***] month period; and

1.2.2. following the License Effective Date with respect to each Collaboration Program, Biogen will use its Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product from each such Collaboration Program for which Biogen has exercised an Option in accordance with this Agreement.

1.3. **High Interest Targets**.

1.3.1. **High Interest Target List**. Subject to the replacement rights set forth in Section 1.3.2 below, the Parties will maintain, through the Neurology JSC, a list of mutually-agreed gene targets that are of high interest as potential Collaboration Targets (each such target, a "***High Interest Target***" and such list the "***High Interest Target List***") according to the following procedure:

(a) As of the Effective Date, the Parties have agreed upon a written list containing the initial [***] High Interest Targets;

(b) On [***], the number of High Interest Targets on the High Interest Target List will be reduced to [***] High Interest Targets. By [***], Biogen will provide Ionis a written notice designating the [***] gene targets (from the [***] gene targets listed on the High Interest Target List) that will remain as High Interest Targets;

(c) Each time after the Effective Date that a Collaboration Target is designated under Section 1.4.1, Section 1.4.2 or Section 2.3, the number of High Interest Targets for purposes of the High Interest Target List will be reduced by [***], and the High Interest Target so designated as a Collaboration Target will no longer be a High Interest Target for purposes of the High Interest Target List; and

(d) Upon the earlier of the (i) [***]; and (ii) [***], the High Interest Target List will be dissolved and no gene target will thereafter be a High Interest Target.

1.3.2. **Replacement**. At any time prior to the [***], Biogen may, in accordance with the terms of this Agreement, propose a replacement of a High Interest Target on the High Interest Target List, in which case Ionis and Biogen will mutually agree to replace such High Interest Target with a different gene target for purposes of the High Interest Target List; *provided*, *however*, that Ionis may only choose not to agree to replace a High Interest Target on the High Interest Target List with a gene target proposed by Biogen if, at the time of such proposal, [***], a "***Dispositive Disagreement Condition***"). If Ionis notifies Biogen within [***] days after receipt of Biogen's request to add a gene target as a High Interest Target that a Dispositive Disagreement Condition exists with respect to such gene target, the members of the Neurology JSC will discuss such Dispositive Disagreement Condition and work together in good faith to promptly repeat a similar process as set forth in this Section 1.3.2 until Biogen and Ionis have selected a replacement target. With respect to any replacement under this Section 1.3.2, (A) the gene target substituted-in will thereafter be a High Interest Target on the High Interest Target List; and (B) the gene target removed will no longer be a High Interest Target on the High Interest Target List. The Parties acknowledge and agree that, as of August 4, 2014, [***] has been designated as a Collaboration Target (as such term is defined in the Neurology II Agreement) that is an ALS Target (as such term is defined in the Neurology II Agreement) under the Neurology II Agreement and is no longer a Collaboration Target under this Agreement or the subject of this Agreement.

1.3.3. **Replacement Limit**. Notwithstanding the foregoing, the Parties may not replace more than one High Interest Target in any rolling [***] month period, without Ionis' written consent (the "***Replacement Limit***"); *provided* that replacing-in another gene target under Section 1.5.6 will not count for purposes of calculating the Replacement Limit.

1.4. **Collaboration Targets**.

1.4.1. **Designation**. The maximum number of Collaboration Targets will be three. Subject to the substitution rights set forth in Section 1.4.2 below, as of the Effective Date, the first Collaboration Target is [***]. At any time from [***] through [***], Biogen may designate the second Collaboration Target from the High Interest Target List, and at any time from [***] through the [***] anniversary of the Effective Date, Biogen may designate the third Collaboration Target from the High Interest Target List.

1.4.2. **Substitution**. With respect to any Collaboration Target that [***], Biogen may substitute such Collaboration Target with a gene target from the High Interest Target List by providing written notice to Ionis designating the gene target it is removing as a Collaboration Target and the High Interest Target from the High Interest Target List it is now designating as a Collaboration Target. Upon such substitution, (a) Ionis will begin a Collaboration Program on the High Interest Target so substituted-in as a Collaboration Target; and (b) Ionis' obligations, and Biogen's rights, under this Agreement with respect to the removed gene target will terminate, and the removed gene target will no longer be a Collaboration Target. *Notwithstanding the foregoing*, Biogen may not substitute more than [***] Collaboration Target (the "***Substitution Limit***"), without Ionis' written consent; *provided* that substituting-in an Accelerated Target under Section 2.3 or another High Interest Target under Section 1.5.6 or Section 10.2.4(a) will not count for purposes of calculating the Substitution Limit.

1.5. **Ionis' Research and Development Responsibilities**.

1.5.1. **Collaboration Program Research Plans**. Ionis will carry out its drug discovery efforts for each Collaboration Program pursuant to the applicable Collaboration Program Research Plan in a manner consistent with its internal practices for other gene targets with the goal of achieving Target Sanction and identifying a Development Candidate for the applicable Collaboration Program as soon as practicable. Ionis will update each Collaboration Program Research Plan as needed and submit it to the Neurology JSC for its review and comment. In addition, once a Collaboration Program achieves Target Sanction, the Neurology JSC will begin preliminary discussions regarding an appropriate development plan for the contemplated Development Candidate under such Collaboration Program.

For each Collaboration Program, Ionis will provide the Neurology JSC:

(a) promptly (but no later than [***]) following the designation of a Collaboration Target, an initial research plan delineating the experiments that should be conducted to achieve Target Sanction for such Collaboration Target; and

(b) the initial plan approved by Ionis' RMC in connection with a Target Sanction under a Collaboration Program to identify a Development Candidate, as may be modified from time to time to address the discovery, research and optimization activities Ionis will conduct under the applicable Collaboration Program (together, each such plan under Sections 1.5.1(a) and 1.5.1(b), a "***Collaboration Program Research Plan***").

Ionis will reasonably consider the comments provided by the Neurology JSC on each Collaboration Program Research Plan.

1.5.2. Development Candidates; Development Plans; Option Acceleration.

(a) Ionis will notify Biogen in writing within [***] days of designating a Development Candidate and will provide Biogen the applicable Development Candidate Data Package. For each Development Candidate under a Collaboration Program within [***] after designation of such Development Candidate, the Parties will mutually agree on an appropriate development plan for such Development Candidate through completion of the [***] (each, a "***Development Plan***") and will update Schedule 5.1.1 to add Specific Performance Milestone Events related to Biogen's Development and Commercialization of the Development Candidate following the License Effective Date for the applicable Collaboration Program, which Specific Performance Milestone Events will be generally consistent with Biogen's development timelines for its other drug development programs of similar stage and market potential. Prior to the License Effective Date with respect to a Collaboration Program, in the event the Parties are unable to agree upon the PoC Trial Design for a particular Collaboration Program, in lieu of mediation pursuant to Section 12.1.2, [***] will have final decision-making authority with respect to the PoC Trial Design. If the Parties are unable to agree upon the Specific Performance Milestone Events for a particular Collaboration Program, the matter will be resolved in accordance with Section 12.1, including, for the avoidance of doubt, mediation pursuant to Section 12.1.2, if necessary. Ionis will update each Development Plan as needed, but at least once Annually, and submit it to the Neurology JSC for its review and comment; *provided*, *however*, that [***], must be unanimously agreed to by the Neurology JSC. In addition, prior to the Initiation of the first Clinical Study under the Development Plan for a Collaboration Program, the Parties will endeavor to mutually agree on a communication plan regarding the public disclosure of data and results arising from such Collaboration Program; *provided*, *that* if the Parties cannot agree on such a communication plan, then [***] will have final decision-making authority regarding any such communications occurring prior to the License Effective Date with respect to a Collaboration Program.

(b) After designation of such Development Candidate, the Neurology JSC will agree on an initial estimate of the expected cost for Ionis to conduct the work [***] specified in the applicable Development Plan, including Ionis' expected [***] and [***] costs (each, a "***Cost Estimate***"). The initial Cost Estimate [***] shall be agreed on by the Neurology JSC no later than [***] months prior to the anticipated [***]. Based on the Cost Estimates, the Neurology JSC will establish the [***] and [v] milestone payments for such Collaboration Program, which payments will be equal to (i) [***]; plus (ii) [***]. The Parties will promptly negotiate in good faith using the Ionis/Biogen Preexisting Development Agreements as a basis for Cost Estimates and, if the total milestone payment [***] is more than $[***], the Parties will apportion such total milestone payment into smaller milestone payments in accordance with SCHEDULE 1.5.2(b); *provided, however*, that if [***], then the Neurology JSC shall determine whether and how to apportion such total milestone payment into smaller milestone payments. Each such smaller milestone payment shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following [***]. If the total milestone payment [***] is $[***] or less, then such milestone payment shall become due in its entirety upon [***], and shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following [***]. As part of this process, Ionis will provide the Neurology JSC with a good faith estimate of the cost to conduct the work necessary to develop such Development Candidates under the applicable Development Plan using a similar methodology as used under the Ionis/Biogen Preexisting Development Agreements. [***] months prior to the [***], using the process set forth above, the Neurology JSC will re-assess the total cost of such [***] and, if the cost has changed from the initial Cost Estimate, the Neurology JSC will adjust the applicable milestone payment accordingly, with any such adjustment to be agreed in writing to no later than the date that is [***] months prior to the [***]. Once there is less than [***] months prior to the [***], or such [***], if there are any changes to such [***] in accordance with this Agreement that result in an increase to the cost of such [***], then (A) if such cost is increased by more than [***], such increased costs will constitute an additional milestone payment to be paid in accordance with the provisions of this Section 1.5.2(b), or (B) if such cost is increased by [***], such increase will not affect the milestone payments for such [***] established under this Section 1.5.2(b), but instead will be handled in accordance with Section 1.8. For clarity, with respect to any increase in the cost of a [***] by more than [***]% under clause (A) of the preceding sentence, if such increased costs total $[***] or less and such [***], then such increased costs shall become due in their entirety immediately, and shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen. Once the Neurology JSC has agreed on a Cost Estimate and/or the [***] milestone payments for such Collaboration Program are established under this Section 1.5.2(b) or Section 1.8, such agreement will be documented in a written side letter, in the form and format attached hereto as APPENDIX 3, which shall be executed by both Parties.

(c) Ionis will not be required to conduct any Development activities for a Development Candidate if an initial Development Plan, Specific Performance Milestone Events and the corresponding Cost Estimates have not been agreed to pursuant to this Section 1.5.2. Prior to such time as the Parties mutually agree on such Cost Estimate and/or the applicable [***] milestone payments and have executed a written side letter with respect to the foregoing in accordance with Section 1.5.2(b), Ionis may, in its discretion, commence Development activities for which it is responsible under this Agreement; *provided, however*, that Biogen will not be responsible for any costs of such Development activities if commenced by Ionis prior to the execution of any such side letter unless and until such a side letter has been executed by the Parties, and in no event will Biogen be responsible for any amounts incurred by Ionis for such Development activities in excess of amounts set forth in the side letter executed by the Parties with respect to such Development activities.

(d) If the PoC Trial for a Collaboration Program will be [***] or more, or require more than [***], then, if Ionis provides to Biogen the notice described in the following sentence, Ionis will not be required to conduct such PoC Trial for such Collaboration Program. Ionis will notify Biogen within [***] after finalization of the initial PoC Trial Design (or each time there is a material change thereto) for a Collaboration Program pursuant to Section 1.5.2(a) if Ionis elects not to conduct such PoC Trial for such Collaboration Program (such notice, an "***Option Acceleration Notice***"). If Ionis has delivered an Option Acceleration Notice as provided in this Section 1.5.2(d), Biogen will have [***] from its receipt of the data generated under the [***] for the first Phase 1 Trial for such Collaboration Program (an "***Option Acceleration Deadline***") to exercise its Option for the applicable Collaboration Program. If Biogen does not exercise its Option for the applicable Collaboration Program by the applicable Option Acceleration Deadline, Biogen's Option under Section 3.1 with respect to such Collaboration Program will expire and such Collaboration Program will terminate. In addition, after Biogen's receipt of an Option Acceleration Notice with respect to a particular Collaboration Program, [***] will have final decision-making authority with respect to [***] to the extent related to the PoC Trial for the applicable Collaboration Program.

(e) The Neurology JSC will attach each Development Plan and associated Cost Estimates to the minutes of the Neurology JSC for the first meeting following agreement regarding such Development Plan and Cost Estimates by the Parties.

1.5.3. **Drug Development**. Ionis will use Commercially Reasonable Efforts to conduct all activities under each Development Plan on the timeline set forth in the applicable Development Plan, including the following Development activities under this Agreement:

(a) Subject to Section 1.6 below, Develop each Development Candidate through [***]; *provided*, *however*, that Ionis may discontinue such Development if at any time after having consulted, and having given good faith consideration to the recommendations of the Neurology JSC and a mutually-agreed Third Party expert, Ionis in good faith believes that continuing such Development would (i) pose an unacceptable risk or threat of harm in humans, or (ii) violate any Applicable Law, ethical principles, or principles of scientific integrity. Prior to discontinuing Development of a Development Candidate, Ionis will provide Biogen with reasonable advance notice of such discontinuation, including the grounds for Ionis' determination. If Ionis elects to discontinue Development of a Development Candidate pursuant to this Section 1.5.3(a), Biogen may, in its discretion, elect to continue Development of the Development Candidate by providing Ionis with written notice of Biogen's exercise of the Option within [***] after Ionis' written notice to Biogen of such discontinuation. If Biogen timely exercises its Option under this Section 1.5.3(a), then [***].

(b) ***Phase 1 Trials***. Each Phase 1 Trial will be conducted in accordance with the applicable Phase 1 Trial Design set forth in the applicable Development Plan. Ionis will keep Biogen informed of the progress and status of each Phase 1 Trial. When [***] a Phase 1 Trial, Ionis will notify Biogen in writing within [***] days. Ionis will provide Biogen with the [***] as soon as practicable after such notice.

(c) ***PoC Trial***. Each PoC Trial will be conducted in accordance with the PoC Trial Design set forth in the applicable Development Plan. Ionis will keep Biogen informed of the progress and status of each PoC Trial. When Ionis [***] a PoC Trial under the applicable Development Plan, Ionis will notify Biogen in writing within [***] days after such [***]. Ionis will provide Biogen with the [***] as soon as practicable after such notice. If Biogen exercises its Option prior to the Initiation of the first PoC Trial for a Collaboration Program, Biogen will keep Ionis informed of the progress and status of the PoC Trial for such Collaboration Program. When Biogen completes such PoC Trial, Biogen will notify Ionis in writing within [***] days after such completion, and will provide Ionis with [***] as soon as practicable after such notice.

1.5.4. **Briefing of the Neurology JSC; Conduct of Research and Development**. At each regularly scheduled meeting of the Neurology JSC, Ionis will provide to the Neurology JSC progress updates on (a) the status of each Collaboration Program generally; (b) Ionis' research activities on the High Interest Targets conducted pursuant to Section 2.3; (c) activities conducted under each Collaboration Program Research Plan, including progress towards Target Sanction or Development Candidate, as applicable; and (d) activities conducted under the Development Plans for each Development Candidate, in each case, together with a summary of data associated with Ionis' research and/or Development activities for each Collaboration Program. Ionis will conduct its work under each Collaboration Program in a good scientific manner, and in compliance with all applicable good laboratory practices and cGMP, and all Applicable Laws.

1.5.5. **Clinical Supplies by Ionis**. Ionis, at its expense, will supply API (on its own or through a CMO approved by Biogen) and Clinical Supplies to support the Research and Development activities under each Collaboration Program Research Plan and each Development Plan through the License Effective Date for such Collaboration Program. If Biogen exercises an Option at least [***] prior to the planned Initiation of the PoC Trial for the applicable Collaboration Program, Biogen may elect to either have (a) Ionis supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen), in which case Biogen will pay Ionis an amount equal to [***], or (b) a CMO supply Clinical Supplies for such PoC Trial in accordance with the Manufacturing Agreement entered into with such CMO. If Biogen exercises an Option prior to, but less than [***] before, the planned Initiation of the PoC Trial for the applicable Collaboration Program, Ionis will supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen) and Biogen will pay Ionis an amount equal to [***].

1.5.6. **Collaboration with Third Parties**. Ionis may engage one or more academic or non-profit institutions to conduct work under any Collaboration Program Research Plan or Development Plan or to conduct drug discovery activities to identify a High Interest Target Development Candidate pursuant to Section 2.3; *provided*, *however*, that (a) with respect to any such academic or non-profit institution engaged to conduct such activities with respect to a Collaboration Target, where such engagement occurs after the date such Collaboration Target is designated, or (b) with respect to any such academic or non-profit institution engaged to conduct such activities with respect to one of the remaining High Interest Targets, where such engagement occurs after the later of [***] or the date such High Interest Target is designated, (i) prior to engaging such academic or non-profit institution to conduct such activities, Ionis will consult with Biogen in good faith with respect to the terms of any agreement or amendment to an existing agreement to be entered into with such institution and consider Biogen's comments with respect thereto in good faith and (ii) if Ionis enters into any such agreement or amendment on terms objected to by Biogen in a written notice provided to Ionis prior to the execution thereof, it shall promptly so notify Biogen, which notice will include a copy of such agreement or amendment, and within [***] days following Biogen's receipt of such notice, Biogen may elect to replace the applicable High Interest Target or Collaboration Target with a different gene target in accordance with the procedures set forth in Section 1.3.2 or Section 1.4.2, as applicable, and such replacement will not be counted for purposes of determining whether Biogen has exceeded the Replacement Limit or Substitution Limit, as applicable.

1.6. **Research and Development Costs and Expenses**.

1.6.1. **Research and Development Costs Paid by Ionis**. Until the License Effective Date with respect to a Collaboration Program, Ionis will be responsible for all research and Development activities for each Development Candidate under the Collaboration Program Research Plan and Development Plan with respect to such Collaboration Program and, except as otherwise provided under Section 1.6.2(a), all costs and expenses associated therewith.

1.6.2. **Development Costs Paid by Biogen**.

(a) **Before the License Effective Date**. Prior to the License Effective Date with respect to a Collaboration Program, Biogen will be responsible for paying any Biogen-Approved Costs resulting from Biogen-Approved Changes using the payment mechanisms set forth in Section 1.8.

(b) **Additional Activities Approved by Biogen**. If, with respect to a particular Collaboration Program, Biogen desires that either Ionis or a Third Party [***] or conduct other work to support Approval of a Product, including [***], prior to the License Effective Date with respect to such Collaboration Program, and Ionis agrees to perform such work, Biogen will pay the costs of conducting such work using the payment mechanism set forth in Section 1.8.

(c) **After the License Effective Date**. After the License Effective Date with respect to a Collaboration Program, Biogen will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Products with respect to such Collaboration Program, including any work performed by Ionis at Biogen's request, and all supply chain planning and decision-making. All such work performed by Ionis at Biogen's request will be conducted and reimbursed pursuant to a budget agreed upon by the Parties.

1.7. **Drug Discovery and Drug Development Terms**.

1.7.1. The term for the conduct of the Drug Discovery Program will begin on the Effective Date and will end upon the earlier of (a) designation of a Development Candidate for each Collaboration Program and (b) the [***] anniversary of the Effective Date (the "***Drug Discovery Term***"); *provided, however*, that if Ionis is still conducting work under a Collaboration Program Research Plan on the date of expiration of the Drug Discovery Term, the Drug Discovery Term will be automatically extended until the earlier of the (i) date on which Ionis completes all activities under each such Collaboration Program Research Plan and (ii) the [***] anniversary of the Effective Date; *provided further* that if, as a result of Ionis' breach, Biogen has substituted a High Interest Target for a Collaboration Target pursuant to Section 10.2.4(a), and Ionis is conducting activities under the applicable Collaboration Program Research Plan on the date on which the Drug Discovery Term would otherwise expire, the Drug Discovery Term will be extended for a reasonable period of time (not to exceed the [***] anniversary of the date of such substitution) to allow Ionis to complete such activities.

1.7.2. The term for the conduct of the Drug Development Program will begin on the designation of the first Development Candidate and will end upon the earlier of (a) [***] for a Development Candidate under each Collaboration Program, which the Parties estimate will be approximately [***] years after the Effective Date, (b) exercise by Biogen of each of its Options for each Collaboration Program; (c) the termination of the last Collaboration Program; and (d) mutual agreement of the Parties to terminate the Drug Development Program.

1.7.3. Upon the end of the Drug Discovery Term, subject to Section 1.7.4, (a) Ionis will no longer have an obligation to perform any activities under Section 1.5; (b) any Collaboration Programs that have not reached the Development Candidate stage will no longer be Collaboration Programs and the applicable gene targets associated therewith will no longer be Collaboration Targets; (c) Ionis' obligations and Biogen's rights under this Agreement with respect to such gene target and any ASOs targeting such gene target will then terminate, and Ionis will be free to Develop and Commercialize on its own or with a Third Party such gene target and any Compounds targeting such gene target; and (d) Ionis will own any data generated under the Collaboration Program for such gene target and any Compounds targeting such gene target. For clarity, except to the extent explicitly set forth in the foregoing, the expiration of the Drug Discovery Term will not affect Biogen's rights or Ionis' obligations with respect to Collaboration Programs under this Agreement that have reached the Development Candidate stage by the end of the Drug Discovery Term, including, but not limited to, Ionis' obligation under Section 1.5.3 to Develop each such Development Candidate under the remaining Collaboration Programs through the [***].

1.7.4. If, despite Ionis' Commercially Reasonable Efforts, by the end of the Drug Discovery Term, Ionis has not designated a Development Candidate for a particular Collaboration Program, then if at any time during the [***] period after the end of the Drug Discovery Term Ionis' RMC designates an ASO discovered by Ionis that is designed to bind to the RNA that encodes the Collaboration Target that was the subject of such Collaboration Program as a development candidate ready to start IND-Enabling Toxicology Studies (such ASO, a "***Carryover Development Candidate***"), then, Ionis will notify Biogen and will provide Biogen with the data package presented to Ionis' RMC to approve such Carryover Development Candidate. Biogen will then have [***] days from its receipt of such package to elect to enter into an agreement (or amendment to this Agreement) for an option and license under the same terms as set forth in this Agreement (except that no additional upfront payment under Section 6.1 will be due). If, within [***] days after Biogen's receipt of such notice from Ionis, Biogen provides Ionis with written notice that it accepts such offer from Ionis for such Carryover Development Candidate, the Parties will execute an agreement (or amendment to this Agreement) regarding such Carryover Development Candidate containing the same terms as those described herein. If Biogen either notifies Ionis that it declines the offer for such Carryover Development Candidate, or Biogen does not provide Ionis with written notice during such [***] day period that Biogen accepts such offer from Ionis for such Carryover Development Candidate, then Ionis will be free to research, develop, manufacture and commercialize such Carryover Development Candidate (and/or any other ASO designed to bind to the RNA that encodes the gene target targeted by such Carryover Development Candidate) by itself or with or for a Third Party.

1.8. **Additional Activities Requested by Biogen**. Biogen will pay Ionis (a) costs resulting from requests from Biogen that Ionis perform additional work under this Agreement, including, the cost of Ionis' time incurred in performing such work at the then-applicable Ionis FTE Rate ("***FTE Costs***"), the cost of [***], and any [***] incurred by Ionis in performing such work, or (b) Additional Plan Costs resulting from Biogen-Approved Changes (such costs, collectively "***Biogen-Approved Costs***"). For clarity, the Biogen-Approved Costs shall include Additional Plan Costs for a [***] that result from changes to such [***] made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.5.2(b), if such cost is increased by [***] as described in Section 1.5.2(b)). For the avoidance of doubt, if such cost is increased by [***] as described in Section 1.5.2(b)), such increased costs will constitute an additional milestone payment to be paid in accordance with the provisions of Section 1.5.2(b), and will not be handled under this Section 1.8. Ionis will permit Biogen to review, negotiate (with Ionis) and approve (including through the Neurology JSC) all Biogen-Approved Costs; *provided* Biogen will provide a substantive, good faith response within [***] days of Ionis' request for approval. For clarity (1) this Section 1.8 will not be used to establish the initial milestone payments under Section 1.5.2(b), and (2) expenses paid under this Section 1.8 are not subject to reconciliation. Once Biogen-Approved Costs are mutually agreed under this Section 1.8, such agreement will be documented in a written side letter, in the form and format attached hereto as Appendix 3, which shall be executed by both Parties. Prior to such time as the Parties mutually agree on such Biogen-Approved Costs and have executed a written side letter with respect to the foregoing, Ionis may, in its discretion, commence Development activities for which it is responsible under this Agreement; *provided*, *however*, that Biogen will not be responsible for any costs of such Development activities if commenced by Ionis prior to the execution of any such side letter unless and until such a side letter has been executed by the Parties, and in no event will Biogen be responsible for any amounts incurred by Ionis for such Development activities in excess of amounts set forth in the side letter executed by the Parties with respect to such Development activities.

1.8.1. For Biogen-Approved Costs resulting from [***], or from [***] that are made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.5.2(b), Biogen will pay Ionis for such Biogen-Approved Costs [***] within [***] days after receipt of the applicable invoice by Biogen following [***], or the date that Biogen agrees to such changes to such [***], as applicable; *provided, however*, that if such Biogen-Approved Costs total more than $[***], the Parties will apportion such total Biogen-Approved Costs into smaller milestone payments in accordance with SCHEDULE 1.5.2(b) (or, if such Biogen-Approved Costs result from changes to a [***], then the Neurology JSC shall determine whether and how to apportion such Biogen-Approved Costs into smaller milestone payments). Each such smaller milestone payment shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following the event that triggered such milestone payment. If such Biogen-Approved Costs total $[***] or less, then such Biogen-Approved Costs shall become due in their entirety upon [***] or the date that the Parties agree to such Biogen-Approved Costs, if such [***], and shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following [***] or the date of such agreement regarding the Biogen-Approved Costs, as applicable.

1.8.2. For Biogen-Approved Costs resulting from [***], Biogen will pay Ionis, in accordance with any applicable [***] entered into by the Parties after the Effective Date, for [***]% of such Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen following Biogen's request or approval for such [***], and the remaining [***]% within [***] days after receipt of the applicable invoice by Biogen following [***].

1.8.3. For any Biogen-Approved Cost that (i) has an Estimated Biogen-Approved Cost of less than [***] and (ii) does not result from [***], from [***] that are made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.5.2(b) or from [***], Ionis will invoice Biogen directly for such Biogen-Approved Cost in advance, on a [***] basis based upon the applicable Estimated Biogen-Approved Costs and Biogen will pay the invoices submitted pursuant to this Section 1.8.3 for such Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen. For purposes of this Section 1.8.3, "***Measurement Period***" means each [***].

1.8.4. For any Biogen-Approved Costs that (i) has an Estimated Biogen-Approved Cost of $[***] or more and (ii) does not result from [***], from [***] that are made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.5.2(b) or from [***], Ionis will invoice Biogen directly for such Biogen-Approved Cost in advance on a [***] basis based upon the applicable Estimated Biogen-Approved Costs and Biogen will pay the invoices submitted pursuant to this Section 1.8.4 for such Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen. For purposes of this Section 1.8.4, "***Measurement Period***" means each [***].

1.8.5. Within [***] days after the end of the applicable Measurement Period, Ionis will provide Biogen with a written statement (i) reconciling the [***] the Estimated Biogen-Approved Costs and the [***] within the Biogen-Approved Costs (the "***Actual Biogen-Approved Costs***") incurred by Ionis during the just-ended Measurement Period and (ii) confirming that the FTE Costs portion of the Estimated Biogen-Approved Costs is a reasonable approximation of the actual FTE Costs incurred by Ionis during the just-ended Measurement Period. If the Estimated Biogen-Approved Costs exceed the Actual Biogen-Approved Costs for such period, Ionis will offset all such excess payments against any future invoices under this Agreement until Biogen has recouped all such overpayments. If the Estimated Biogen-Approved Costs are less than the Actual Biogen-Approved Costs for such period, Ionis will invoice Biogen for the remaining amounts owed to Ionis, and Biogen will pay such invoices within [***] days of receipt of such invoice. In the case where additional activities under this Section 1.8 are performed by a Third Party, the Parties will arrange for the Third Party to directly bill Biogen and for Biogen to pay such Third Party directly.

1.9. **Biogen's Participation in Regulatory Meetings**. Prior to the License Effective Date for each Collaboration Program:

(a) Ionis will not initiate discussions with a Regulatory Authority regarding the [***] for a Collaboration Program until Ionis and Biogen have mutually agreed upon such [***], as applicable.

(b) To the extent practical, prior to any scheduled meeting with a Regulatory Authority regarding the [***] for a Collaboration Program, (i) the Parties will discuss and mutually agree upon the timing and objectives for such meeting and (ii) Ionis will provide Biogen with (A) an invitation to attend at least one pre-meeting rehearsal with Ionis and (B) an opportunity to discuss the strategy for such meeting with Ionis. In addition, Ionis will allow Biogen to participate in any such meeting under the direction of Ionis.

(c) In each case, to the extent regarding the [***] for a Collaboration Program, Ionis will promptly provide Biogen with (i) final copies of all material correspondence with and submission to any Regulatory Authority promptly following submission thereof, (ii) a copy of material communications received from a Regulatory Authority, and (iii) a copy of the minutes from each meeting with a Regulatory Authority.

(d) Ionis will provide Biogen with a draft of all correspondence with and submissions to any Regulatory Authority that materially impact the [***] for a Collaboration Program sufficiently in advance of providing such correspondence or submission to the applicable Regulatory Authority to enable Biogen to have a meaningful opportunity to provide comments on the contents thereof. The contents of such correspondence or submission to any Regulatory Authority must reflect the Development Plan. The Parties will mutually agree on the contents of all such correspondence or submissions; *provided* that if mutual agreement is not obtained prior to a Regulatory Authority's requirement for a response, Ionis will consider in good faith including any comments provided by Biogen to such correspondence or submissions.

1.10. **Impact of [***] Development Path**. If the Parties mutually agree to amend a Development Plan where such amended plan contemplates [***], then the Parties will make appropriate changes to the operational terms of this Agreement (e.g., [***]) to reflect such [***] development plan, consistent with the comparable provisions necessary to support the development plan under the [***].

1.11. **Research and Development Management**.

1.11.1. **Neurology JSC**. The Parties will establish a joint steering committee (the "***Neurology JSC***") to provide advice and make recommendations on the conduct of activities under each Collaboration Program. The Neurology JSC will consist of two representatives appointed by Ionis and two representatives appointed by Biogen. Each Neurology JSC member will be a senior scientific staff leader or have other experience and expertise appropriate for the stage of development of the Collaboration Programs. Each Party will designate one of its two representatives who is empowered by such Party to make decisions related to the performance of such Party's obligations under this Agreement to act as the co-chair of the Neurology JSC. The co-chairs will be responsible for overseeing the activities of the Neurology JSC consistent with the responsibilities set forth in Section 1.11.2. SCHEDULE 1.11.1 sets forth certain Neurology JSC governance matters agreed to as of the Effective Date. The Neurology JSC will determine the Neurology JSC operating procedures at its first meeting, including the Neurology JSC's policies for replacement of Neurology JSC members, policies for participation by additional representatives or consultants invited to attend Neurology JSC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JSC meetings. Ionis and Biogen will use reasonable efforts to schedule meetings of the Neurology JSC to take place at the same location and on the same dates as meetings of the joint development and steering committees under the Ionis/Biogen Additional Agreements, to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses. Once a Development Candidate is designated under a Collaboration Program, the Parties will consider in good faith creating a separate subcommittee of the Neurology JSC to govern the activities under this Agreement with respect to such Collaboration Program.

1.11.2. **Role of the Neurology JSC**. Without limiting any of the foregoing, subject to Section 1.11.3, the Neurology JSC will perform the following functions, some or all of which may be addressed directly at any given Neurology JSC meeting:

(a) maintain the list of Collaboration Targets and the High Interest Target List, as such lists may be updated from time to time in accordance with this Agreement, and attach such lists to the minutes of the next meeting of the Neurology JSC following any update to the High Interest Target List or Collaboration Targets;

(b) review and provide advice on the Collaboration Program Research Plan for each Collaboration Program, and the Development Plan for each Development Candidate;

(c) review the overall progress of Ionis' efforts to achieve Target Sanction with respect to each Collaboration Program that has not achieved Target Sanction status;

(d) review the overall progress of Ionis' efforts to discover, identify, optimize and select the Development Candidate for each Collaboration Program;

(e) amend each Collaboration Program Research Plan for each Collaboration Program, and the Development Plan for each Development Candidate upon unanimous agreement;

(f) agree on Cost Estimates and the [***] milestone payments under Section 1.5.2(b);

(g) approve Biogen-Approved Costs pursuant to Section 1.8;

(h) if the milestone payment agreed upon in writing by the Parties pursuant to Section 1.5.2(b) with respect to a [***] exceeds $[***], establishing whether and how such payment shall be apportioned into smaller milestone payments as described in Section 1.5.2(b);

(i) if any Biogen-Approved Costs that result from [***] exceed $[***], establishing whether and how such payments shall be apportioned into smaller milestone payments as described in Section 1.8.1;

(j) review and provide advice on the Phase 1 Trial Design and the PoC Trial Design for each Collaboration Program; and

(k) such other review and advisory responsibilities as may be assigned to the Neurology JSC pursuant to this Agreement.

1.11.3. Decision-Making.

(a) Decisions by the Neurology JSC will be made by unanimous consent, with each Party's representatives having, collectively, one vote. At any given meeting of the Neurology JSC, quorum will have deemed to be reached if a voting representative of each Party is present or participating in such meeting. No action taken at any meeting of the Neurology JSC will be effective unless there is a quorum at such meeting. Unless otherwise specified in this Agreement, no action will be taken with respect to a matter for which the Neurology JSC has not reached unanimous consensus.

(b) Ionis will give due consideration to, and consider in good faith, the recommendations and advice of the Neurology JSC regarding the conduct of the Collaboration Program. Subject to Section 1.5.1 and Section 1.5.2(a), prior to the License Effective Date for a particular Collaboration Program, Ionis will have the final decision-making authority regarding [***]. After the License Effective Date for a particular Collaboration Program, Biogen will have the final decision-making authority regarding [***] for such Collaboration Program, *provided*, *however*, that [***]. Except as otherwise permitted by Section 1.5.2(a) and Section 1.11.2(e), the Neurology 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.

1.11.4. **Term of the Neurology JSC**. Ionis' obligation to participate in the Neurology JSC, or any of its subcommittees, will terminate upon Biogen's exercise (or expiration) of the Option for the last Collaboration Program. Thereafter, Ionis will have the right, but not the obligation, to participate in Neurology JSC meetings upon Ionis' request.

1.11.5. **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager under this Agreement (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the Neurology JSC and performing the activities listed in SCHEDULE 1.11.5.

ARTICLE 2
EXCLUSIVITY COVENANTS

2.1. **Exclusivity; Right of First Negotiation**.

2.1.1. **Exclusivity Covenants**.

(a) **Ionis' Exclusivity Covenants During the Drug Discovery Term for High Interest Targets**. On a High Interest Target-by-High Interest Target basis, Ionis agrees that, except in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.3, Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, it will not work for the benefit of any Third Party (including the grant of any license to any Third Party) with respect to the discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes such High Interest Target in the Field from the Effective Date until the date on which the High Interest Target List is dissolved in accordance with Section 1.3.1(d).

(b) **The Parties' Exclusivity Covenants During the Option Period for Collaboration Targets**. On a Collaboration Target-by-Collaboration Target basis, each Party agrees that, except in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, it will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field from the date such gene target was designated a Collaboration Target under this Agreement through the earlier of (i) the License Effective Date with respect to the Collaboration Program for such Collaboration Target and (ii) the expiration or earlier termination of the applicable Option Period.

(c) **Ionis' Exclusivity Covenant after the License Effective Date**. On a Collaboration Target-by-Collaboration Target basis, except as set forth in Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, after the License Effective Date for the Collaboration Program with respect to the applicable Collaboration Target, Ionis will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(i) discovery, research or development of an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field until [***]; and

(ii) on a country-by-country basis, commercializing an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field until [***].

(d) **Biogen's Exclusivity Covenant After the License Effective Date**. After the License Effective Date for a particular Collaboration Program, Biogen's exclusivity obligations under Section 2.1.1(b) with respect to the Collaboration Target that is the subject of such Collaboration Program will be extended and will continue for so long as and to the extent of Ionis' exclusivity obligations under Section 2.1.1(c).

Except as expressly set forth in Section 2.1.2, Section 2.1.3, or Section 10.4.3, in no event will Ionis have the right to [***].

2.1.2. **Right of First Negotiation for Follow-On Compounds**. On a Collaboration Program-by-Collaboration Program basis, during the period commencing on the Effective Date and ending upon (i) if the applicable Option is not exercised in accordance with this Agreement, [***] or (ii) if the applicable Option is exercised in accordance with this Agreement, [***] (such period, the "***ROFN Period***"), Ionis hereby grants to Biogen a right of first negotiation to develop and commercialize any Follow-On Compound developed by or on behalf of Ionis, which right of first negotiation is granted on the following terms and conditions:

(a) Within [***], Biogen may provide Ionis with a non-binding, good faith written notice expressing Biogen's desire for Ionis to identify a Follow-On Compound with respect to the Collaboration Target that is the subject of such Collaboration Program (a "***Follow-On Interest Notice***"). If (i) Biogen does not, within such [***] period, provide Ionis with a Follow-On Interest Notice, or (ii) Biogen does timely provide Ionis with a Follow-On Interest Notice but the Parties do not agree on a [***] related to such Follow-On Compound by 5:00 pm (Eastern Time) on the [***] following the License Effective Date for such Collaboration Program, then, Ionis may work independently or with any of its Affiliates or any Third Party with respect to the discovery, research, development and manufacture of a Follow-On Compound with respect to such Collaboration Target; *provided*, *however*, that during the ROFN Period, Ionis will not grant any license (or an option to obtain such a license) under any intellectual property owned, controlled or licensed by Ionis to make, use or sell any Follow-On Compound (a "***Follow-On Agreement***") with respect to such Collaboration Target *unless and until* Ionis provides a written notice to Biogen (a "***Follow-On Negotiation Notice***"), which notice identifies [***]. Ionis will not initiate negotiations regarding or enter into such a Follow-On Agreement with any Third Party until [***] (each, a "***ROFN Termination Event***").

(b) If Biogen or one of its Affiliates responds within [***] after its receipt of a Follow-On Negotiation Notice indicating that Biogen or one of its Affiliates desires to negotiate with Ionis regarding the proposed Follow-On Agreement, Ionis and Biogen or one of its Affiliates will negotiate in good faith with each other until the [***] after the date Ionis provided Biogen the Follow-On Negotiation Notice (or such other period as mutually agreed by the Parties) (the "***Negotiation Period***") regarding a mutually satisfactory Follow-On Agreement (which may take the form of an amendment to this Agreement). During the Negotiation Period, Ionis will make at least [***] to Biogen or its Affiliate setting forth all material business and legal terms on which Ionis would be willing to enter into the proposed Follow-On Agreement with Ionis; *provided* that neither Party will have any obligation to enter into any such Follow-On Agreement. If the Negotiation Period expires before Biogen or its Affiliate and Ionis have entered into such a Follow-On Agreement, Ionis will have no further obligation to negotiate with Biogen or its Affiliates with respect to such Follow-On Agreement and Ionis will be free to negotiate and enter an agreement with a Third Party with respect to a Follow-On Agreement [***]; *provided*, *however*, that Ionis will not enter into any such Follow-On Agreement with any Third Party unless the terms and pricing of such Follow-On Agreement, [***] during the Negotiation Period. If, with respect to any Follow-On Compound that was the subject of the Follow-On Agreement previously discussed by the Parties, after the end of the Negotiation Period and prior to Ionis entering into a Follow-On Agreement with a Third Party, [***] regarding the Follow-On Compound, Ionis' obligations and Biogen's rights under Section 2.1.2(a) and this Section 2.1.2(b) will reset and Ionis will provide Biogen with a new Follow-On Negotiation Notice.

(c) Any Follow-On Agreement entered into by Ionis with a Third Party in accordance with Section 2.1.2(b) will be a Permitted License to the extent related to the Follow-On Compound.

(d) Notwithstanding anything to the contrary in this Agreement, until [***], Ionis will provide to Biogen a Follow-On Negotiation Notice for each [***] pursuant to this Section 2.1.2, *unless* Ionis enters into a Follow-On Agreement with a Third Party pursuant to this Section 2.1.2 and the terms of such agreement do not permit Ionis to grant Biogen rights with respect to the applicable Follow-On Compound.

2.1.3. Limitations and Exceptions to Exclusivity Covenants.

(a) Notwithstanding anything to the contrary in this Agreement, Ionis' practice of the following will not violate Section 2.1.1:

(i) The discovery, research, development, manufacture or commercialization of Gene-Editing Products or messenger RNA;

(ii) Any activities pursuant to the Prior Agreements as in effect on the Effective Date;

(iii) The granting of, or performance of obligations under, Permitted Licenses;

(iv) The discovery, research, development, manufacture or commercialization of one or more Pre-Existing Competitive Products in accordance with Section 12.5.1; and

(v) The limited continuation of discovery, research, development, manufacture or commercialization of Acquired Competitive Product(s) as permitted under Section 12.5.2(a) and in accordance with Section 12.5.2(a) and Section 12.6.

(b) Notwithstanding anything to the contrary in this Agreement, Biogen's practice of the following will not violate Section 2.1.1:

(i) The discovery, research, development, manufacture or commercialization of Gene-Editing Products or messenger RNA;

(ii) The discovery, research, development, manufacture or commercialization of one or more Pre-Existing Competitive Products in accordance with Section 12.5.1; and

(iii) The limited continuation of discovery, research, development, manufacture or commercialization of Acquired Competitive Product(s) as permitted under Section 12.5.2(a) and in accordance with Section 12.5.2(a) and Section 12.6.

2.2. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes a Collaboration Target in the Field with the intent of treating a neurological or neuromuscular disease. Ionis and Biogen are subject to exclusivity obligations under Section 2.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to the RNA that encodes a gene that is *not* a Collaboration Target (or with respect to Ionis, that is *not* a High Interest Target, to the extent Section 2.1.1(a) still applies) for any indication, even if such products are designed to treat a neurological or neuromuscular disease.

2.3. **Consequences of Ionis-Discovered High Interest Target Development Candidate**. Ionis may work for itself (but not for the benefit of a Third Party) to conduct drug discovery activities to identify a High Interest Target Development Candidate, including drug screening, identification, characterization, optimization, and, subject to Section 1.5.6, research collaborations with academic or non-profit institutions. Ionis will notify the Neurology JSC of any such activities and keep the Neurology JSC reasonably apprised of the status thereof. If Ionis designates a High Interest Target Development Candidate targeting a particular High Interest Target (such target, an "***Accelerated Target***"), Ionis may notify Biogen in writing regarding Ionis' designation of such High Interest Target Development Candidate and will provide Biogen the applicable Development Candidate Data Package; *provided*, *however*, that unless otherwise agreed to by Biogen in writing, Ionis may not provide Biogen more than [***] in any rolling [***] month period. Within [***] following Biogen's receipt of the applicable Development Candidate Data Package, Biogen may (a) if Biogen has not designated all three Collaboration Targets, designate the Accelerated Target as a Collaboration Target, or (b) if Biogen has designated all three Collaboration Targets, substitute-out a Collaboration Target in exchange for substituting-in the Accelerated Target as a Collaboration Target (pursuant to the procedures set forth in Section 1.4.2). If Biogen does not, within such [***] period, designate the Accelerated Target as a Collaboration Target pursuant to clause (a) or (b) of this Section 2.3, then, such Accelerated Target will no longer be a High Interest Target and Ionis may work independently or with any of its Affiliates or any Third Party with respect to the discovery, research, development, and commercialization of ASOs (or any other compounds) targeting such Accelerated Target.

ARTICLE 3
EXCLUSIVE OPTION

3.1. Option.

3.1.1. Advance Data Disclosure. On or about 90 days before the date on which Ionis estimates that the database will be locked for the first PoC Trial for a particular Collaboration Program that is being conducted by Ionis (each an "***Estimated Lock Date***"), Ionis will provide Biogen with a written notice of such Estimated Lock Date. If Biogen provides written notice to Ionis [***] after Biogen's receipt of the notice regarding the Estimated Lock Date that Biogen has a good faith intention to exercise the Option for the applicable Collaboration Program under Section 3.1.3, then as soon as reasonably practicable after Ionis receives such notice from Biogen, Ionis will provide Biogen with an early preview of the information to be included in the [***] for the applicable Collaboration Program to the extent then in Ionis' possession and not already provided to Biogen, to assist Biogen with its decision of whether to exercise the Option. Within 15 Business Days after Biogen's receipt of such data, Biogen will provide Ionis with a [***] notice of whether Biogen still intends to exercise the Option for the applicable Collaboration Program; *provided*, *however*, that Biogen's failure to do so will not be deemed a breach of this Agreement.

3.1.2. PoC Trial Completion Notice. On a Collaboration Program-by-Collaboration Program basis where Ionis conducts the first PoC Trial, Ionis will provide to Biogen or its designated Affiliate (a) a copy of the most recent Investigator's Brochure for the applicable Product, (b) written notice from Ionis regarding completion of the first PoC Trial, and (c) the PoC Data Package for such Collaboration Program, to the extent not already provided to Biogen under Section 3.1.1 above (such notice and package, a "***PoC Trial Completion Notice***") promptly, and in any event within [***] days after database lock for the PoC Trial for such Collaboration Program. Within 15 days of receipt of the PoC Trial Completion Notice, Biogen or an Affiliate will notify Ionis of any omissions or deficiencies that Biogen or its Affiliate believes in good faith cause the PoC Trial Completion Notice to be incomplete ("***Deficiency Notice***"). Ionis will promptly, and in any event within 15 days of receipt of the Deficiency Notice, resubmit a complete PoC Trial Completion Notice to Biogen or its designated Affiliate, including any information required to be included in the PoC Data Package that Biogen identified in the Deficiency Notice. If the Parties do not agree as to whether the PoC Trial Completion Notice is complete, the matter will be referred to the Executives for resolution. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete PoC Trial Completion Notice.

3.1.3. Option and Option Deadline. On a Collaboration Program-by-Collaboration Program basis, Ionis hereby grants to Biogen and its Affiliates an exclusive option to obtain the license set forth in Section 4.1.1 with respect to such Collaboration Program (each an "***Option***"). Each Option will be available to Biogen and its Affiliates until 5:00 pm (Eastern Time) on the [***] following Biogen's receipt of a complete PoC Trial Completion Notice for the applicable Collaboration Program (the "***Option Deadline***"); *provided*, *however*, that if Biogen determines that an HSR Filing is required to be made under the HSR Act to exercise the Option and notifies Ionis of such determination within [***] after Biogen's receipt of the complete PoC Trial Completion Notice, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the Option Deadline will be extended until 5:00 pm (Eastern Time) on the fifth Business Day after the HSR Clearance Date. If, by the Option Deadline, Biogen or its designated Affiliate (a) notifies Ionis in writing that it wishes to exercise the applicable Option, and (b) pays to Ionis the license fee set forth in Section 6.3, Ionis will, and hereby does, grant to Biogen or its designated Affiliate the license set forth in Section 4.1.1. If, by the Option Deadline, Biogen or its designated Affiliate has not both (y) provided Ionis a written notice stating that Biogen is exercising its Option, and (z) paid Ionis the license fee in accordance with Section 6.3, then Biogen's Option for the applicable Collaboration Program will expire and Sections 10.4.2(a), 10.4.2(b), 10.4.2(c) and 10.4.2(e) will apply.

3.1.4. HSR Compliance.

(a) **HSR Filing**. If Biogen notifies Ionis pursuant to Section 3.1.3 that an HSR Filing is required to exercise an Option under this Agreement, then each of Biogen and Ionis will, within five Business Days after such notice from Biogen (or such later time as may be agreed to in writing by the Parties), file with the United States Federal Trade Commission ("***FTC***") and the Antitrust Division of the United States Department of Justice ("***DOJ***"), any HSR Filing required with respect to the transactions contemplated hereby. The Parties will cooperate with one another to the extent necessary in the preparation of any such HSR Filing. Each Party will be responsible for its own costs and expenses (other than filing fees, which Biogen will pay) associated with any HSR Filing.

(b) **HSR Clearance**. In furtherance of obtaining HSR Clearance for an HSR Filing filed under Section 3.1.4(a), Ionis and Biogen will use their respective commercially reasonable efforts to resolve as promptly as practicable any objections that may be asserted with respect to this Agreement or the transactions contemplated by this Agreement under any antitrust, competition or trade regulatory law. In connection with obtaining such HSR Clearance from the FTC, the DOJ or any other governmental authority, Biogen and its Affiliates will not be required to (i) sell, divest (including through a license or a reversion of licensed or assigned rights), hold separate, transfer or dispose of any assets, operations, rights, product lines, businesses or interest therein of Biogen or any of its Affiliates (or consent to any of the foregoing actions); or (ii) litigate or otherwise formally oppose any determination (whether judicial or administrative in nature) by a governmental authority seeking to impose any of the restrictions referenced in clause (i) above.

3.2. Restrictions on Ionis' Right to Grant Diagnostic Rights; Right to Negotiate Diagnostic Rights.

3.2.1. On a Product-by-Product basis, Ionis hereby grants to Biogen and its Affiliates an option (the "Diagnostic Option") to negotiate during the Full Royalty Period the terms of an agreement under which [***]. The Diagnostic Option will be available to Biogen and its Affiliates until the expiration of the [***].

3.2.2. During the [***], Ionis (a) has the right to [***], and (b) will not [***].

3.2.3. If, during the [***], Ionis grants any Third Party a [***], then Ionis will promptly notify Biogen of such [***] and will offer Biogen a [***].

ARTICLE 4
LICENSE GRANTS

4.1. License Grants to Biogen.

4.1.1. Development and Commercialization Licenses. Subject to the terms and conditions of this Agreement, on a Collaboration Program-by-Collaboration Program basis, effective upon the License Effective Date for a particular Collaboration Program in accordance with this Agreement, Ionis grants to Biogen a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products under such Collaboration Program in the Field.

4.1.2. Sublicense Rights; CMO Licenses.

(a) Subject to the terms and conditions of this Agreement, and on a Collaboration Program-by-Collaboration Program basis, Biogen will have the right to grant sublicenses under the licenses granted under Section 4.1.1 above and Section 4.3.1(b) below:

(i) under the Ionis Core Technology Patents, Ionis Product-Specific Patents and Ionis Know-How, to an Affiliate of Biogen or a Third Party; and

(ii) under the Ionis Manufacturing and Analytical Patents and Ionis Manufacturing and Analytical Know-How, solely to (A) [***] or (B) [***];

provided that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within [***] days of first learning of any breach of such sublicense terms, Biogen fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.1.2, which failure would cause an adverse effect on Ionis, then Biogen hereby grants Ionis the right to enforce such sublicense terms on Biogen's behalf and will cooperate with Ionis (which cooperation will be at Biogen's sole expense and will include, Biogen joining any action before a court or administrative body filed by Ionis against such Sublicensee if and to the extent necessary for Ionis to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen will provide Ionis with a true and complete copy of any sublicense granted pursuant to this Section 4.1.2 within [***] days after the execution thereof.

(b) In connection with Biogen's selecting and engaging one or more CMOs to supply Clinical Supplies under Section 4.3.1(b) or after the License Effective Date with respect to a Collaboration Program, or supply API and Finished Drug Product for Commercialization, Ionis will, at Biogen's option, either (i) grant a license from Ionis to [***] under the [***] to the extent necessary for [***], which Ionis agrees it will grant to [***], or, (ii) permit Biogen to grant a sublicense from Biogen to [***]. Each such manufacturing agreement between Biogen and a CMO will contain [***]. Biogen will provide Ionis with a true and complete copy of any manufacturing agreement entered into with a CMO within [***] days after the execution thereof. Notwithstanding the foregoing, if Ionis fails to comply with the terms of this Section 4.1.2(b) and does not cure such failure within 90 days after written notice from Biogen specifying the details of any such failure, then Biogen will have the right to [***].

(c) **Effect of Termination on Sublicenses**.

(i) If this Agreement terminates for any reason, then any Sublicensee of Biogen will, from the effective date of such termination, automatically become a direct licensee of Ionis with respect to the rights sublicensed to the Sublicensee by Biogen; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by Biogen, and (iii) such Sublicensee agrees to pay directly to Ionis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Biogen. Biogen agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Ionis and if requested, the Sublicensee.

(ii) If this Agreement terminates for any reason, then any Sublicensee of Biogen under Section 4.3.1(c) and any Sublicensee of Ionis under Section 4.5.2 will, from the effective date of such termination, automatically become a direct licensee of the applicable Party with respect to the rights sublicensed to the Sublicensee by the other Party hereunder; *so long as* (A) such Sublicensee is not in breach of its sublicense agreement, (B) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to such Sublicensee, and (C) with respect to Sublicensees of Ionis, such Sublicensee agrees to pay directly to Biogen such Sublicensee's payments under Section 4.4.2 to the extent applicable to the rights sublicensed to it by Ionis. Each Party agrees that it will confirm clause (A) of this Section 4.1.2(c)(ii) in writing at the request and for the benefit of the other Party and if requested, the Sublicensee.

4.1.3. **No Implied Licenses**. All rights in and to the Licensed Technology not expressly licensed to Biogen under this Agreement are hereby retained by Ionis or its Affiliates. All rights in and to Biogen Technology not expressly licensed or assigned to Ionis under this Agreement, are hereby retained by Biogen or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

4.1.4. **License Conditions; Limitations**. Subject to Section 6.8, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are subject to and limited by (a) any applicable Third Party Obligations, (b) the Prior Agreements, and (c) the Ionis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Biogen in writing (or via electronic data room) prior to Biogen's exercise of the applicable Option. Ionis will disclose to Biogen any Third Party Obligations Ionis believes apply to applicable Products each time Ionis provides Biogen with (x) the [***]; and (z) the [***], and Biogen will have the right to elect to exclude any Third Party Patent Rights and Know-How to which such Third Party Obligations apply by providing Ionis written notice prior to the License Effective Date for a particular Collaboration Program. If, prior to the License Effective Date with respect to a Collaboration Program, Biogen provides Ionis with such a written notice to exclude certain Third Party Patent Rights and Know-How, such Third Party Patent Rights and Know-How will not be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement. If Biogen does not provide Ionis with such a written notice to exclude such Third Party Patent Rights and Know-How prior to the License Effective Date for such Collaboration Program, then such Third Party Patent Rights and Know-How (and any Third Party Obligations to the extent applicable to Products) will be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement.

4.1.5. **Trademarks for Products**. If Biogen exercises an Option for a Collaboration Program hereunder, to the extent that (a) Ionis owns any trademark(s) specific to a Product under such Collaboration Program, which trademark(s) Ionis used prior to the License Effective Date for such Collaboration Program, and (b) Biogen reasonably believes such trademark(s) would be necessary or useful for the marketing and sale of the applicable Product, then upon Biogen's request and at Biogen's sole cost and expense relating to such assignment, Ionis will assign its rights and title to such trademark(s) to Biogen or one or more designated Affiliates sufficiently in advance of the First Commercial Sale of the Product to enable Biogen or its Affiliates to offer such Product for sale under such trademark(s). Other than trademarks owned by Ionis prior to such License Effective Date, Biogen or its designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining, and, subject to Section 10.4, will be the exclusive owner of, all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products.

4.2. **Assignment of Ionis Product-Specific Patents; Grant Back to Ionis**.

4.2.1. After Biogen has obtained the license for a particular Collaboration Program under Section 4.1.1 and following review and consideration by the Joint Patent Committee, Ionis will assign to Biogen or one or more of its designated Affiliates, Ionis' ownership interest in (a) all Ionis Product-Specific Patents related to such Collaboration Program in the Field that are owned by Ionis (whether solely owned or jointly owned with one or more Third Parties), and (b) any Jointly-Owned Program Patents Covering Products related to such Collaboration Program, and thereafter, subject to Section 7.2.4, Ionis will have no further right to control any aspect of the Prosecution and Maintenance of such Ionis Product-Specific Patents and such Jointly-Owned Program Patents. The assignment of Patent Rights assigned in this Section 4.2.1 will occur within [***] days of Biogen obtaining the applicable license under Section 4.1.1.

4.2.2. Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), Biogen grants to Ionis a worldwide, sublicensable license under any Ionis Product-Specific Patents and Jointly-Owned Program Patents assigned to Biogen under Section 4.2.1 [***], (b) to conduct activities under other Collaboration Program Research Plans and (c) to [***] to the extent permitted by this Agreement.

4.3. Enabling Licenses.

4.3.1. Licenses During the Option Period.

(a) Subject to the terms and conditions of this Agreement, Ionis hereby grants Biogen a worldwide, non-exclusive, sublicensable (but only as permitted in Section 4.3.1(c) below), royalty-free license under the Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patents solely to conduct Manufacturing and drug substance process and formulation development activities with respect to any Compound or Product under any Collaboration Program during the Option Period for such Collaboration Program; *provided* that the grant of rights pursuant to this Section 4.3.1(a) shall not include the right to Manufacture any Compound or Product for Commercialization purposes.

(b) Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), [***] for Biogen to conduct (i) Manufacturing of Compounds or Products under any Collaboration Program or (ii) any Biogen Activities that are Development activities with respect to any Collaboration Program in accordance with this Agreement, in each case ((i) and (ii) during the Option Period), Ionis hereby grants Biogen a worldwide, non-exclusive, sublicensable (but only as permitted in Section 4.1.2 above), royalty-free license under the Licensed Technology. Biogen will [***] arising under any Third Party agreement as a result of granting Biogen the license under this Section 4.3.1(b) within [***] days after Biogen's receipt of the applicable invoice. For clarity, the grant of rights pursuant to this Section 4.3.1(b) shall not include the right to Commercialize any such Product or to Manufacture any such Product for Commercialization.

(c) **Biogen's Right to Sublicense**. Biogen will have the right to grant sublicenses under the license granted under Section 4.3.1(a) above (i) in the case of a sublicense of Biogen's right to conduct Manufacturing of Compounds or Products, other than any sublicense to conduct manufacturing in support of drug substance process and formulation development activities, solely to (A) [***] or (B) [***] and (ii) in the case of a sublicense of Biogen's right to conduct drug substance process and formulation development activities, including manufacturing in support thereof, to any [***]. If, within [***] days after first learning of any breach of such sublicense terms by any such Sublicensee, Biogen fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.3.1(c), which failure would cause an adverse effect on Ionis, then Biogen hereby grants Ionis the right to enforce such sublicense terms on Biogen's behalf and will cooperate with Ionis (which cooperation will be at Biogen's sole expense and will include Biogen joining any action before a court or administrative body filed by Ionis against such Sublicensee if and to the extent necessary to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen will provide Ionis with a true and complete copy of any sublicense granted to a Third Party pursuant to this Section 4.3.1(c) within [***] days after the execution thereof. For the avoidance of doubt, Section 4.1.2(c)(ii) shall apply to sublicenses granted under this Section 4.3.1(c).

4.3.2. **Enabling Licenses to Biogen**.

(a) Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), Ionis hereby grants Biogen an irrevocable, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.2(c)) license under any Ionis Program Technology Controlled by Ionis or its Affiliates at any time during the Agreement Term, to research, develop, manufacture, have manufactured and commercialize (i) a product that is being developed or commercialized by Biogen, its Affiliates or its Sublicensee under any Ionis/Biogen Additional Agreement or this Agreement, (ii) products that do not include an Oligonucleotide as an active pharmaceutical ingredient, and (iii) Gene-Editing Products. The licenses in clause (ii) and clause (iii) of this Section 4.3.2(a) and in Section 4.3.2(b) are royalty-free; *except* that if a product that is not a Product being sold by Biogen, its Affiliates or Sublicensees is Covered by a Target Related Ionis Program Claim in a country, then on a country-by-country basis Biogen will pay to Ionis a royalty equal to [***]% of Net Sales of such product sold by Biogen, its Affiliates or Sublicensees so long as such product is Covered by such Target Related Ionis Program Claim in such country. A "***Target Related Ionis Program Claim***" means a Valid Claim that (A) is within an Ionis Program Patent that is solely owned by Ionis, (B) Covers a product being sold by Biogen, its Affiliates or Sublicensee and (C) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

(b) Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), Ionis hereby grants Biogen an irrevocable, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.2(c)) license under any Ionis Program Know-How and any Enabled Core Program Patents, in each case, Controlled by Ionis or its Affiliates at any time during the Agreement Term, to research, develop, manufacture, have manufactured and commercialize any product, including products that include an Oligonucleotide as an active pharmaceutical ingredient.

(c) Biogen may share any raw data included in the Ionis Program Know-How licensed to Biogen under Sections 4.3.2(a) and 4.3.2(b) for use in connection with the performance of its obligations or exercise of its rights under this Agreement or any Ionis/Biogen Additional Agreement, and Biogen may share the conclusions drawn from or based on the review of such raw data with any Third Party. Other than in accordance with the foregoing sentence, Biogen shall not share with any Third Party that is not an academic or non-profit institution or a contractor acting on Biogen's behalf any raw data included in such Ionis Program Know-How or any tangible embodiments thereof to the extent such raw data and tangible embodiments constitute Confidential Information of Ionis.

4.3.3. Enabling Licenses to Ionis.

(a) Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), Biogen hereby grants Ionis an irrevocable, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.3(c)) license under any Biogen Program Technology Controlled by Biogen or its Affiliates at any time during the Agreement Term other than any Biogen Results licensed to Ionis under Section 4.4.1, to research, develop, manufacture, have manufactured and commercialize (a) products that include an Oligonucleotide as an active pharmaceutical ingredient (other than products that include an Oligonucleotide that is designed to bind to the RNA that encodes the same target as a product that is being developed or commercialized by Biogen, its Affiliates or Sublicensee pursuant to an Option or exclusive license granted from Ionis under this Agreement or any Ionis/Biogen Additional Agreement) and (b) Gene-Editing Products. The licenses set forth in this Section 4.3.3(a) and in Section 4.3.3(b) are royalty-free; *except* that if a product that is not a Discontinued Product being sold by Ionis, its Affiliates or Sublicensee is Covered by a Target Related Biogen Program Claim in a country, then on a country-by-country basis Ionis will pay to Biogen a royalty equal to [***]% of net sales of such product sold by Ionis, its Affiliates or Sublicensees, for so long as such product is Covered by such Target Related Biogen Program Claim in such country. For the purpose of the foregoing royalty calculation, "net sales" will be calculated [***]. The provisions of Sections 6.9, 6.10, 6.11 and 6.12 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 4.3.3(a). A "***Target Related Biogen Program Claim***" means a Valid Claim that (i) is within a Biogen Program Patent that is solely owned by Biogen, (ii) Covers a product being sold by Ionis, its Affiliates or Sublicensee and (iii) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

(b) Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), Biogen hereby grants Ionis an irrevocable, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.3(c)) license under any Biogen Program Know-How and any Enabled Core Program Patents, in each case, Controlled by Biogen or its Affiliates at any time during the Agreement Term, to research, develop, manufacture, have manufactured and commercialize any product, including products that do not include an Oligonucleotide as an active pharmaceutical ingredient.

(c) Ionis may share any raw data included in the Biogen Program Know-How licensed to Ionis under Sections 4.3.3(a) and 4.3.3(b) for use in the performance of its obligations or exercise of its rights under this Agreement or any Ionis/Biogen Additional Agreement, and Ionis may share the conclusions drawn from or based on the review of such raw data with any Third Party. Other than in accordance with the foregoing sentence, Ionis shall not share with any Third Party that is not an academic or non-profit institution or a contractor acting on Biogen's behalf any raw data included in such Biogen Program Know-How or any tangible embodiments thereof to the extent such raw data and tangible embodiments constitute Confidential Information of Biogen.

4.4. Licenses to Ionis for Biogen Results.

4.4.1. Subject to the terms and conditions of this Agreement, Biogen hereby grants Ionis an irrevocable, worldwide, non-exclusive, sublicensable license under the Biogen Results Controlled by Biogen or its Affiliate at any time during the Agreement Term, to research, develop, make, have made, import, export, use and sell (a) products that include an Oligonucleotide as an active pharmaceutical ingredient (other than products that include an Oligonucleotide that is designed to bind to the RNA that encodes the same target as a product that is being developed or commercialized by the Parties pursuant to an Option or exclusive license granted from Ionis under this Agreement or the Ionis/Biogen Additional Agreements) and (b) Gene-Editing Products.

4.4.2. The license granted in Section 4.4.1 shall be [***] with respect to any [***]. Such license will be [***] with respect to any [***] as follows: on a country-by-country, product-by-product and Biogen Manufacturing Program Patent-by-Biogen Manufacturing Program Patent basis, Ionis will pay to Biogen [***]. If one or more Biogen Manufacturing Program Patents expires, is invalidated or otherwise ceases to Cover a product bearing royalties as set forth above, the applicable royalty rate under this Section 4.4.2 shall be recalculated to reflect the number of Biogen Manufacturing Program Patents then-Covering such product. For the purpose of the foregoing royalty calculation, [***] will be calculated as follows: [***]. If Ionis grants a sublicense under this Section 4.4 to an entity that is an Ionis Affiliate at the time Ionis grants such sublicense, such applicable sublicense will [***]. The provisions of Section 6.9, Section 6.10, Section 6.11 and Section 6.12 shall apply, mutatis mutandis, to any royalty payments by Ionis to Biogen under this Section 4.4.2.

4.5. **Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis.**

4.5.1. If requested by Ionis, Biogen shall grant a direct, [***] license under the Biogen Results to [***] on the same terms as set forth in Section 4.4 with respect to sublicenses of Ionis. Biogen shall endeavor in good faith to grant such license within [***] days of any such request by Ionis.

4.5.2. Ionis will have the right to grant sublicenses under the licenses granted under Section 4.4, provided that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within [***] days after first learning of any breach of such sublicense terms, Ionis fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.5.2, which failure would cause an adverse effect on Biogen, Ionis hereby grants Biogen the right to enforce such sublicense terms on Ionis' behalf and will cooperate with Biogen (which cooperation will be at Ionis' sole expense and will include, Ionis joining any action before a court or administrative body filed by Biogen against such Sublicensee if and to the extent necessary for Biogen to have legal standing before such court or administrative body) in connection with enforcing such terms. Ionis will provide Biogen with a true and complete copy of any sublicense granted pursuant to this Section 4.5.2 within [***] days after the execution thereof.

4.6. **Ownership of and Assistance with Regulatory Filings**. If requested by Biogen, Ionis' and Biogen's regulatory teams will meet and begin to prepare a plan, which plan will be complete no later than [***] prior to such anticipated filing date, for drafting and reviewing the sections of the NDA and MAA for the applicable Product (including establishing responsibilities for drafting and reviewing common technical document ("***CTD***") modules, authorship, plan activity timelines and associated costs and expenses) to ensure a smooth transition to Biogen, accelerate CTD completion and facilitate rapid NDA and MAA filing. The Parties will act in good faith and mutually agree upon each such plan; *provided*, *however*, that after exercising an Option for the applicable Collaboration Program, Biogen will have final decision-making authority with respect to the [***]. Once such plan is complete, each Party will use Commercially Reasonable Efforts to execute their respective tasks and responsibilities under such plan in the time frames set forth in such plan. After the License Effective Date for a particular Collaboration Program, if Biogen requests, Ionis will assist Biogen in preparing regulatory filings for the Product, under terms negotiated in good faith between Ionis and Biogen, including payment for Ionis' time at Ionis' then applicable FTE Rate plus any reasonable out of pocket expenses incurred by Ionis in providing such assistance.

4.7. Subcontracting.

4.7.1. Subject to the terms of this Section 4.7, each Party will have the right to engage Third Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement. Each Party will be responsible for any income or non-income taxes that arise as a result of such Party's use of any Third Party subcontractors hereunder, including payroll, income, withholding (including from subsequent payments) sales and use, VAT, customs, duties excise or property taxes, and such taxes will not be reimbursable expenditures.

4.7.2. Ionis agrees that, where Biogen wishes to (sub)contract with a Third Party with respect to any of the rights granted under Section 4.3.1(a), Ionis shall, within [***] days of any request by Biogen, provide Biogen with a letter of authorization as necessary for Biogen to be able to contract with such Third Party in accordance with the terms of this Agreement. Biogen will ensure that any Third Party (sub)contractors Biogen uses to conduct the process development or manufacturing activities contemplated by Section 4.3.1(a) will be obligated to assign to Biogen all right, title and interest in and to any inventions developed by such (sub)contractors in the performance of such activities. Biogen will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits, diminishes or encumbers the rights granted to Ionis under the Manufacturing Process Development Terms. In addition, after the Amendment Date, Biogen will use reasonable efforts to include, in any agreement with a (sub)contractor that has substantial material obligations related to the Development, Manufacture or Commercialization of a Product, provisions requiring that, in the event the applicable Option with respect to a Collaboration Program of which such Products are the subject is terminated, expires unexercised or this Agreement is terminated, such (sub)contractor would enter into an agreement with Ionis with respect to such Product that is substantially similar to such (sub)contractor's agreement with Biogen and would reasonably cooperate with Ionis to facilitate the transition of such Product to Ionis following such termination or expiration of such Option, including the transfer to Ionis of data and information in such (sub)contractor's possession related to the Product.

4.8. Technology Transfer after the License Effective Date. On a Collaboration Program-by-Collaboration Program basis, Ionis will promptly, but no later than [***] days after the License Effective Date for a Collaboration Program hereunder, deliver to Biogen or one or more designated Affiliates:

4.8.1. **Ionis Know-How**. All Ionis Know-How in Ionis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 4.1.1 and Section 10.4.1(b), and Ionis will and does hereby assign to Biogen all of Ionis' right, title and interest in and to the IND for the applicable Development Candidate, together with all Regulatory Materials (including drafts) that relate to the applicable Development Candidate and any orphan drug designations with respect to such Development Candidate, to the extent applicable; *provided that*, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Ionis shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products other than the Development Candidate, *provided, further that* such excerpts or portions shall not include (i) any non-public data or information, in each case, related solely to the applicable Development Candidate, or (ii) any Confidential Information of Biogen, and (y) for clarity, such assignment of Ionis' right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Ionis intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence that are not in the public domain and do not relate to Ionis' antisense oligonucleotide chemistry platform, Ionis shall, at least [***] days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Biogen of such intent and provide to Biogen a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Biogen with respect to such proposed excerpt or portion prior to submission thereof. To assist with the transfer of such Ionis Know-How, Ionis will make its personnel reasonably available to Biogen during normal business hours for up to [***] ([***]) of Ionis' time for each Collaboration Program to transfer such Ionis Know-How under this Section 4.8.1. Thereafter, if requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, which Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable Ionis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance.

4.8.2. **Ionis Manufacturing and Analytical Know-How**. Solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf to Manufacture API in Biogen's own or an Affiliate's manufacturing facility, all Ionis Manufacturing and Analytical Know-How in Ionis' Control relating to applicable Products, that is necessary for the exercise by Biogen, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1. Upon Biogen's request, subject to Section 4.1.2, Ionis will provide up to [***] for [***] ([***]) of its time for each Collaboration Program to transfer such Ionis Manufacturing and Analytical Know-How under this Section 4.8.2 to any Third Party Manufacturing API, Clinical Supplies or Finished Drug Product on Biogen's behalf solely to Manufacture API, Clinical Supplies or Finished Drug Product in accordance with the terms of this Agreement. Thereafter, if requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, for which assistance Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable Ionis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance.

4.8.3. **API and Product**. Upon Biogen's written request, Ionis will sell to Biogen any bulk API, Clinical Supplies and Finished Drug Product, and any intermediates, impurity markers and reference standards relating to a Product in Ionis' possession at the time of the License Effective Date for the applicable Collaboration Program, at a price equal to [***].

4.8.4. **Trial Master File**. Upon Biogen's written request, Ionis will provide to Biogen or its designated Affiliate a copy of Ionis' trial master file for such Collaboration Program (such trial master file, the "***Trial Master File***") promptly, and in any event within [***] days after Ionis' receipt of such written request. Within [***] days after receipt of the Trial Master File, Biogen or an Affiliate may notify Ionis of any omissions or deficiencies that Biogen or its Affiliate believes in good faith cause the Trial Master File to be incomplete (such notice, a "***Trial Master File Deficiency Notice***"). Ionis will promptly, and in any event within [***] days after receipt of the Trial Master File Deficiency Notice, resubmit a complete Trial Master File to Biogen or its designated Affiliate, including any information required to be included in a Trial Master File that Biogen requests be included in the Trial Master File. If the Parties do not agree as to whether the Trial Master File is complete, the matter will be referred to the Executives for resolution. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete Trial Master File. If Ionis is the Commercializing Party of a Discontinued Product, this Section 4.8.4 will apply to such Discontinued Product *mutatis mutandis* such that Biogen will transfer to Ionis Biogen's trial master file for such Discontinued Product.

4.8.5. **Results**.

(a) Each Party shall share with the other Party on an Annual basis (preferably at in-person meetings) the results of such Party's manufacturing process development activities, including all data, the identity and location of vendors, information and results received from vendors, and planned additional work, (i) in the case of Biogen, to the extent arising under the Manufacturing Process Development Terms (all Know-How and Patent Rights within the foregoing, the "***Biogen Results***") and (ii) in the case of Ionis, to the extent arising under or otherwise subject to a disclosure obligation of Ionis under this Agreement (all Know-How and Patent Rights within the foregoing, the "***Ionis Results***" and, collectively with the Biogen Results, the "***Results***"). All intellectual property matters with respect to the Results, including any Patent Rights therein, will be governed by the intellectual property provisions of this Agreement, and the Know-How and Patent Rights included in the Ionis Results shall constitute Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patent Rights, respectively, under this Agreement. If requested by either Party, Biogen and Ionis will establish a manufacturing committee to facilitate the exchange of Results between the Parties. For clarity, Biogen shall have the right, in its sole discretion, to determine whether to seek patent protection for any Biogen Results that are not jointly owned with Ionis, and Biogen shall control and be responsible for all aspects of the Prosecution and Maintenance of any Patent Right within such Biogen Results (each, a "***Biogen Manufacturing Program Patent***") in accordance with Section 7.2.2(c) of this Agreement. Biogen shall notify Ionis within [***] days if Biogen files a patent application Controlled by Biogen or its Affiliates that claims any Biogen Results and shall provide Ionis with a copy of such patent application. Ionis will have no obligation to incorporate any Biogen Results into Ionis' manufacturing process.

(b) For clarity, the Manufacturing Process Development Terms, and not the enabling licenses set forth in Section 4.3.2 and Section 4.3.3, shall govern with respect to all Results.

ARTICLE 5
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. **Biogen Diligence**. Following the License Effective Date with respect to a Collaboration Program, Biogen will be solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of the applicable Products; and Biogen will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product from each Collaboration Program for which an Option has been exercised. If Biogen exercises an Option for a Product involving a Collaboration Target added in accordance with Section 1.3.2 that is associated with [***], Biogen will use Commercially Reasonable Efforts to Develop such Product for use in a [***].

5.1.1. **Specific Performance Milestone Events**. Without limiting any of the foregoing, following the License Effective Date for a Collaboration Program, Biogen will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.1.1, as such schedule may be updated from time to time in accordance with Section 1.5.2(a) ("***Specific Performance Milestone Events***") for a Product under such Collaboration Program on the timeline set forth in SCHEDULE 5.1.1; *provided*, *however*, [***].

5.1.2. **Integrated Development Plan**. On a Product-by-Product basis, Biogen will prepare a Development and global integrated Product plan outlining key aspects of the Development of each Product through Approval as well as key aspects of worldwide regulatory strategy, market launch, and Commercialization, including Product sales and forecasts (each, an "***Integrated Development Plan***" or "***IDP***"). Biogen will prepare the IDP no later than [***] after the License Effective Date for a Collaboration Program, and the IDP will contain information consistent in scope and content with the information Biogen's senior management uses for internal decision-making for such Product. Once Biogen has prepared such plans, Biogen will update the IDP consistent with Biogen's standard practice and provide such updates to Ionis [***]. Biogen and Ionis will meet [***] basis to discuss the draft of the IDP and Biogen will consider, in good faith, any proposals and comments made by Ionis for incorporation in the final IDP. Notwithstanding the foregoing, Biogen's obligations to provide Ionis with information or reports with respect to a Product under this Section 5.1.2 will terminate if [***].

5.1.3. **Investigator's Brochure**. After the License Effective Date with respect to a Collaboration Program, Ionis will provide to Biogen an up-to-date version of the Investigator's Brochure for the applicable Product. After the License Effective Date with respect to a Collaboration Program, Biogen will keep Ionis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions of the Investigator's Brochure for each Product to Ionis [***] and when Development of such Product results in any substantive change to the safety or risk to the Product. Biogen's obligations under this Section 5.1.3 will terminate with respect to a Product if [***].

5.1.4. **Regulatory Matters**.

(a) **IND-Holder**. Subject to this Section 5.1.4, Ionis will be the IND-holder and will be responsible for all communications with Regulatory Authorities regarding the Collaboration Programs prior to the applicable License Effective Date. Biogen will be the IND-holder and holder of any orphan drug designation after the applicable License Effective Date for each Collaboration Program in accordance with Section 3.1.3, and, except as otherwise provided in this Section 5.1.4, shall thereafter have sole decision-making authority with respect to the matters set forth in this Section 5.1.4.

(b) **Participation in Regulatory Meetings**. With respect to a Collaboration Program, each Party will promptly provide the other Party with as much advance written notice as practicable of any meetings that such first Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product under such Collaboration Program or that directly relate to Ionis' antisense oligonucleotide chemistry platform, and will allow two representatives of the other Party to participate in any such meetings under the direction of such first Party; *provided*, *however*, that, if such first Party is Ionis, Ionis may exclude Biogen from any portion of such meeting that does not pertain to such Product; and *provided*, *further*, that, if such first Party is Biogen, Biogen may exclude Ionis from any portion of such meeting that does not pertain to such Product or to Ionis' antisense oligonucleotide chemistry platform.

(c) **Regulatory Communications**. With respect to a Collaboration Program, each Party will provide the other Party with copies of documents and communications submitted to (including drafts thereof) and received from Regulatory Authorities [***] that materially impact the Development or Commercialization of Products under such Collaboration Program for such other Party's review and comment, and such first Party will consider in good faith including any comments provided by such other Party to such documents and communications. Each Party will promptly notify the other Party upon receipt of any such documents or communications from any Regulatory Authority [***].

(d) **Class Generic Claims**. To the extent Biogen intends to make any claims in a Product label or regulatory filing that are class generic to ASOs, Biogen will provide such claims and regulatory filings to Ionis in advance and will consider in good faith any proposals and comments made by Ionis; *provided*, *however*, that Biogen is not obligated to incorporate such proposals and comments in any such claims and regulatory filings.

5.1.5. **Applicable Laws**. Biogen will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the Laws and regulations of the country and the state and local government wherein such activities are conducted.

5.2. **Global Safety Database; Pharmacovigilance Agreement**.

5.2.1. **Pharmacovigilance Agreement**. As soon as reasonably practicable following designation of a particular Development Candidate, and in any event no later than [***] prior to the date on which Ionis anticipates filing an IND for the associated Product with a Regulatory Authority, the Parties will enter into a Safety Data Exchange Agreement relating to the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with such Product occurring prior to the First Commercial Sale in any country on terms substantially the same as the terms of the Safety Data Exchange Agreement to be entered into by the Parties with respect to adverse events associated with products developed under the Ionis/Biogen Additional Agreements. No later than [***] prior to the date on which Biogen reasonably anticipates that it will exercise an Option, Biogen will so notify Ionis and the pharmacovigilance departments of each of Ionis and Biogen will meet and determine the approach to be taken for the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with the applicable Product occurring after such First Commercial Sale, consistent with the provisions of this Section 5.2. Such approach will be documented in a separate and appropriate written pharmacovigilance agreement between the Parties which will control with respect to the subject matter covered therein (the "***Pharmacovigilance Agreement***"). Such agreement will specify that the owner of the IND for a Product will be the global commercial safety database owner for such Product with primary responsibility for maintaining such database, and that Ionis will be and remain the owner of the Ionis Internal ASO Safety Database with primary responsibility for maintaining such database. Such agreement will also specify that, prior to Biogen's exercise of the applicable Option, Ionis will communicate updates on safety data regarding a Product to Biogen through monthly telephone calls between the drug safety representatives of Biogen and Ionis. Biogen and Ionis will jointly review and discuss safety issues arising under any Collaboration Program that may have implications on any Development Plan for such Collaboration Program. Biogen may suggest actions to address Product safety data or audit findings, and Ionis will consider all such suggestions in good faith. The Pharmacovigilance Agreement will be in accordance with, and will enable the Parties and their Affiliates or licensees or Sublicensees, as applicable, to fulfill, local and international regulatory reporting obligations to Regulatory Authorities and other Applicable Law.

5.2.2. Ionis' Antisense Safety Database.

(a) Ionis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Ionis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Ionis compounds, after the License Effective Date with respect to a Collaboration Program, Biogen will cooperate in connection with populating the Ionis Internal ASO Safety Database. To the extent collected by Biogen and in the form in which Biogen uses/stores such information for its own purposes, Biogen will provide Ionis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products as soon as practicable following the date such information is available to Biogen (but not later than [***] days after Biogen's receipt of such information). In connection with any reported serious adverse event, Biogen will provide Ionis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, Biogen will provide Ionis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within [***] days following the date such information is filed or is available to Biogen, as applicable. Furthermore, Biogen will promptly provide Ionis with any supporting data and answer any follow-up questions reasonably requested by Ionis. All such information disclosed by Biogen to Ionis will be Biogen Confidential Information; *provided*, *however*, that Ionis may disclose any such Biogen Confidential Information to (i) Ionis' other partners pursuant to Section 5.2.2(b) below if such information is regarding class generic properties of ASOs, or (ii) any Third Party, in each case, so long as Ionis does not disclose the identity of a Product or Biogen. Biogen will deliver all such information to Ionis for the Ionis Internal ASO Safety Database to Ionis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Ionis). Biogen will also cause its Affiliates and Sublicensees to comply with this Section 5.2.2(a).

(b) From time to time, Ionis utilizes the information in the Ionis Internal ASO Safety Database to conduct analyses to keep Ionis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Ionis identifies safety or other related issues that may be relevant to a Product (including any potential class-related toxicity), Ionis will promptly (and in no event later than 5 Business Days following identification by Ionis) inform Biogen of such issues and, if requested, provide the data supporting Ionis' conclusions.

5.3. **Research and Manufacturing Records**. Each Party shall maintain, consistent with its then-current internal policies and practices, and cause its employees and subcontractors to maintain, consistent with its internal policies and Applicable Law, for at least ten years, records and laboratory notebooks, inventory, purchase and invoice records and Manufacturing records in each case with respect to the Products in sufficient detail and in a good scientific manner appropriate for (i) inclusion in filings with Regulatory Authorities for such Products, and (ii) obtaining and maintaining intellectual property rights and protections, including Patent Rights for such Products. Such records and laboratory notebooks shall be complete and accurate in all material respects and shall fully and properly reflect all work done, data and developments made, and results achieved. Each Party shall allow the other Party, to the extent necessary for such regulatory or intellectual property protection purposes, to inspect or copy such records, subject to redaction by such Party.

ARTICLE 6
FINANCIAL PROVISIONS

6.1. **Option Fee**. In partial consideration for Biogen's Options hereunder, within five Business Days following the Effective Date, Biogen will pay Ionis an Option fee equal to $10,000,000 for each of the three Collaboration Programs for an aggregate payment of $30,000,000.

6.2. **Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Biogen's Options, on a Collaboration Program-by-Collaboration Program basis, Biogen will pay to Ionis the milestone payments as set forth in TABLE 1 below when a milestone event (each, a "***Pre-Licensing Milestone Event***") listed in TABLE 1 is first achieved by a Product under such Collaboration Program:

TABLE 1

Pre-Licensing Milestone Event	Milestone Event Payment
[***]	$[***]
[***]	[***]
[***]	[***]

On a Collaboration Program-by-Collaboration Program basis, Biogen will pay to Ionis the Milestone Event payments as set forth in TABLE 1 after the applicable Milestone Event is first achieved by a Product under such Collaboration Program, even if Biogen has exercised the applicable Option prior to achievement of the Milestone Event; *provided*, *however*, that if Biogen exercises the Option prior to achievement of the [***] Milestone Event, then the milestone payment for achievement of the [***] Milestone Event will be [***].

6.3. **License Fee**. On an Option-by-Option basis, together with Biogen's written notice to Ionis stating that Biogen is exercising such Option in accordance with this Agreement, Biogen will pay to Ionis a license fee of $[***]; *provided*, *however*, that if Biogen exercises the Option prior to the [***], the license fee for such Option will be [***].

6.4. **Milestone Payments for Achievement of Post-Licensing Milestone Events**. On a Collaboration Program-by-Collaboration Program basis, Biogen will pay to Ionis the milestone payments as set forth in TABLE 2 below when a milestone event (each, a "***Post-Licensing Milestone Event***") listed in TABLE 2 is first achieved by a Product under such Collaboration Program:

TABLE 2

Post-Licensing Milestone Event	Milestone Event Payment
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

On a Collaboration Program-by-Collaboration Program basis, if Biogen exercises an Option prior to the [***], Biogen will pay to Ionis [***] upon the earlier of (a) [***]. For the avoidance of doubt, if such $[***] payment is paid pursuant to clause (b) of the preceding sentence, such payment will be in addition to the amount due upon the occurrence of the corresponding Post-Licensing Milestone Event under TABLE 2 above.

Notwithstanding anything to the contrary in this Section 6.4, if Biogen exercises an Option for a Product involving a Collaboration Target added in accordance with Section 1.3.2, and [***], then Biogen will pay to Ionis (i) [***] of the applicable amount set forth in TABLE 2 above when such Product achieves a Post-Licensing Milestone Event for the first time and (ii) [***] of the applicable amount set forth in TABLE 2 above when such Product achieves a Post-Licensing Milestone Event for the second time.

6.5. **Limitations on Milestone Payments; Exceptions; Notice**.

6.5.1. On a Product-by-Product basis, the $[***] milestone payment is creditable against the first Milestone Event payment for [***]. For example, if the [***] Milestone Event is achieved by a Product in the [***], then the milestone payment for such Milestone Event is [***] the first to occur of the (a) [***] (b) [***] or (c) [***] milestone payments for such Product.

6.5.2. On a Collaboration Program-by-Collaboration Program basis, except as set forth in the second paragraph under TABLE 2 above, each milestone payment set forth in TABLE 1 and TABLE 2 above will be paid only once upon the first achievement of the Milestone Event regardless of how many Products under such Collaboration Program achieve such Milestone Event.

6.5.3. If a particular Milestone Event is not achieved because Development activities transpired such that achievement of such earlier Milestone Event was unnecessary or did not otherwise occur, then upon achievement of a later Milestone Event the Milestone Event payment applicable to such earlier Milestone Event will also be due. For example, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] Milestone Event, both the [***] and [***] Milestone Event payments are due.

6.5.4. Each time a Milestone Event is achieved under this ARTICLE 6, Biogen will send Ionis, or Ionis will send Biogen, as the case may be, a written notice thereof promptly (but no later than [***]) following the date of achievement of such Milestone Event and such payment will be due within [***] of the date such notice was delivered.

6.5.5. For clarity, the provisions of this Agreement (including the milestone payments and license fees set forth in Section 6.2, Section 6.3 and Section 6.4) shall not apply with respect to the Collaboration Program (as such term is defined in the Neurology II Agreement) for [***]; instead, royalties, milestone payments and license fees with respect to the [***] will be due in accordance with the Neurology II Agreement.

6.6. Royalty Payments to Ionis.

6.6.1. **Biogen Full Royalty**. As partial consideration for the rights granted to Biogen hereunder, subject to the provisions of this Section 6.6.1 and Section 6.6.2, Biogen will pay to Ionis royalties on a Collaboration Program-by-Collaboration Program basis, on Annual worldwide Net Sales of Products included in the applicable Collaboration Program sold by Biogen, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 3 below (the "***Biogen Full Royalty***"):

TABLE 3

Royalty Tier	Annual Worldwide Net Sales of Products		Royalty Rate
1	For the portion of Annual worldwide Net Sales	< $[***]	[***]%
2	For the portion of Annual worldwide Net Sales	≥ $[***] but < $[***]	[***]%
3	For the portion of Annual worldwide Net Sales	≥ $[***] but < $[***]	[***]%
4	For the portion of Annual worldwide Net Sales	≥ $[***]	[***]%

Annual worldwide Net Sales will be calculated by [***].

(a) Biogen will pay Ionis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and Biogen will provide reports and payments to Ionis consistent with Section 6.9. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Full Royalty Period.

(b) For purposes of clarification, any Ionis Product-Specific Patents assigned to Biogen as set forth in Section 4.2.1 will still be considered Ionis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 6.

(c) For clarity, the provisions of this Agreement (including Section 6.6) shall not apply to Net Sales of Products under the Collaboration Program (as such term is defined in the Neurology II Agreement) for [***]; instead, royalties, milestone payments and license fees with respect to the [***] will be due in accordance with the Neurology II Agreement.

6.6.2. **Application of Royalty Rates**. All royalties set forth under Section 6.6.1 are subject to the provisions of this Section 6.6.2, and are payable as follows:

(a) **Full Royalty Period**. Biogen's obligation to pay Ionis the Biogen Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), or (iii) the [***] anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Full Royalty Period***").

(b) **Competition from Generic Products**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, if, within the [***], a Generic Product is sold in a country, then the Biogen Full Royalty rate used to pay Ionis royalties on such Product in such country will be reduced to [***]% of the otherwise applicable Biogen Full Royalty rate. For the purpose of determining the [***] for a particular Product under this Section 6.6.2(b), if requested by Biogen, Ionis and Biogen will meet and confer and mutually agree upon the Parties' best estimate of when the Full Royalty Period [***] in each country where Products are being sold.

(c) **Reduced Royalty Period**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in TABLE 3 of Section 6.6.1, Biogen will pay Ionis royalty rates (the "***Biogen Reduced Royalty***") on Net Sales of Products calculated on a Calendar Year-by-Calendar Year basis by [***]; *provided*, *however*, that the Biogen Reduced Royalty rate in each country will in no event exceed the [***].

(d) **Limitation on Aggregate Reduction for Biogen Royalties**.

(i) In no event will the aggregate royalty reductions under Section 6.6.2(b) and Section 6.6.2(c) reduce the royalties payable to Ionis on Net Sales of a Product in any given period to an amount that is less than [***] for such Product.

(ii) In no event will the aggregate royalty offsets under Section 6.8.3(b) and Section 6.8.3(d) reduce the royalties payable to Ionis on Net Sales of a Product in any given period to an amount that is less than the greater of [***].

For example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is less than [***]%, then the offsets under Section 6.8.3(b) and Section 6.8.3(d) will not apply during such Calendar Year but the full Royalty Quotient reduction pursuant to Section 6.6.2(c) will apply.

As an additional example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is [***], and the [***] in such Calendar Year are [***] of the applicable royalty rates in TABLE 3 of Section 6.6.1, then Biogen may apply the offsets under Section 6.8.3(b) and Section 6.8.3(d) until the actual royalty payment made to Ionis in such Calendar Year is equal to [***]% of the applicable royalty rates in TABLE 3 of Section 6.6.1.

(e) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis, other than [***], Biogen's obligation to make royalty payments hereunder for such Product in such country will end on the expiration of the Reduced Royalty Period in such country. "***Reduced Royalty Period***" means, on a country by country basis, the period commencing upon the expiration of the [***] for such Product in such country and ending when the [***].

(f) **Royalty Examples**. SCHEDULE 6.6.2(f) attached hereto contains examples of how royalties will be calculated under this Section 6.6.

(g) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.6.2, different royalty rates apply to Net Sales of Products from different countries, Biogen will [***] such Net Sales [***]. SCHEDULE 6.6.2(g) attached hereto contains examples of how Net Sales of Products from different countries at different royalty rates will be [***].

6.7. Reverse Royalty Payments to Biogen for a Discontinued Product.

6.7.1. Reverse Royalty for a Discontinued Product. If Ionis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which Biogen has paid Ionis the license fee under Section 6.3, then following the First Commercial Sale of such Discontinued Product by Ionis or its Affiliates or Sublicensees, Ionis will pay Biogen or its designated Affiliate a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product ("***Reverse Royalties***"). Ionis' obligation to pay Biogen Reverse Royalties will [***].

6.7.2. Applicable Royalty Provisions. In addition to this Section 6.7, the definition of Net Sales in APPENDIX 1 and the other provisions contained in this ARTICLE 6 governing payment of royalties from Biogen to Ionis will govern the payment of Reverse Royalties from Ionis to Biogen under this Section 6.7, *mutatis mutandis*, including the provisions of Sections 6.6.2, 6.8, 6.9, 6.10, 6.11, and 6.12.

6.8. Third Party Payment Obligations.

6.8.1. Existing Ionis In-License Agreements.

(a) Certain of the Licensed Technology Controlled by Ionis as of the Effective Date licensed to Biogen under Section 4.1.1 were in-licensed or were acquired by Ionis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.8.1 or in a separate written agreement between the Parties (all such license or purchase agreements being the "***Ionis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Ionis to such Third Parties under the Ionis In-License Agreements based on the Development and Commercialization of a Product by Biogen under this Agreement.

(b) Any payment obligations arising under the Ionis In-License Agreements as existing on the Effective Date as they apply to Products will be paid by [***] as [***].

6.8.2. **New In-Licensed Ionis Product-Specific Patents; Ionis Manufacturing and Analytical Patents**. If after the Effective Date, Ionis obtains Third Party Patent Rights necessary or useful to Develop, Manufacture or Commercialize a Product that would have been considered an Ionis Product-Specific Patent had Ionis Controlled such Patent Rights on the Effective Date, to the extent Controlled by Ionis, Ionis will include such Third Party Patent Rights in the license granted to Biogen under Section 4.1.1 if Biogen agrees in writing to pay Ionis as [***].

6.8.3. **Additional Core IP In-License Agreements**.

(a) Biogen will promptly provide Ionis written notice of any Additional Core IP Biogen believes it has identified and Ionis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Core IP. If Ionis obtains such a Third Party license, Ionis will include such Additional Core IP in the license granted to Biogen under Section 4.1.1, and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

(b) If, however, Ionis elects not to obtain such a license to such Third Party intellectual property, Ionis will so notify Biogen, and Biogen may obtain such a Third Party license and, subject to Section 6.6.2(d)(ii), Biogen may offset an amount equal to [***]% of any [***] paid by Biogen under such Third Party license against any [***] of this Agreement in such country for [***].

(c) If it is unclear whether certain intellectual property identified by Biogen pursuant to Section 6.8.3(a) is Additional Core IP under Section 6.8.3(b), Ionis will send written notice to such effect to Biogen, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is Additional Core IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether Biogen is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.8.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

(d) Notwithstanding the determination of the Third Party lawyer under Section 6.8.3(c), if a Third Party Controlling Additional Core IP is awarded a judgment from a court of competent jurisdiction arising from its claim against Biogen asserting that [***], Biogen will be permitted to [***].

6.8.4. **Other Third Party Payments**.

(a) **Ionis' Third Party Agreements**. Except as otherwise expressly agreed to by Biogen under clause (c) of Section 1.3.2 or Section 6.8.2, after the License Effective Date for a particular Collaboration Program, Biogen will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Ionis where either [***].

(b) **Biogen's Third Party Agreements**. Without limiting any applicable [***] under Section 6.8.3(b), Biogen will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Biogen as they apply to Products.

6.9. **Payments**.

6.9.1. **Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Biogen will make royalty payments to Ionis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used and the aggregate reduction to gross sales to arrive at Net Sales. Following the end of the first full Calendar Quarter subsequent to the First Commercial Sale in a Major Market of any Product (but not in any subsequent Calendar Quarter unless there is a material change in the amount of any reduction to gross sales or the methodology used by Biogen to calculate any such reduction), Biogen will also include in such report a description of the reductions to gross sales to arrive at Net Sales, broken down by each category of reduction listed in clauses (a) through (d) of the definition of "Net Sales" and a non-binding qualitative analysis describing how Biogen anticipates such reductions may fluctuate over time. If no royalties are payable in respect of a given Calendar Quarter, then Biogen will submit a written royalty report to Ionis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, Biogen will provide Ionis a [***] report estimating the total Net Sales of, and royalties payable to Ionis for Products projected for such Calendar Quarter.

6.9.2. **Mode of Payment**. All payments under this Agreement will be (a) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (b) made by wire transfer of immediately available funds to an account designated by Ionis in writing, and (c) non-creditable [***], irrevocable and non-refundable. Whenever for the purposes of calculating the royalties payable under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by applying the monthly average rate of exchange calculated by using the foreign exchange rates published in Bloomberg during the applicable month starting two Business Days before the beginning of such month and ending two Business Days before the end of such month as utilized by Biogen, in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout Biogen's operations.

6.9.3. **Records Retention**. Commencing with the First Commercial Sale of a Product, Biogen will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Ionis to confirm the accuracy of the Net Sales or royalties paid by Biogen hereunder.

6.10. **Audits**. After the License Effective Date for a particular Collaboration Program, during the Agreement Term and for a period of [***] thereafter, at the request and expense of Ionis, Biogen will permit an independent certified public accountant of nationally recognized standing appointed by Ionis, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding [***]. As a condition to examining any records of Biogen, such auditor will sign a nondisclosure agreement reasonably acceptable to Biogen in form and substance. Any and all records of Biogen examined by such independent certified public accountant will be deemed Biogen's Confidential Information. Upon completion of the audit, the accounting firm will provide both Biogen and Ionis with a written report disclosing whether the royalty payments made by Biogen are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of Biogen, it is shown that Biogen's payments under this Agreement were less than the royalty amount which should have been paid, then Biogen will make all payments required to be made by paying Ionis the difference between such amounts to eliminate any discrepancy revealed by said inspection within [***] days of receiving the Audit Report, with interest calculated in accordance with Section 6.12. If, as a result of any inspection of the books and records of Biogen, it is shown that Biogen's payments under this Agreement were greater than the royalty amount which should have been paid, then [***]; *provided*, *however*, that if [***]. Ionis will pay for such audit, except that if Biogen is found to have underpaid Ionis by more than [***] of the amount that should have been paid, Biogen will reimburse Ionis' reasonable costs of the audit.

6.11. **Taxes**.

6.11.1. **Taxes on Income**. Each Party will be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

6.11.2. **Withholding Tax**. The Parties agree to cooperate with one another and use reasonable efforts to lawfully avoid or reduce tax withholding or similar obligations in respect of royalties, milestone payments, and other payments, including from subsequent payments, made by the paying Party to the receiving Party under this Agreement. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so.

6.11.3. **Tax Cooperation**. Ionis will provide Biogen with any and all tax forms that may be reasonably necessary in order for Biogen to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following Biogen's timely receipt of such tax forms from Ionis, Biogen will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Laws. Ionis will provide any such tax forms to Biogen upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.11.

The provisions of this Section 6.11 are to be read in conjunction with the provisions of Section 12.4 below.

6.12. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (a) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus 1% or (b) the maximum rate permissible under Applicable Law.

ARTICLE 7
INTELLECTUAL PROPERTY

7.1. **Ownership**.

7.1.1. **Ionis Technology and Biogen Technology**. As between the Parties, Ionis will own and retain all of its rights, title and interests in and to the Licensed Know-How and Licensed Patents and Biogen will own and retain all of its rights, title and interests in and to the Biogen Know-How and Biogen Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement.

7.1.2. **Agreement Technology**. As between the Parties, Biogen is and will be the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Biogen or its Affiliates under this Agreement ("***Biogen Program Know-How***") and any Patent Rights that claim or cover Biogen Program Know-How ("***Biogen Program Patents***" and together with the Biogen Program Know-How, the "***Biogen Program Technology***"), and will retain all of its rights, title and interests thereto, subject to any rights or licenses expressly granted by Biogen to Ionis under this Agreement. As between the Parties, Ionis is and will be the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Ionis or its Affiliates under this Agreement ("***Ionis Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Ionis Program Patents***" and together with the Ionis Program Know-How, the "***Ionis Program Technology***"), and will retain all of its rights, title and interests thereto, subject to any assignment, rights or licenses expressly granted by Ionis to Biogen under this Agreement. Any Know-How discovered, developed, invented or created jointly under this Agreement by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf ("***Jointly-Owned Program Know-How***") and any Patent Rights that claim or cover such Jointly-Owned Program Know-How ("***Jointly-Owned Program Patents***" and together with the Jointly-Owned Program Know-How, the "***Jointly-Owned Program Technology***"), are and will be owned jointly by Biogen and Ionis on an equal and undivided basis, including all rights, title and interests thereto, subject to any rights or licenses expressly granted by one Party to the other Party under this Agreement. Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Program Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the Laws of any jurisdiction to require any such consent or accounting. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, invention or creation of any Jointly-Owned Program Technology. The Biogen Program Patents, Ionis Program Patents and Jointly-Owned Program Patents are collectively referred to herein as the "***Program Patents***."

7.1.3. **Joint Patent Committee**.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, with responsibilities including (i) the preparation of the intellectual property strategy to govern the Parties' activities set forth in the Collaboration Program Research Plans and the activities set forth in this ARTICLE 7, (ii) making recommendations following discussion by the Parties regarding Third Party intellectual property rights that may be necessary or useful to perform activities under, and the intellectual property considerations to be taken into account in, Collaboration Program Research Plans, (iii) making recommendations with respect to intellectual property considerations to be taken into account in each Development Plan, (iv) the preparation of recommendations with respect to intellectual property considerations in connection with proposed Development Candidates for consideration by the Parties, (v) assessing and making recommendations to the Neurology JSC prior to the Completion of IND-Enabling Toxicology Studies regarding any Patent Rights of any Third Party that may be necessary or useful for the Development, Manufacture or Commercialization of any Development Candidate that is the subject of such IND-Enabling Toxicology Studies and (vi) evaluating any activities under a Collaboration Program Research Plan or Development Plan that are proposed to be conducted with an academic or non-profit collaborator and making recommendations as to where and with whom such activities should be conducted, and in each case will cooperate with respect to any such activities. Ionis' obligation to participate in the JPC will terminate on the later of (A) the end of the Drug Discovery Term and (B) Biogen's exercise of (or the expiration or termination of) the last Option. Thereafter, Ionis will have the right, but not the obligation, to participate in JPC meetings, but shall nevertheless continue to coordinate with Biogen with respect to the activities set forth in this ARTICLE 7 during the Agreement Term.

(b) The JPC will discuss a strategy and make recommendations with regard to intellectual property considerations (i) with respect to the Parties' activities under the Collaboration Program, Drug Discovery Program and the Drug Development Program, promptly following the Amendment Date and (ii) with respect to each Collaboration Program, promptly after such Collaboration Program is designated, which strategies shall include (A) considerations for identifying potential inventions and making inventorship determinations, (B) considerations when selecting each Development Candidate, (C) considerations for Prosecution and Maintenance, defense and enforcement of Ionis Product-Specific Patents that would be or are licensed to Biogen under Section 4.1.1 in connection with a Product, Biogen Product-Specific Patents and Jointly-Owned Program Patents, (D) defense against allegations of infringement of Third Party Patent Rights and (E) licenses to Third Party Patent Rights or Know-How, in each case ((A) through (E)) to the extent such matter would be reasonably likely to have a material impact on the Agreement or the ownership of intellectual property or the licenses granted hereunder. The applicable strategy and the JPC's recommendations, as applicable, will be considered in good faith in the performance of the Collaboration Program Research Plans and Development Plans, the preparation of the intellectual property assessment to be included in each Development Candidate Data Package and by the Party entitled to designate a Development Candidate or prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(c) Ionis or Biogen (as applicable) will provide the Joint Patent Committee with notice of any Know-How or Patent Rights discovered, developed, invented or created jointly by such Party and a Third Party in the performance of activities under the Collaboration Program Research Plans or Development Plans or solely by a Third Party performing activities under the Collaboration Program Research Plans or Development Plans on such Party's behalf (such Know-How and Patent Rights, the "***Collaborator IP***") promptly after such Party receives notice or otherwise becomes aware of the existence of such Collaborator IP. The JPC will determine whether any such Collaborator IP would be infringed or misappropriated (as applicable) by the Development, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration by Ionis for potential designation as a Development Candidate. If the JPC (or independent patent counsel engaged pursuant to Section 7.1.3(b)) determines that any Collaborator IP would be infringed or misappropriated (as applicable) by the Development, Manufacture or Commercialization of such Development Candidate or Compound, [***]; *provided* that if such Party is unable to obtain [***] license to such Collaborator IP or if the Parties mutually agree that it is not necessary to obtain [***] license, then such Party shall use commercially reasonable efforts to obtain [***] license to such Collaborator IP from such Third Party (any such [***] with such Third Party, a "***Collaborator License***"), and in each case, such Party will endeavor to obtain in such Collaborator License the right to sublicense such Collaborator IP to the other Party on terms that contain no greater restrictions on the other Party's use of such Collaborator IP than those set forth in this Agreement.

(d) Notwithstanding any provision to the contrary in this Agreement, including Section 6.8, if Collaborator IP (other than Additional Core IP) arises from activities performed by a Third Party under the applicable Collaboration Program Research Plan, Development Plan or IDP, then any payment obligations arising under the applicable Collaborator License based on the Development or Commercialization of a Product will be [***] as follows: (i) in the case where [***] enters into such Collaborator License, [***] will be solely responsible for paying any payment obligations that [***], *except* that [***] will be solely responsible for paying any payment obligations that [***] under any such Collaborator Licenses that [***] approved prior to execution thereof and (ii) in the case where [***] enters into such Collaborator License, [***] will be [***] responsible for paying any payment obligations that [***].

(e) With respect to any such Collaborator IP licensed by Ionis under a Collaborator License with such Third Party, Biogen will have the right in accordance with Section 4.1.4 to elect to exclude any such Collaborator IP from the applicable license granted to Biogen under Section 4.1.1 by providing Ionis written notice prior to the License Effective Date for the applicable Collaboration Program. If, Biogen timely provides Ionis with such a written notice to exclude certain of such Collaborator IP from such license, then such Collaborator IP will not be included in the Licensed Technology licensed with respect to such Collaboration Program under this Agreement. If Biogen does not provide Ionis with such a written notice to exclude such Collaborator IP prior to the License Effective Date for the applicable Collaboration Program hereunder, then such Collaborator IP (and any Third Party Obligations to the extent applicable to Products) will be included in the Licensed Technology licensed with respect to the applicable Collaboration Program under this Agreement.

(f) In case of a dispute in the Joint Patent Committee over whether any Collaborator IP would be infringed or misappropriated (as applicable) by the Development, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration by Ionis for potential designation as the Development Candidate, at the non-contracting Party's request, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties, taking into account any existing prior art. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be borne by the non-contracting Party.

(g) In addition, the Joint Patent Committee will be responsible for the determination of inventorship of Patent Rights that claim or cover Know-How discovered, developed, invented or created under this Agreement in accordance with United States patent Laws. In case of a dispute in the Joint Patent Committee (or otherwise between Ionis and Biogen) over inventorship of Program Patents, if the Joint Patent Committee cannot resolve such dispute, then such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

(h) The JPC will comprise an equal number of members from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this ARTICLE 7. The JPC will determine by unanimous consent of its members the JPC operating procedures at its first meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which will be codified in the written minutes of the first JPC meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the Executives for input and resolution pursuant to Section 12.1. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

7.2. Prosecution and Maintenance of Patents.

7.2.1. Patent Filings. Subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.4(a), the Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 7.2.2 and Section 7.2.3 will endeavor to obtain patent protection for the applicable Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit.

7.2.2. Licensed Patents and Biogen Patents.

(a) **Licensed Patents In General**. Prior to the License Effective Date for a Collaboration Program, and subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.4(a), Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of all Licensed Patents that are the subject of such license grant for such Collaboration Program, subject to this Section 7.2.2(a) and Section 7.2.3. During the Agreement Term, Ionis will control and be responsible for all aspects of the Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents. Ionis will use commercially reasonable efforts to diligently Prosecute and Maintain all Jointly-Owned Program Patents for which Ionis has the right to Prosecute and Maintain. On a Collaboration Program-by-Collaboration Program basis, until the earlier of the License Effective Date with respect to such Collaboration Program and the expiration or termination of Biogen's right to be granted such license, Ionis will use commercially reasonable efforts to diligently Prosecute and Maintain all Ionis Product-Specific Patents that are the subject of such Collaboration Program to the extent that Ionis has the right to Prosecute and Maintain such Patent Rights.

(b) **Licensed Patents After License Effective Date**. Upon the License Effective Date with respect to a Collaboration Program, Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of all the Ionis Product-Specific Patents and Jointly-Owned Program Patents that are subject to the license under Section 4.1.1 for such Collaboration Program to the same extent Ionis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such License Effective Date, subject to Section 7.2.3, and will grant Ionis the license set forth in Section 4.2.2.

(c) **Biogen Patents**. Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of all Biogen Patents, subject to Section 7.2.3.

7.2.3. Jointly-Owned Program Patents. Subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.4(a), Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that do not Cover Products. Prior to the License Effective Date for a Collaboration Program and subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.4(a), Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such Collaboration Program. After the License Effective Date for a Collaboration Program, Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such Collaboration Program.

7.2.4. Other Matters Pertaining to Prosecution and Maintenance of Patents.

(a) Ionis will keep Biogen reasonably informed through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded) as to material developments with respect to the Prosecution and Maintenance of (i) those Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents that Cover any Development Candidate or Product and (ii) the Ionis Product-Specific Patents and Jointly-Owned Program Patents, in each case ((i) and (ii)), for which Ionis has the responsibility to Prosecute and Maintain pursuant to Section 7.2.2, Section 7.2.3 or this Section 7.2.4, including by providing copies of material data as it arises. Ionis will timely provide Biogen the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance, including the countries in which such Patent Rights are filed, and will consider Biogen's input with respect to such strategic aspects in good faith but which will not be binding on Ionis. Additionally, Ionis will promptly provide to Biogen drafts of all patent-related filings and communications related to the such Patent Rights, including copies of office actions or other correspondence that Ionis receives from any patent office, drafts of office action responses or other correspondence that Ionis provides to any patent office, and copies and drafts of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, in each case, for Biogen's review and comment, and Ionis will consider in good faith any reasonable comments timely provided by Biogen with respect to such draft filings and communications.

(b) Following the License Effective Date with respect to a particular Collaboration Program, Biogen will keep Ionis reasonably informed through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded) as to material developments with respect to the Prosecution and Maintenance of Product-Specific Patents or Jointly-Owned Program Patents for which Biogen has the responsibility to Prosecute and Maintain pursuant to Section 7.2.2, Section 7.2.3 or this Section 7.2.4, including by providing copies of material data as it arises and will provide Ionis the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance, which input Biogen will consider in good faith but which Biogen will not be required to implement. Following the License Effective Date with respect to a particular Collaboration Program, Biogen will have final decision-making authority with respect to the Prosecution and Maintenance, enforcement and defense of such Product-Specific Patents or Jointly-Owned Program Patents related to such Collaboration Program, including any Proceeding related to the infringement of such Patent Rights and any patent term extensions related to such Patent Rights.

(c) If Biogen elects (i) not to file and prosecute patent applications for the Jointly-Owned Program Patents or Ionis Product-Specific Patents that have been licensed or assigned to Biogen under this Agreement or the Biogen Product-Specific Patents ("***Biogen-Prosecuted Patents***") in a particular country, (ii) not to continue the Prosecution and Maintenance (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) of any Biogen-Prosecuted Patent in a particular country or (iii) not to file and prosecute patent applications for the Biogen-Prosecuted Patent in a particular country following a written request from Ionis to file and prosecute in such country, then in each case ((i) – (iii)), Biogen will so notify Ionis promptly in writing of its intention (including a reasonably detailed rationale for doing so) with sufficient time to enable Ionis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and except as set forth in Section 7.2.4(d), Ionis will have the right, but not the obligation, to file, prosecute, maintain, enforce or otherwise pursue such Biogen-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Biogen will cooperate with Ionis to file for, or continue to Prosecute and Maintain, enforce or otherwise pursue such Biogen-Prosecuted Patent in such country in Ionis' own name, but only to the extent that Biogen is not required to take any position with respect to such abandoned Biogen-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by Biogen under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Ionis assumes responsibility for the Prosecution and Maintenance of any such Biogen-Prosecuted Patent under this Section 7.2.4(c), then Ionis will have no obligation to notify Biogen if Ionis intends to abandon such Biogen-Prosecuted Patent.

(d) Notwithstanding Section 7.2.4(c) above, if, after having consulted with outside counsel, Biogen reasonably determines that filing or continuing to prosecute a patent application in a particular country for a Biogen-Prosecuted Patent (the "***Conflicting Patent Right***") is reasonably likely to adversely affect the scope, validity or enforceability of a patent application or issued patent in a particular country for another Biogen-Prosecuted Patent (the "***Superior Patent Right***"), in each case where both the Conflicting Patent Right and the Superior Patent Right if issued would meet the criteria set forth in clause (i) of Section 6.6.2(a), then *so long as* Biogen continues to Prosecute and Maintain the Superior Patent Right in accordance with this Agreement, Ionis will not have the right under Section 7.2.4(c) above to file or prosecute the Conflicting Patent Right.

(e) If, during the Agreement Term, Ionis intends not to file or intends to abandon in any jurisdiction any Ionis Product-Specific Patent for which Ionis is responsible for Prosecution and Maintenance without first filing a continuation or substitution, then, if Biogen's right to obtain a license under Section 4.1.1 to such Ionis Product-Specific Patent has not expired or terminated, Ionis will notify Biogen of such intention at least [***] days before such Patent Right will become abandoned, and Biogen will have the right, but not the obligation, to assume responsibility and final decision-making authority for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice. Notwithstanding anything to the contrary in this Agreement, if Biogen assumes responsibility for the Prosecution and Maintenance of any such Ionis Product-Specific Patent under this Section 7.2.4(e), then Biogen will have no obligation to notify Ionis if Biogen intends to abandon such Ionis Product-Specific Patent.

(f) The Parties, through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded), will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Program Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, following which determination such a divisional or continuation filing will be made.

(g) If the Party responsible for Prosecution and Maintenance of a Jointly-Owned Program Patent pursuant to Section 7.2.3 intends to abandon such Jointly-Owned Program Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least [***] days before such Jointly-Owned Program Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility and final decision-making authority for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interests in and to such Jointly-Owned Program Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Program Patents under this Section 7.2.4(g), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(h) In addition, the Parties will consult, through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded), and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

7.3. Patent Costs.

7.3.1. Jointly-Owned Program Patents. Unless the Parties agree otherwise, Ionis and Biogen will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Program Patents; *provided* that either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Program Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interests in and to such Jointly-Owned Program Patents.

7.3.2. Licensed Patents and Biogen Patents. Except as set forth in Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2; *provided, however*, that after the License Effective Date for a Collaboration Program, Biogen will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Ionis Product-Specific Patents related to such Collaboration Program.

7.4. Defense of Claims Brought by Third Parties.

7.4.1. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Product, (a) Ionis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to the License Effective Date for the applicable Collaboration Program at its sole cost and expense and (b) Biogen will have the first right, but not the obligation, to defend against any such Proceeding initiated after the License Effective Date for the applicable Collaboration Program at its sole cost and expense. If the Party having the first right to defend against such Proceeding (the "***Lead Party***") elects to defend against such Proceeding, then the Lead Party will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of the other Party, not to be unreasonably withheld, conditioned or delayed). The other Party will reasonably assist the Lead Party in defending such Proceeding and cooperate in any such litigation at the request and expense of the Lead Party. The Lead Party will provide the other Party with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4, and the Lead Party will keep the other Party apprised of the progress of such Proceeding. Notwithstanding the foregoing, (i) if Ionis is the Lead Party, then Ionis will cooperate in good faith with Biogen on the institution, prosecution and control of such Proceeding, will provide Biogen with copies of filings, submissions and communications related to such Proceeding in sufficient time to allow Biogen to review and comment thereon, and will incorporate any reasonable comments timely provided by Biogen with respect to such filings, submissions and communications and (ii) if Biogen is the Lead Party and Ionis is a named party, then Biogen will cooperate in good faith with Ionis on the institution, prosecution and control of such Proceeding and will provide Ionis the timely opportunity to have reasonable input into the strategic aspects of such Proceeding, which Biogen will consider in good faith but which Biogen will not be required to implement. If the Lead Party elects not to defend against a Proceeding, then the Lead Party will so notify the other Party in writing within [***] days after the Lead Party first receives written notice of the initiation of such Proceeding, and the other Party (the "***Step-In Party***") will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter the Step-In Party will have the sole right to direct the defense thereof, including the right to settle such claim. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

7.4.2. **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, then Ionis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. Biogen will reasonably assist Ionis in defending such Proceeding and cooperate in any such litigation at the request and expense of Ionis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Ionis will provide Biogen with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Ionis becomes aware and that is of the type described in this Section 7.4.2, and Ionis will promptly furnish Biogen with a copy of each communication relating to the alleged infringement received by Ionis.

7.4.3. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 7.4.1 and Section 7.4.2, to the extent that a Party's defense against a Third Party claim of infringement under this Section 7.4 involves (a) the enforcement of the other Party's Know-How or Patent Rights (e.g., a counterclaim of infringement), or (b) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 7.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (i.e., each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

7.5. Enforcement of Patents against Competitive Infringement.

7.5.1. Duty to Notify of Competitive Infringement. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any conflicting obligation of confidentiality with respect to any Licensed Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes a Collaboration Target in the Field ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided, however*, that for cases of Competitive Infringement under Section 7.5.8 below, such written notice will be given within 10 days.

7.5.2. Prior to License Grant. For any Competitive Infringement with respect to a Product occurring after the Effective Date but before the License Effective Date for the Collaboration Program of which such Product is the subject, Ionis will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto, by counsel of its own choice, and Biogen will have the right to be represented in that action by counsel of its own choice at its own expense. Ionis will provide Biogen with prompt written notice of the commencement of any such Proceeding, and Ionis will keep Biogen apprised of the progress of such Proceeding. Additionally, Ionis will provide Biogen with copies of filings, submissions and communications related to such Proceeding in sufficient time to allow Biogen to review and comment thereon, and will consider in good faith any reasonable comments timely provided by Biogen with respect to such filings, submissions and communications. Subject to the preceding sentence, Ionis will have the sole right to control such litigation. If Ionis fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, which extension will apply only in the event that Ionis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Biogen will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided* that Ionis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Ionis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.2 to the extent involving any Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents.

7.5.3. **Biogen Enforcement Rights**. Notwithstanding Section 7.5.2 and Section 7.5.4, in the case where a Third Party is infringing an Ionis Core Technology Patent and a Patent Right Controlled by Biogen by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes a High Interest Target or a Collaboration Target in the Field, then the Party with knowledge of such infringement will promptly notify the other Party in writing. If Biogen also enforces any Patent Rights Controlled by Biogen (including any Ionis Product-Specific Patents assigned by Ionis to Biogen under this Agreement) against such infringement, then Biogen may elect to have Ionis and Biogen enforce the applicable Ionis Core Technology Patents and the applicable Patent Rights Controlled by Biogen against such infringing Third Party.

7.5.4. **Following License Grant**. For any Competitive Infringement with respect to a particular Product (except for a Discontinued Product) occurring after the License Effective Date for the Collaboration Program of which such Product is the subject, so long as part of such Proceeding Biogen also enforces any Patent Rights Controlled by Biogen (including any Ionis Product-Specific Patents assigned by Ionis to Biogen under this Agreement) being infringed that Cover the Product, then Biogen will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Ionis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* Biogen will have the right to control such litigation. If Biogen fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, if Biogen has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Ionis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Biogen will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Ionis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.4 to the extent involving any Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents.

7.5.5. **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 7.5, then the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 7.5.6, the costs and expenses of each Party incurred pursuant to this Section 7.5.5(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.5, then the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement or where such Proceeding relates to Jointly-Owned Program Patents.

7.5.6. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds constituting direct or actual damages for acts of infringement occurring prior to the License Effective Date for the Collaboration Program of which the applicable Product is the subject will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after the License Effective Date for the Collaboration Program of which the applicable Product is the subject [***]; then

(d) any remaining proceeds constituting punitive or treble damages will be allocated between the Parties as follows: the Party initiating the Proceeding will receive and retain [***]% of such proceeds and the other Party will receive and retain [***]% of such proceeds.

7.5.7. **Settlement**. Notwithstanding anything to the contrary under this ARTICLE 7, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 7 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right.

7.5.8. **35 USC §271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 7.5, solely with respect to Licensed Patents that have not been assigned to Biogen under this Agreement for a Competitive Infringement under 35 USC §271(e)(2), the time period set forth in Section 7.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of 25 days, so that, to the extent the other Party has the right, pursuant to Section 7.5.2 to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement.

7.6. **Other Infringement**.

7.6.1. **Jointly-Owned Program Patents**. With respect to the infringement of a Jointly-Owned Program Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.6.1 will be shared as follows: (a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (b) any remaining proceeds constituting direct damages will be [***], and (c) any remaining proceeds constituting punitive or treble damages will be allocated as follows: (i) if the Parties jointly initiate a Proceeding pursuant to this Section 7.6.1, [***]; and (ii) if only one Party initiates the Proceeding pursuant to this Section 7.6.1, such Party will receive [***]% of such proceeds and the other Party will receive [***]% of such proceeds.

7.6.2. **Patents Solely Owned by Ionis**. Ionis will retain all rights to pursue an infringement of any Patent Right solely owned by Ionis which is other than a Competitive Infringement and Ionis will retain all recoveries with respect thereto.

7.6.3. **Patents Solely Owned by Biogen**. Biogen will retain all rights to pursue an infringement of any Patent Right solely owned by Biogen which is other than a Competitive Infringement and Biogen will retain all recoveries with respect thereto.

7.7. **Patent Listing**.

7.7.1. **Biogen's Obligations**. Biogen will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Biogen will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Biogen will retain final decision-making authority as to the listing of all applicable Patent Rights for the Product that are not Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

7.7.2. **Ionis' Obligations**. Ionis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Ionis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Ionis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **Joint Research Agreement under the Leahy-Smith America Invents Act**. Notwithstanding anything to the contrary in this ARTICLE 7, neither Party will have the right to make an election under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act when exercising its rights under this ARTICLE 7 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, each Party will use reasonable efforts to cooperate and coordinate their activities with the other Party 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).

7.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 7 will be subject to the Third Party rights and obligations under any (a) New Third Party License, the restrictions and obligations of which Biogen has agreed to under Section 6.8.2, (b) Prior Agreements and (c) Ionis In-License Agreements; *provided*, *however*, that, to the extent that Ionis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Biogen hereunder and this Agreement purports to grant any such rights to Biogen, Ionis will act in such regard with respect to such Patent Rights at Biogen's direction.

7.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 7, Ionis retains the sole right to Prosecute and Maintain Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Ionis and Covering the Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents is at risk.

7.11. **Patent Term Extension**. The Parties will cooperate with each other in gaining patent term extension wherever applicable to the Product. After the License Effective Date for the Collaboration Program of which such Product is the subject, Biogen will have the sole right to determine which relevant patents will be extended.

ARTICLE 8
REPRESENTATIONS AND WARRANTIES

8.1. **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants to the other Party, as of the Amendment Date, that:

8.1.1. such Party is duly organized, validly existing and in good standing under the Laws of the jurisdiction of its incorporation or organization and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

8.1.2. such Party has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

8.1.3. this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid and binding obligation, enforceable against it in accordance with the terms hereof;

8.1.4. the execution, delivery and performance of this Agreement by such Party will not constitute a default under or conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, or violate any Law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

8.1.5. no government authorization, consent, approval, license, exemption of or filing or registration with any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, under any Applicable Laws, rules or regulations currently in effect, is or will be necessary for, or in connection with, the transaction contemplated by this Agreement or any other agreement or instrument executed in connection herewith, or for the performance by it of its obligations under this Agreement and such other agreements; and

8.1.6. it has not employed (and, to the best of its knowledge, has not used a contractor or consultant that has employed) and in the future will not employ (or, to the best of its knowledge, use any contractor or consultant that employs (*provided* that such Party may reasonably rely on a representation made by such contractor or consultant)) any Person debarred by the FDA (or subject to a similar sanction of EMA or foreign equivalent), or any Person which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMA or foreign equivalent), in the conduct of the Pre-Clinical Studies or Clinical Studies of the Product and its activities under each Collaboration Program.

8.2. **Representations and Warranties of Ionis**. Ionis hereby represents and warrants to Biogen, as of the Effective Date, that:

8.2.1. To the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to Biogen under Section 4.1.1 upon the exercise of the Option for a Product arising under the Collaboration Programs) under any intellectual property owned or Controlled by Ionis or its Affiliates as of the Effective Date that would be required in order for Biogen to further Develop and Commercialize a Product.

8.2.2. The Licensed Technology existing as of the Effective Date constitutes all of the Patent Rights and Know-How Controlled by Ionis as of the Effective Date that are necessary to Develop, Manufacture or Commercialize Compounds contemplated under the Collaboration Programs in the Field. Ionis has not previously assigned, transferred, conveyed or otherwise encumbered its rights, title and interests in the Licensed Technology in a manner that conflicts with any rights granted to Biogen hereunder.

8.2.3. Neither Ionis nor its Affiliates owns or Controls any Patent Rights or Know-How covering formulation or delivery technology as of the Effective Date that would be useful or necessary in order for Biogen to further Develop or Commercialize Compounds contemplated under the Collaboration Programs.

8.2.4. Schedule 8.2.4(a), Schedule 8.2.4(b) and Schedule 8.2.4(c) set forth true, correct and complete lists of all Ionis Core Technology Patents, and Ionis Manufacturing and Analytical Patents that apply to the Compounds contemplated under the Collaboration Programs as of the Effective Date (the "***Ionis Platform Technology***"), respectively, and indicates whether each such Patent Right is owned by Ionis or licensed by Ionis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Ionis Controls such Patent Rights existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Patent Rights it purports to grant to Biogen under this Agreement.

8.2.5. There are no claims, judgments or settlements against or owed by Ionis or its Affiliates or pending against Ionis or, to the best of Ionis' knowledge, threatened against Ionis, in each case relating to the Ionis Platform Technology, Ionis Manufacturing and Analytical Know-How, Ionis Know-How, Collaboration Targets or High Interest Targets that could impact activities under this Agreement. To the best of Ionis' knowledge, there are no claims, judgments or settlements against or owed by any Third Party that is party to a Prior Agreement, or pending or threatened claims or litigation against any Third Party that is party to a Prior Agreement, in each case relating to the Ionis Platform Technology, Ionis Manufacturing and Analytical Know-How, Ionis Know-How, Collaboration Targets or High Interest Targets that would impact activities under this Agreement.

8.2.6. At the Effective Date (a) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude that any Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude the inventorship of each Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent is not properly identified on each patent, and (c) all official fees, maintenance fees and annuities for the Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent have been paid and all administrative procedures with governmental agencies have been completed.

8.2.7. Ionis has set forth on Schedule 6.8.1 or in a separate written agreement with Biogen true, correct and complete lists of the agreements with Third Party licensors or sellers pursuant to which Ionis has licensed or acquired the Licensed Technology Controlled by Ionis as of the Effective Date licensed to Biogen under Section 4.1.1 that is necessary or useful to conduct the research, Development, Manufacture or Commercialization of any High Interest Target listed on the High Interest Target List as of the Effective Date and any Compounds as contemplated under the Collaboration Program targeting [***]. All Ionis In-License Agreements are in full force and effect and have not been modified or amended. Neither Ionis nor, to the best knowledge of Ionis, the Third Party licensor in an Ionis In-License Agreement is in default with respect to a material obligation under such Ionis In-License Agreement, and neither such party has claimed or has grounds upon which to claim that the other party is in default with respect to a material obligation under, any Ionis In-License Agreement.

8.2.8. Schedule 8.2.8 is a complete and accurate list of all agreements that create Third Party Obligations with respect to the Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents that affect the rights granted by Ionis to Biogen under this Agreement.

8.3. **Ionis Covenants**. Ionis hereby covenants to Biogen that, except as expressly permitted under this Agreement:

8.3.1. Ionis will promptly amend Schedule 8.2.4(a), Schedule 8.2.4(b) and Schedule 8.2.4(c) and submit such amended Schedules to Biogen if Ionis becomes aware that any Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents or Ionis Product-Specific Patents are not properly identified on such Schedule.

8.3.2. during the Agreement Term, Ionis will maintain and not breach any Ionis In-License Agreements and any agreements with Third Parties entered into after the Effective Date ("***New Third Party Licenses***") that provide a grant of rights from such Third Party to Ionis that are Controlled by Ionis and are licensed or may become subject to a license from Ionis to Biogen for the Development Candidate under this Agreement;

8.3.3. Ionis will promptly notify Biogen of any material breach by Ionis or a Third Party of any New Third Party License, and in the event of a breach by Ionis, will permit Biogen to cure such breach on Ionis' behalf upon Biogen's request;

8.3.4. Ionis will not amend, modify or terminate any Ionis In-License Agreement or New Third Party License in a manner that would adversely affect Biogen's rights hereunder without first obtaining Biogen's written consent, which consent may be withheld in Biogen's sole discretion;

8.3.5. Ionis will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits or encumbers the rights granted to Biogen under this Agreement;

8.3.6. Ionis will cause its Affiliates to comply with the terms of Section 2.1 and will not permit any Affiliates to conduct any activities that Ionis is prohibited from conducting under Section 2.1;

8.3.7. all employees and contractors of Ionis performing Development activities hereunder on behalf of Ionis will be obligated to assign all rights, title and interests in and to any inventions developed by them, whether or not patentable, to Ionis or such Affiliate, respectively, as the sole owner thereof; and

8.3.8. If, after the Effective Date, Ionis becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Biogen to further Develop, Manufacture or Commercialize a Product, and Biogen has exercised its Option and the license granted to Biogen under this Agreement is in effect, Ionis will make such technology available to Biogen on commercially reasonable terms.

8.4. **DISCLAIMER. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. BIOGEN AND IONIS UNDERSTAND THAT EACH PRODUCT IS THE SUBJECT OF ONGOING RESEARCH AND DEVELOPMENT AND THAT NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF EACH PRODUCT.**

ARTICLE 9
INDEMNIFICATION; INSURANCE

9.1. **Indemnification by Biogen**. Biogen will indemnify, defend and hold harmless Ionis and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses including the reasonable fees of attorneys (collectively "***Losses***") arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("***Claims***") based upon:

9.1.1. the gross negligence or willful misconduct of Biogen, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with Biogen's performance of its obligations or exercise of its rights under this Agreement;

9.1.2. any breach of any representation or warranty or express covenant made by Biogen under ARTICLE 8 or any other provision under this Agreement;

9.1.3. the Development or Manufacturing activities that are conducted by or on behalf of Biogen or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Ionis pursuant to this Agreement); or

9.1.4. the Commercialization of a Product by or on behalf of Biogen or its Affiliates or Sublicensees;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Ionis or its Affiliates, licensees, Sublicensees or contractors, and its or their respective directors, officers, employees and agents or other circumstance for which Ionis has an indemnity obligation pursuant to Section 9.2.

9.2. **Indemnification by Ionis**. Ionis will indemnify, defend and hold harmless Biogen and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses arising out of or resulting from any and all Claims based upon:

9.2.1. the gross negligence or willful misconduct of Ionis, its Affiliates or Sublicensees or its or their respective directors, officers, employees and agents, in connection with Ionis' performance of its obligations or exercise of its rights under this Agreement;

9.2.2. any breach of any representation or warranty or express covenant made by Ionis under ARTICLE 8 or any other provision under this Agreement;

9.2.3. any Development or Manufacturing activities that are conducted by or on behalf of Ionis or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Biogen pursuant to this Agreement); or

9.2.4. any development, manufacturing or commercialization activities that are conducted by or on behalf of Ionis or its Affiliates or Sublicensees with respect to a Discontinued Product;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Biogen or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance for which Biogen has an indemnity obligation pursuant to Section 9.1.

9.3. **Procedure**. If a Person entitled to indemnification under Section 9.1 or Section 9.2 (an "***Indemnitee***") seeks such indemnification, such Indemnitee will (a) inform the indemnifying Party in writing of a Claim as soon as reasonably practicable after such Indemnitee receives notice of such Claim, (b) permit the indemnifying Party to assume direction and control of the defense of the Claim (including the sole right to settle such Claim at the sole discretion of the indemnifying Party; *provided* that (i) such settlement or compromise does not admit any fault or negligence on the part of the Indemnitee, or impose any obligation on, or otherwise materially adversely affect, the Indemnitee or other Party and (ii) the indemnifying Party first obtain the written consent of the Indemnitee with respect to such settlement, which consent will not be unreasonably withheld), (c) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the Claim, and (d) undertake reasonable steps to mitigate any Losses with respect to the Claim. The provisions of Section 7.4 will govern the procedures for responding to a Claim of infringement described therein. Notwithstanding anything in this Agreement to the contrary, the indemnifying Party will have no liability under Section 9.1 or Section 9.2, as the case may be, for Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

9.4. **Insurance**.

9.4.1. **Ionis' Insurance Obligations**. Ionis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement; *provided* that at a minimum, Ionis will maintain, in force from [***] days prior to enrollment of the first patient in a Clinical Study, a [***] insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate. Ionis will furnish to Biogen evidence of such insurance upon request.

9.4.2. **Biogen's Insurance Obligations**. Biogen will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement; *provided* that at a minimum, Biogen will maintain, in force from [***] days prior to enrollment of the first patient in a Clinical Study, a [***] insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate and, *provided further* that such coverage is increased to at least $[***] at least [***] days before Biogen initiates the First Commercial Sale of a Product hereunder. Biogen will furnish to Ionis evidence of such insurance upon request. Notwithstanding the foregoing, Biogen may self-insure to the extent that it self-insures for its other products, but at a minimum will self-insure at levels that are consistent with levels customarily maintained against similar risks by similar companies in Biogen's industry.

9.5. **LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR (A) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9, (B) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OF THIS AGREEMENT, (C) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.4.3(a) BY BIOGEN OR ITS AFFILIATES OR (D) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

ARTICLE 10
TERM; TERMINATION

10.1. **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 10, will continue in full force and effect until this Agreement expires as follows:

10.1.1. on a country-by-country basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to all Products (or Discontinued Product(s)) in such country;

10.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to all Products (or Discontinued Products) in all countries pursuant to Section 10.1.1; and

10.1.3. where every Option has expired as a result of Biogen not providing Ionis a written notice stating Biogen is exercising such Options and paying Ionis the applicable license fees under Section 6.3 by the Option Deadline, or as a result of Section 1.5.2(d) or Section 10.4.2.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 is the "***Agreement Term***."

10.2. **Termination of the Agreement**.

10.2.1. **Biogen's Termination for Convenience**. At any time following payment by Biogen of the upfront fee under Section 6.1, subject to Section 10.4.1 below, Biogen will be entitled to terminate this Agreement as a whole, or terminate this Agreement in part with respect to a particular Collaboration Program, for convenience by providing 90 days written notice to Ionis of such termination.

10.2.2. **Termination for Failure to Divest Competitive Product**. If, after the acquisition by a Party of a Third Party that is developing or commercializing an Acquired Competitive Product or an Acquired Competitive Program, such Party does not, by the end of the Collaboration Divestiture Period, divest itself of a Competitive Product or Competitive Program, as applicable, or terminate the development and commercialization of such Acquired Competitive Product or activities under such Acquired Competitive Program or assign this Agreement to a Third Party that is not itself developing or commercializing a Competitive Product or engaged in a Competitive Program, as set forth in Section 12.5.2, then the non-acquiring Party may terminate this Agreement solely with respect to the Collaboration Program(s) affected thereby immediately upon providing written notice to the acquiring Party.

10.2.3. **Termination Due to Failure to Obtain HSR Clearance**.

(a) If the Parties make an HSR Filing with respect to a Collaboration Program under Section 3.1.4 of this Agreement and the HSR Clearance Date has not occurred on or prior to 90 days after the effective date of the latest HSR Filing made by the Parties, this Agreement will terminate solely with respect to such Collaboration Program (i) at the election of either Party immediately upon notice to the other Party, if the FTC or the DOJ has instituted (or threatened to institute) any action, suit or proceeding including seeking, threatening to seek or obtaining a preliminary injunction under the HSR Act against Biogen and Ionis to enjoin or otherwise prohibit the transactions contemplated by this Agreement related to such Collaboration Program, or (ii) at the election of either Party, immediately upon notice to the other Party, if the Parties have not resolved any and all objections of the FTC and DOJ as contemplated by Section 3.1.4(b). Notwithstanding the foregoing, this Section 10.2.3 will not apply if an HSR Filing is not required to fully perform this Agreement with respect to a Collaboration Program.

(b) If this Agreement is terminated with respect to a Collaboration Program in accordance with Section 10.2.3(a), then, *until* [***] as follows:

(i) If Ionis [***]; and

(ii) If Ionis, its Affiliates or the licensee [***].

Nothing in this Section 10.2.3(b) obligates Ionis to (A) [***] or (B) [***].

10.2.4. Termination for Material Breach.

(a) **Biogen's Right to Terminate**. If Biogen believes that Ionis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.5.3, which is governed by Section 10.2.5 below), then Biogen may deliver notice of such material breach to Ionis. If the breach is curable, Ionis will have [***] days to cure such breach. If Ionis fails to cure such breach within the [***] day period, or if the breach is not subject to cure, Biogen may terminate this Agreement with respect to the Collaboration Program affected by such breach by providing written notice to Ionis. Without limiting the foregoing, breach by a Party of ARTICLE 2 of this Agreement constitutes a material breach of this Agreement with respect to the Collaboration Program affected by such breach. Notwithstanding the foregoing, if Biogen is entitled to terminate this Agreement under this Section 10.2.4(a) with respect to a breach by Ionis that negatively and materially impacts the value of a particular Collaboration Program, in lieu of such termination (and as its sole and exclusive remedy for such breach), Biogen may elect to substitute another High Interest Target for the applicable Collaboration Target by sending Ionis a written notice within [***] days of Biogen becoming aware of such breach, in which case, such substitution will not be counted for purposes of determining whether Biogen has exceeded the Substitution Limit.

(b) **Ionis' Right to Terminate**. If Ionis believes that Biogen is in material breach of (i) a payment obligation under ARTICLE 6 or (ii) one or more material provisions of this Agreement where such material breaches have occurred multiple times over the course of at least a [***] period (where such material breach is not a single continuous event) demonstrating a pattern of failing to timely comply with Biogen's obligations under this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 5.1, which is governed by Section 10.2.5 below), then Ionis may deliver notice of such material breach to Biogen. If the breach is curable, Biogen will have [***] days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within [***] days following such notice). If Biogen fails to cure such breach within the [***] day or [***] day period, as applicable, or if the breach is not subject to cure, Ionis in its sole discretion may terminate this Agreement with respect to the Collaboration Program affected by such breach by providing written notice thereof to Biogen.

10.2.5. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Ionis, in Biogen's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.5.3 prior to the License Effective Date with respect to a particular Collaboration Program, Biogen will notify Ionis and, within [***] days thereafter, Ionis and Biogen will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Ionis' use of Commercially Reasonable Efforts in Section 1.5.3. Following such a meeting, if Ionis fails to use Commercially Reasonable Efforts as contemplated by Section 1.5.3 with respect to such Collaboration Program, then subject to Section 10.2.6 below, Biogen will have the right, at its sole discretion, to (i) terminate this Agreement as it relates to the applicable Collaboration Program or, (ii) prior to the License Effective Date for such Collaboration Program, Biogen may elect to trigger the alternative remedy provisions of Section 10.3 below as it relates to the applicable Collaboration Program in lieu of terminating this Agreement for such Collaboration Program by providing written notice to Ionis. This Section 10.2.5(a) sets forth Biogen's sole and exclusive remedies if Ionis fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.5.3 prior to the License Effective Date for a particular Collaboration Program.

(b) If Biogen, in Ionis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 5.1 with respect to a Collaboration Program above, Ionis will notify Biogen and, within [***] days thereafter, Ionis and Biogen will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Biogen's use of Commercially Reasonable Efforts in Section 5.1. Following such a meeting, if Biogen fails to use Commercially Reasonable Efforts with respect to the applicable Collaboration Program as contemplated by Section 5.1, then subject to Section 10.2.6 below, Ionis will have the right, at its sole discretion, to terminate this Agreement as it relates to such Collaboration Program.

10.2.6. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.4 or Section 10.2.5 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such [***] day period, then the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.4 or Section 10.2.5, or trigger the substitution right under Section 10.2.4(a) or the alternative remedy provisions of Section 10.2.5, as applicable, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within [***] days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.2.7. **Termination for Insolvency**.

(a) Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within 90 days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

(b) 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(56) of the Bankruptcy Code. The Parties will retain and may fully exercise all of 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 of its obligations under this Agreement.

10.2.8. **Termination for Patent Challenge**. Ionis may terminate this Agreement if Biogen (i) commences or otherwise voluntarily determines to participate in any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (ii) directs, supports or actively assists any other Person in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents and, in each case ((i) or (ii)), within [***] days' written notice from Ionis, Biogen fails to rescind any and all of such actions, *provided*, *however* that, nothing in this clause prevents Biogen from taking any of the actions referred to in this clause and *provided further* that Ionis will not have the right to terminate if Biogen:

(a) takes any such action as described in clause (i) or (ii) above as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order, including asserting invalidity as a defense in any court proceeding brought by Ionis asserting infringement of a Licensed Patent; or

(b) Acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent; or

(c) licenses a product for which Ionis has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent.

10.3. **Alternative Remedies to Termination Available to Biogen Prior to the License Effective Date**. If, prior to the License Effective Date with respect to a particular Collaboration Program, Biogen elects to (i) exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement for such Collaboration Program by providing written notice of such election to Ionis in accordance with Section 10.2.5(a), or (ii) exercise the Option in accordance with [***], then, in each case, *solely with respect to the Collaboration Program giving rise to Biogen's exercise of these alternative remedy provisions*, this Agreement will continue in full force and effect with the following modifications:

(a) Ionis will have no further rights or obligations to Develop the Product under the applicable Collaboration Program or participate in the Neurology JSC, JPC or any other subcommittees or working groups established pursuant to this Agreement. Biogen will solely make all decisions that this Agreement would otherwise require or permit the Neurology JSC, JPC or any other subcommittees or working groups, or the Parties collectively, to make; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis;

(b) effective as of the date of Biogen's notice to Ionis electing the alternative remedy provisions of this Section 10.3, Biogen will be deemed for all purposes of this Agreement to have exercised the applicable Option;

(c) Biogen will have and Ionis grants, the exclusive license granted to Biogen under Section 4.1.1 for the applicable Collaboration Program;

(d) Biogen may exclude Ionis from all discussions with Regulatory Authorities regarding the applicable Products, except to the extent Ionis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(e) Biogen's obligation to make further disclosures of Know-How or other information to Ionis regarding the applicable Products pursuant to this Agreement (including pursuant to Section 4.8 and Section 5.2.2) will terminate, other than reports required by Section 6.9.1, Section 10.4.3 (if applicable), and as reasonably required to permit Ionis to perform its obligations under this Agreement, *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement ;

(f) Ionis will perform its obligations under Section 4.8 with respect to the applicable Product within [***] days of Biogen electing to exercise its alternative remedies under this Section 10.3 or exercising the Option in accordance with [***], and will provide to Biogen and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen in assuming complete responsibility for the Development and Manufacture of the applicable Products in an efficient and orderly manner; and

(g) the financial provisions of ARTICLE 6 as they apply to such Collaboration Program will be modified as follows:

(i) *[***] Payments*. Biogen will [***]; and

(ii) *License Fee*. The license fee set forth in Section 6.3 for the applicable Product will be [***]. Such [***] will be due within 90 days after [***] and Biogen's [***].

The milestone provisions of Section 6.4 and the royalty provisions of Section 6.6 will [***].

10.4. Consequences of Expiration or Termination of the Agreement.

10.4.1. In General. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 at any time and for any reason, the following terms will apply to any Collaboration Program that is the subject of such expiration or termination:

(a) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information, except to the extent such Confidential Information is necessary or useful to conduct activities under a surviving Collaboration Program. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes.

(b) **Perpetual, Royalty-Free Non-Exclusive License**. If Biogen has exercised its Option for a particular Collaboration Program, then upon expiration of the Reduced Royalty Period in all countries in which the applicable Products are being or have been sold, Ionis will and hereby does grant to Biogen a perpetual, nonexclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Ionis Know-How to Manufacture, Develop and Commercialize any Product under such Collaboration Program.

(c) **Accrued Rights**. Termination or expiration of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. For purposes of clarification, milestone payments under ARTICLE 6 accrue as of the date the applicable Milestone Event is achieved even if the payment is not due at that time.

(d) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 4.1.2(c) (Effect of Termination on Sublicenses), Section 4.2.2, Section 4.3.2 (Enabling Licenses to Biogen), Section 4.3.3 (Enabling Licenses to Ionis), Section 4.4 (Licenses to Ionis for Biogen Results), Section 4.5 (Right to Obtain Direct License from Biogen to Ionis Partners; Sublicensees of Ionis), Section 4.8 (Technology Transfer after the License Effective Date) (but only to the extent necessary to satisfy the requirements of Section 10.4.3), Section 6.7 (Reverse Royalty Payments to Biogen for a Discontinued Product), Section 6.9.3 (Records Retention), Section 6.10 (Audits), Section 7.1.1 (Ionis Technology and Biogen Technology), Section 7.1.2 (Agreement Technology), Section 7.4.2 (Discontinued Product) Section 8.4 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.2.3(b), Section 10.2.7 (Termination for Insolvency), Section 10.4 (Consequences of Expiration or Termination of the Agreement) (except Section 10.4.4 (Remedies Available to Biogen for Ionis' Material Breach After the License Effective Date)), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections). In addition, subject to Section 10.4.3(d)(vi) (if applicable), the following provisions of this Agreement will survive the expiration or termination of this Agreement, solely as they relate to Jointly-Owned Program Patents: Section 7.2.3 (Jointly-Owned Program Patents), Section 7.2.4 (Other Matters Pertaining to Prosecution and Maintenance of Patent Rights), Section 7.3.1 (Jointly-Owned Program Patents), Section 7.4 (Defense of Claims Brought by Third Parties), Section 7.5 (Enforcement of Patents against Competitive Infringement) and Section 7.6.1 (Jointly-Owned Program Patents).

10.4.2. **Termination Prior to the License Effective Date**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 prior to or on the License Effective Date with respect to a Collaboration Program, or Biogen's Option for an applicable Collaboration Program expires pursuant to Section 3.1.3, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to each Collaboration Program that is the subject of such expiration or termination:

(a) Biogen's Option under Section 3.1 will expire and Ionis will be free to Develop and Commercialize the applicable Product (and any other applicable Compounds) on its own or with a Third Party.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Collaboration Program(s).

(c) To the extent requested by Ionis, Biogen will promptly (i) assign to Ionis any manufacturing agreements with a CMO identified by Ionis to which Biogen is a party, solely to the extent such manufacturing agreements relate to the terminated Collaboration Program and (ii) transfer to Ionis all data, results and information (including Biogen's Confidential Information and any regulatory documentation (including drafts)) related to the testing and Clinical Studies under the terminated Collaboration Program(s) in the possession of Biogen and its contractors to the extent such data, results and information were generated by or on behalf of Biogen under this Agreement; and Ionis will pay all out-of-pocket direct Third Party costs and expenses in transferring such data, results and information together with Biogen's FTE Cost in transferring such data, results and information.

(d) If Biogen terminates this Agreement for convenience with respect to a Collaboration Program after the 30th day following Biogen's receipt of the Development Candidate Data Package for such Collaboration Program, but prior to or on the License Effective Date for such Collaboration Program, then Biogen will [***].

(e) Except as explicitly set forth in Section 10.4.1(a), Section 10.4.1(c) or Section 10.4.1(d), Biogen will have no further rights and Ionis will have no further obligations with respect to each terminated Collaboration Program.

10.4.3. **Termination After the License Effective Date**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after the License Effective Date for a Collaboration Program, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to any Collaboration Program that is the subject of such termination:

(a) The applicable licenses granted by Ionis to Biogen under this Agreement will terminate and Biogen, its Affiliates and Sublicensees will cease selling the applicable Products, unless Ionis elects to have Biogen continue to sell the applicable Products as part of the Transition Services to the extent provided in Section 10.4.5.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Collaboration Program(s).

(c) Except as explicitly set forth in Section 10.4.1(a), Biogen will have no further rights and Ionis will have no further obligations with respect to the terminated Collaboration Program.

(d) If (i) Biogen terminates the Agreement under Section 10.2.1 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement under Section 10.2.4(b) (Ionis' Right to Terminate) or Section 10.2.5 (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply *solely with respect to the terminated Collaboration Program(s)*:

(i) Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Technology Controlled by Biogen as of the date of such reversion that Covers the applicable Discontinued Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Product(s) in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) Within [***] days following the date of the termination, Biogen will assign back to Ionis any Product-Specific Patents and Ionis' interest in any Program Patents that relate to the applicable Discontinued Product(s) previously assigned by Ionis to Biogen under this Agreement;

(iii) Within [***] days following the date of the termination, Biogen will transfer to Ionis for use with respect to the Development and Commercialization of the applicable Discontinued Product(s), any Know-How data, results, and copies of Regulatory Materials in the possession of Biogen as of the date of such reversion to the extent related to such Discontinued Product(s), and any other information or material specified in Section 4.8, *provided that*, for the avoidance of doubt, as between the Parties, title to any intellectual property that is Biogen Technology within any of the foregoing will remain with Biogen subject to the license granted to Ionis under Section 10.4.3(d)(i), except as otherwise provided in Section 10.4.3(d)(iv) below;

(iv) Within [***] days following the date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's right, title and interest in and to all Regulatory Materials, including any NDA, IND and orphan drug designation that relate to the applicable terminated Product(s), *provided that*, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Biogen shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products under the Ionis/Biogen Additional Agreements or products that do not include an Oligonucleotide as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include an Oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (y) for clarity, such assignment of Biogen's right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Biogen intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence, Biogen shall, at least [***] days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Ionis of such intent and provide to Ionis a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Ionis with respect to such proposed excerpt or portion prior to submission thereof;

(v) Within [***] days following the date of the termination, Biogen will, and does hereby, exclusively license to Ionis any trademarks that are specific to a Discontinued Product(s) solely for use with such Discontinued Product(s), in accordance with Section 4.1.5, *mutatis mutandis*; *provided*, *however*, that in no event will Biogen have any obligation to license to Ionis any trademarks used by Biogen both in connection with the Product and in connection with the sale of any other product or service, including any BIOGEN- or BIOGEN-formative marks;

(vi) Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents arising from the terminated Collaboration Program, and Biogen will provide Ionis with (and will instruct its counsel to provide Ionis with) all of the information and records in Biogen's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Program Patents; *provided*, *however*, that if Ionis intends to abandon any such Jointly-Owned Program Patents without first filing a continuation or substitution, then Ionis will notify Biogen of such intention at least [***] days before such Patent Right will become abandoned, and Biogen will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense with counsel of its own choice; and

(vii) Ionis will have the obligation to pay royalties to Biogen under Section 6.7 with respect to the applicable Discontinued Product(s). Such payments will be governed by the financial provisions in Section 6.9, and the definition of Net Sales will apply to sales of Discontinued Product(s) by Ionis, in each case *mutatis mutandis*.

(e) If Ionis terminates this Agreement due to Biogen's material breach or Biogen terminates this Agreement for convenience, then upon Ionis' written request pursuant to a mutually agreed supply agreement, Biogen will sell to Ionis any bulk API, Clinical Supplies and Finished Drug Product in Biogen's possession at the time of such termination, at a price equal to [***].

(f) To the extent requested by Ionis, Biogen will promptly assign to Ionis any manufacturing agreements solely to the extent related to the applicable Discontinued Products and identified by Ionis to which Biogen is a party.

10.4.4. Remedies Available to Biogen for Ionis' Material Breach After the License Effective Date.

(a) **Termination of Committees and Information Sharing**. If, after the License Effective Date for a particular Collaboration Program, Ionis materially breaches this Agreement and fails to cure such breach within the time periods set forth under Section 10.2.4(a), and Biogen does not wish to terminate this Agreement in its entirety (an "***Ionis Breach Event***"), then, in addition to any other remedies Biogen may have under this Agreement or otherwise, Biogen will have the right to do any or all of the following in Biogen's discretion *solely with respect to the Collaboration Programs that are the subject of the Ionis Breach Event*:

(i) Terminate Ionis' right to participate in the Neurology JSC, JPC and any other subcommittees or working groups established pursuant to this Agreement;

(ii) Terminate Ionis' participation in any ongoing research and development programs under the applicable Collaboration Program and Biogen's funding obligations associated therewith;

(iii) Solely make all decisions required or permitted to be made by such committees or the Parties collectively under this Agreement in connection with the Development and Commercialization of the applicable Product; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis;

(iv) Exclude Ionis from all discussions with Regulatory Authorities regarding applicable Products, *except* to the extent Ionis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(v) Terminate Biogen's obligation to make further disclosures of Know-How or other information to Ionis pursuant to this Agreement related to the applicable Products, including pursuant to Section 4.8 and Section 5.2.2, other than reports required by Section 6.9.1, Section 10.4.3 (if applicable), and as reasonably required to permit Ionis to perform its obligations under this Agreement, *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement; and

(vi) If Ionis has not completed the Development activities that are its responsibility under the applicable Collaboration Program Research Plan and Development Plan, then Biogen may, but will not be obligated to, assume all responsibility for all such Development activities that would have otherwise been Ionis' responsibility under this Agreement.

Ionis will cooperate with the foregoing and provide to Biogen and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen in assuming complete responsibility for the Development and Manufacture of the applicable Products in an efficient and orderly manner.

(b) **Biogen's Right of Setoff**. If there is [***] and Biogen does not wish to [***], then, in addition to any other remedies Biogen may have under this Agreement or otherwise, Biogen may setoff against any amounts owed to Ionis pursuant to ARTICLE 6 (Financial Provisions) *solely* with respect to the Collaboration Program that is the subject of the [***] (the "***Setoff Amount***"). If Biogen exercises its setoff right under this Section 10.4.4(b), Biogen will provide Ionis with a written certificate, signed by Biogen's Chief Financial Officer, certifying that the amount setoff by Biogen represents [***]. Notwithstanding the foregoing, if Ionis notifies Biogen in writing (a "***Setoff Dispute Notice***") that it disputes Biogen's assertion that Ionis is in material breach of this Agreement or the amount setoff by Biogen (a "***Setoff Dispute***"), then (i) both Parties will participate in the dispute resolution process set forth on SCHEDULE 10.4.4(b), and (ii) pending the Parties' agreement regarding the appropriate setoff (if any) or a determination by the Advisory Panel of the proper amount that Biogen may setoff (if any) in accordance with SCHEDULE 10.4.4(b), Biogen will pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank. If the Parties cannot settle their dispute by mutual agreement, then, in accordance with SCHEDULE 10.4.4(b) the Advisory Panel will determine (A) the amount (if any) that Biogen may setoff against future payments *solely* with respect to the Collaboration Program that is the subject of the Ionis Breach Event to Ionis going forward, and (B) whether any portion of the escrow account should be released to Ionis or returned to Biogen; *provided* that any decision or determination by the Advisory Panel (a "***Panel Decision***") will not be treated as an arbitral award but will be binding on the Parties until and unless a court of competent jurisdiction (the "***Trial Court***") has determined in a judgment regarding some or all of the issues decided in the Panel Decision, and in any Action contemplated by the next sentence hereof the Trial Court will determine the facts and the law *de novo*, and will give a Panel Decision only such persuasive effect, if any, that after review of all of the facts and the law presented to the Trial Court by the Parties, the Trial Court deems appropriate; *provided further* that the escrow agent will comply with a Panel Decision that determines that any portion of the escrow account should be released to Ionis or returned to Biogen. If it is determined in a judgment by the Trial Court that Ionis owes Biogen any damages, then, during the pendency of any appeal of the Trial Court's decision (or, if the Trial Court's decision is not appealed, until Biogen recoups such amount), Biogen may setoff against any future payments *solely* with respect to the Collaboration Programs that are the subject of the Ionis Breach Event to Ionis under this Agreement the amount of any such damages not paid by Ionis. If it is determined in a Trial Court that Biogen has setoff an amount that exceeds the amount of losses, damages and expenses actually incurred by Biogen as a result of Ionis' breach of this Agreement, then Biogen will promptly pay to Ionis the amount of such excess, plus interest on such amount as provided for in Section 6.12 (Interest on Late Payments), with interest accruing from the time Biogen applied such excess setoff. If, with respect to a Setoff Dispute, Ionis provides a Setoff Dispute Notice to Biogen and Biogen fails to do any of the following: (I) appoint a member of the Advisory Panel to the extent required in Section 2 of SCHEDULE 10.4.4(b); (II) meet with the Advisory Panel as required in Section 3 of SCHEDULE 10.4.4(b); or (III) pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank, then Biogen will forfeit its right to set off under this Section 10.4.4(b) and SCHEDULE 10.4.4(b) with respect to any and all Setoff Disputes.

10.4.5. Transition Services.

(a) In the case where (i) Biogen terminates the Agreement under Section 10.2.1 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement under Section 10.2.4(b) (Ionis' Right to Terminate) or Section 10.2.5(b) (Remedies for Failure to Use Commercially Reasonable Efforts) with respect to one or more Products, the terms of this Section 10.4.5 shall apply.

(b) In such event, the Parties wish to provide a mechanism to ensure that patients who were being treated with the applicable Product prior to such termination or who desire access to such Product can continue to have access to such Product until the regulatory and commercial responsibilities for the Product are transitioned from Biogen to Ionis following termination of the applicable Product. As such, Ionis may request Biogen perform transition services as listed on SCHEDULE 10.4.5 and such other transition services that the Parties mutually agree in writing to (i) provide patients with continued access to the applicable Products, (ii) following termination of this Agreement with respect to the applicable Product, transition the responsibilities under all Approvals and ongoing Clinical Studies for the applicable Products to Ionis or its designee and (iii) following termination of this Agreement with respect to the applicable Product, transition the then-current supply process and responsibilities for the Product to Ionis or its designee (collectively, the "***Transition Services***"). Subject to the Parties agreeing on a transition plan as described in Section 10.4.5(c), Biogen will perform such Transition Services using reasonable efforts for a period not to exceed [***] months from the termination date; *provided* that Biogen and Ionis may mutually agree to conduct the Transition Services for a longer period of time. Notwithstanding the provision of the Transition Services under this Section 10.4.5, Ionis shall not conduct activities with respect to any Discontinued Products to the extent prohibited by ARTICLE 2 of this Agreement.

(c) Ionis may elect to have Biogen perform the Transition Services by providing written notice to Biogen no later than the earlier of (i) [***] days following the effective date of the termination and (ii) [***] days following written notice by Biogen to Ionis asking Ionis to confirm if Ionis wishes to have Biogen perform the Transition Services (*provided* that Biogen did not send such a notice earlier than [***] days following the effective date of the termination). If Ionis requests Transition Services, then Ionis shall propose a transition plan setting forth the Transition Services to be performed by Biogen, including delivery and transition dates consistent with those set forth on SCHEDULE 10.4.5, and, for a period of [***] days after such request, the Parties will use good faith efforts to negotiate a mutually agreeable version of such transition plan. In addition, the Parties will, within [***] days after such request, establish a transition committee consisting of at least each Party's Alliance Managers, a representative from each Party's CMC group who was responsible for the Product prior to the termination, and up to two additional representatives from each Party who are from other relevant functional groups to facilitate a smooth transition. While Biogen is providing Transition Services, Biogen and Ionis will mutually agree on talking points and a communication plan to customers, specialty pharmacies, physicians, Regulatory Authorities, patient advocacy groups and clinical study investigators, and Biogen will make all such communication to such entities in accordance with the mutually agreed talking points.

(d) Ionis will pay Biogen for the Transition Services at [***] to perform the Transition Services, calculated [***]. In addition, Ionis will reimburse [***] to perform the Transition Services. Ionis will own all revenue derived from the Product after the termination date and Biogen will remit all such revenues to Ionis no later than the [***] day following the end of the month in which such revenue was received.

(e) Ionis or its designee will be sufficiently prepared to accept the transition of Development, Manufacturing and Commercialization activities with respect to the Products to Ionis or such designee on the timelines set forth on SCHEDULE 10.4.5 for the Transition Services. Biogen will have no liability under this Agreement with respect to a failure of or delay in the Transition Services to the extent caused by any failure or delay by Ionis or its designee in accepting the transition of Development, Manufacturing and Commercialization activities with respect to the Products. In the event that Biogen encounters any delays beyond Biogen's reasonable control, the Parties shall discuss in good faith and agree upon extended timelines for completion of the Transition Services.

ARTICLE 11
CONFIDENTIALITY

11.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "***Disclosing Party***") or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof (collectively, "***Confidential Information***").

11.2. **Prior Confidentiality Agreement Superseded**. As of the Effective Date, this Agreement supersedes the Confidential Disclosure Agreement executed by Ionis and Biogen on February 28, 2011 (including any and all amendments thereto). All information exchanged between the Parties under such Confidential Disclosure Agreement will be deemed Confidential Information hereunder and will be subject to the terms of this ARTICLE 11.

11.3. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (a) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement; *provided* that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (b) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 11.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing the Product, or as otherwise required by Applicable Law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided*, *however*, that if a Receiving Party or any of its Affiliates is required by Law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (c) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (d) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (e) as mutually agreed to in writing by the Parties.

11.4. Press Release; Publications; Disclosure of Agreement.

11.4.1. Appointment of a Communications Lead. Prior to the Initiation of each Clinical Study under the Development Plan for any Collaboration Program for which Biogen has not yet been granted a license under Section 4.1.1 with respect to a Product, the Neurology JSC shall appoint one of the Parties as the communications lead to take the lead role in drafting, coordinating and facilitating the public disclosure of data and results arising from such Clinical Study (the "***Communications Lead***"); *provided*, *however*, that if a single Party is the IND-holder and sponsor of the Clinical Study, and is responsible for the conduct of the Clinical Study, then that Party shall automatically be deemed to be the Communications Lead. The Communications Lead shall be responsible for drafting the initial publication and for coordinating and facilitating the disclosure activities for such Clinical Study as set forth in Sections 11.4.5 and 11.4.6; *provided*, *however*, that if, after having worked together in good faith, the Communications Lead and the other Party cannot agree on a matter related to the public disclosure of data and results arising from such a Clinical Study, then, subject to and without limiting Sections 11.4.5 and 11.4.6, (i) prior to the License Effective Date for such Collaboration Program, Ionis will have final decision-making authority regarding such matter, and (ii) after the License Effective Date for such Collaboration Program, Biogen will have final decision-making authority regarding such matter.

11.4.2. Public Announcements. On or promptly after the Effective Date, the Parties will jointly issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties. Except to the extent required to comply with Applicable Law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.4, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld, conditioned or delayed.

11.4.3. Use of Name. Except as set forth in Section 11.4.11, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

11.4.4. Notice of Significant Events. Each Party will immediately notify (and provide as much advance notice as possible, but at a minimum two Business Days advance notice to) the other Party of any event materially related to a Product (including in such notice any disclosure of starting/stopping of a Clinical Study, clinical data or results, material regulatory discussions, filings, Approval or Biogen's sales projections) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event.

11.4.5. **Prior to the License Effective Date**. Prior to the License Effective Date with respect to a Product, such Product is the sole property of Ionis and, subject to any communication plan for such Product mutually agreed to by the Parties in accordance with Section 1.5.2(a) and to the provisions of this Section 11.4.5 and Section 11.4.7, Ionis will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public; which shall be consistent with its practice with its other compounds and products; *provided* that with respect to any proposed press release or other similar public communication by Ionis disclosing regulatory discussions, the efficacy or safety data or clinical results related to such Product, (a) Ionis will submit such proposed communication to Biogen for review at least two Business Days in advance of such proposed public disclosure, (b) Biogen will have the right to review and recommend changes to such communication, and (c) Ionis will in good faith consider any changes that are timely recommended by Biogen; and *provided further* that, if Biogen conducted or co-conducted a Clinical Study that is the subject of such public announcement, press release or other public disclosure, then any such public announcement, press release or other public disclosure shall be jointly issued by the Parties (unless Biogen expressly waives in writing its right to jointly issue such public announcement, press release or other public disclosure). If Biogen desires to make any public announcement, issue a press release or make any other public disclosure with respect to a Clinical Study that was conducted or co-conducted by Biogen prior to the date Biogen has been granted a license under Section 4.1.1 with respect to a Product, Biogen shall so notify Ionis and shall provide Ionis with a draft thereof at least two Business Days prior to the proposed publication thereof. Ionis may review and provide comments to Biogen and the Parties shall discuss in good faith any such comments and seek to mutually agree on a final version of such proposed public announcement, press release or other public disclosure. Notwithstanding the foregoing, Ionis shall, pursuant to this Section 11.4.5, retain final decision-making authority over (x) whether such proposed public announcement, press release or other public disclosure shall be issued or made, and (y) the content thereof, and in no event shall Biogen issue any such public announcement, press release or other public disclosure under this Section 11.4.5 except in the final version approved by Ionis.

11.4.6. **After the License Effective Date**. After the License Effective Date with respect to a Product, subject to the provisions of this Section 11.4.6 and Section 11.4.7, Biogen will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public, which shall be consistent with its practice with its other compounds and products; *provided* that with respect to any proposed press release or other similar public communication by Biogen disclosing regulatory discussions, the efficacy or safety data or results related to such Product or Biogen's sales projections, (a) Biogen will submit such proposed communication to Ionis for review at least two Business Days in advance of such proposed public disclosure, (b) Ionis will have the right to review and recommend changes to such communication, and (c) Biogen will in good faith consider any changes that are timely recommended by Ionis; and *provided further* that, if Ionis conducted or co-conducted a Clinical Study that is the subject of such public announcement, press release or other public disclosure, then any such public announcement, press release or other public disclosure shall be jointly issued by the Parties (unless Ionis expressly waives in writing its right to jointly issue such public announcement, press release or other public disclosure). If Ionis desires to make any public announcement, issue a press release or make any other public disclosure with respect to a Clinical Study that was conducted or co-conducted by Ionis, Ionis shall so notify Biogen and shall provide Biogen with a draft thereof at least two Business Days prior to the proposed publication thereof. Biogen may review and provide comments to Ionis and the Parties shall discuss in good faith any such comments and seek to mutually agree on a final version of such proposed public announcement, press release or other public disclosure. Notwithstanding the foregoing, Biogen shall, pursuant to this Section 11.4.6, retain final decision-making authority over (i) whether such proposed public announcement, press release or other public disclosure shall be issued or made and (ii) the content thereof, and in no event shall Ionis issue any such public announcement, press release or other public disclosure under this Section 11.4.6 except in the final version approved by Biogen.

11.4.7. **Resolution of Disagreements Regarding Public Announcements**. If the Parties cannot mutually agree on the need for or content of any press release, presentation or other public disclosure under Section 11.4.5 or Section 11.4.6 that is intended to be jointly issued, then either Party may promptly refer for resolution to a "C" level executive of each Party (e.g., a Party's Chief Operating Officer, Chief Executive Officer or Chief Business Officer) or to one of the Party's Neurology JSC members. During the at least two Business Day advance review period described in Section 11.4.5 or Section 11.4.6 (as applicable), such "C" level executives or Neurology JSC members will meet in person at a mutually acceptable time and location or by means of telephone or video conference to discuss in good faith and attempt to resolve such dispute.

11.4.8. **Scientific or Clinical Presentations for Products**. Regarding any proposed scientific publications or public presentations related to summaries of results from any Clinical Studies generated by Ionis or Biogen for a Product, the Parties acknowledge that scientific lead time is a key element of the value of the Products under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least [***] days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Collaboration Programs. If, during such [***] day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such [***] day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (a) delay such proposed publication for up to [***] days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (b) remove the identified disclosures prior to publication. With respect to each Clinical Study, (i) if such Clinical Study is Initiated prior to the date Biogen has been granted a license under Section 4.1.1 with respect to the applicable Product, Ionis shall determine authorship or attribution with respect to any proposed publications regarding the results of such Clinical Study and (ii) if such Clinical Study is Initiated after the date Biogen has been granted a license under Section 4.1.1 with respect to the applicable Product, Biogen shall determine authorship or attribution with respect to any proposed publications regarding the results of such Clinical Study, in each case ((i) and (ii)), by interpreting and applying the authorship and attribution principles of the International Committee of Medical Journal Editors' *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals*, *provided* that (A) in each case, the Party that has the right to determine attribution or authorship in accordance with this Section 11.4.8 shall consider in good faith any reasonable comments timely made by the other Party with respect thereto, (B) any determination of authorship or attribution under this Section 11.4.8 shall be in compliance with the requirements of the applicable journal of the proposed publication and (C) the Party that does not have the right to determine attribution or authorship in accordance with this Section 11.4.8 for any such proposed publication will have the right to have at least one author listed in such publication if such Party conducted or co-conducted such Clinical Study.

11.4.9. **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

11.4.10. **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or the Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

11.4.11. **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the Collaboration Programs or a Product, the other Party's role in discovering and developing the Product or Discontinued Product, as applicable, that the Product is under license from Ionis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: IONS, BIIB).

(a) Biogen understands and acknowledges the importance to Ionis of continuing to be associated with the drugs it discovers under the Collaboration Programs. As such, Biogen agrees that it will use reasonable efforts to prominently acknowledge Ionis' role in the discovery of a Product in any scientific, medical and other Product-related communications to the extent such communications address the research, discovery or commercialization of a Product, by prominently including the words "*Discovered by Ionis*" or equivalent language (collectively, the "***Ionis Attribution Language***") in any such communications; *provided*, *however*, that Biogen shall have no obligation to include the Ionis Attribution Language in any of the following: (i) communications or materials where such inclusion would be prohibited by Applicable Laws or applicable Third Party institutional, corporate or other policies; (ii) communications that Biogen does not control, such as publications with non-Biogen lead authors; (iii) materials primarily focused on or directed to patients, or other materials where Biogen branding is not prominently featured; or (iv) abstracts or other communications with a word limitation, if Biogen reasonably determines that such word limitation would preclude the inclusion of the Ionis Attribution Language; *provided* that in each case, Biogen will use reasonable efforts to have the Ionis Attribution Language included in any such communication, consistent with the efforts that Biogen uses to have statements regarding its own contributions to the Product included in such communication.

(b) Ionis may include the Products (and identify Biogen as its partner for the Products) in Ionis' drug pipeline.

ARTICLE 12
MISCELLANEOUS

12.1. Dispute Resolution.

12.1.1. Escalation. In the event of any Dispute (other than a Setoff Dispute, which Setoff Dispute will be resolved pursuant to Section 12.1.3, or dispute regarding the construction, validity or enforcement of either Party's Patent Rights, which disputes will be resolved pursuant to Section 12.2), either Party may, within [***] days after either Party notifies the other Party that the Dispute has not been resolved (*provided* that such notice cannot be given less than [***] days after the Dispute has arisen), make a written request that the Dispute be referred for resolution to the Executive Vice President, Business Development of Biogen and the Chief Executive Officer of Ionis (the "***Executives***"). Within [***] days of either Party's written request that the Dispute be referred to the Executives, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of a Dispute. Each Party may elect to have such Party's Neurology JSC representatives participate in such meeting, if desired, *provided* that it provides the other Party with reasonable advance notice of such intent so as to enable the other Party to have its Neurology JSC representatives also participate in such meeting, if desired. If the Executives fail to resolve the Dispute within such [***] day period, then the Dispute will be referred to mediation under Section 12.1.2.

12.1.2. Mediation. If a Dispute subject to Section 12.1.1 cannot be resolved pursuant to Section 12.1.1, or if neither Party timely makes the written request that the Dispute be referred to the Executives, the Parties will resolve any such Dispute in accordance with the dispute resolution procedures set forth in SCHEDULE 12.1.2.

12.1.3. Setoff Disputes. Setoff Disputes will be resolved in accordance with Section 10.4.4(b) and SCHEDULE 10.4.4(b).

12.2. Governing Law; Jurisdiction; Venue; Service of Process.

12.2.1. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles.

12.2.2. Subject to the provisions of Section 12.1, each Party by its execution hereof, (a) hereby irrevocably submits to the exclusive jurisdiction of the United States District Court for the District of Delaware (or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Court of Chancery of the State of Delaware, or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Superior Court of the State of Delaware, with respect to the Dispute) for the purpose of any Dispute arising between the Parties in connection with this Agreement (each, an "***Action***") and (b) hereby waives to the extent not prohibited by Applicable Law, and agrees not to assert, by way of motion, as a defense or otherwise, in any such Action, any claim that it is not subject personally to the jurisdiction of the above-named courts, that venue in the above-named courts is improper, that its property is exempt or immune from attachment or execution, that any such Action brought in the above-named courts should be dismissed on grounds of *forum non conveniens*, should be transferred or removed to any court other than the above-named courts, or should be stayed by reason of the pendency of some other proceeding in any other court other than the above-named courts, or that this Agreement or the subject matter hereof may not be enforced in or by such courts and (c) hereby agrees not to commence any such Action other than before the above-named courts. Notwithstanding the previous sentence, a Party may commence any Action in a court other than the above-named court solely for the purpose of enforcing an order or judgment issued by the above-named court.

12.2.3. Each Party hereby agrees that service of process: (a) made in any manner permitted by Delaware law, or (b) made by overnight express courier service (signature required), prepaid, at its address specified pursuant to Section 12.8, will constitute good and valid service of process in any such Action and (c) waives and agrees not to assert (by way of motion, as a defense, or otherwise) in any such Action any claim that service of process made in accordance with clause (a) or (b) does not constitute good and valid service of process.

12.3. **Remedies**. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary restraining order or a preliminary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Agreement, and the Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive relief would be appropriate. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2, and the offsets under Section 6.8.3(c)). Except for the offsets and credits explicitly set forth in Section 6.10, Section 6.8.3(b), Section 6.8.3(d) and Section 10.4.4(b), neither Party will have the right to setoff any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

12.4. **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided* that if Biogen transfers or assigns this Agreement to [***] described in this Agreement, then Biogen (or such Affiliate), will [***] Ionis under ARTICLE 6 for the [***] such that Ionis receives [***] assignment. In addition, Ionis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Biogen's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any purported assignment or transfer made in contravention of this Section 12.4 will be null and void.

The [***].

To the extent Ionis utilizes a [***] in any year, Ionis will [***] to Biogen [***]. To assist Biogen in determining when a refund is due from Ionis pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which Biogen [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which Ionis utilizes a [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.5. Change of Control.

12.5.1. Pre-Existing Competitive Programs of an Acquirer. If, at any time during the Agreement Term, a Change of Control of a Party occurs involving a Person that, at the time of the execution of such Change of Control, is (A) developing or commercializing a (1) Competitive Product or (2) Competitive Indication Product within the Field (such pre-existing Competitive Products and Competitive Indication Products, each, a "***Pre-Existing Competitive Product***") or (B) is engaged in a Competitive Program or Competitive Indication Program (such pre-existing Competitive Programs and Competitive Indication Programs, each, a "***Pre-Existing Competitive Program***," and such Person being hereinafter referred to as a "***Competing Collaboration Acquirer***"), then in each case ((A) and (B)):

(a) such Party shall promptly provide written notice to the other Party of such Change of Control;

(b) if such Change of Control involved Ionis, then Biogen may elect that some or all of the Biogen Reduced Participation and Information Obligations will apply to the Collaboration Programs to which the Pre-Existing Competitive Product or Pre-Existing Competitive Program relate;

(c) such Party shall conduct activities pursuant to Section 12.6 to separate its Development activities under this Agreement from its development activities relating to any Pre-Existing Competitive Product(s) and Pre-Existing Competitive Program(s); and

(d) the research, development, manufacture or commercialization of any Pre-Existing Competitive Product(s) by a Competing Collaboration Acquirer will not be a violation of such Party's exclusivity covenants under Section 2.1.1 and Section 12.5.2(a) will not apply to any such Pre-Existing Competitive Product or Pre-Existing Competitive Program; *provided* that the conditions of Section 12.5.1(a) and Section 12.5.1(c) are satisfied.

12.5.2. Acquired Competitive Programs; Acquired Associated Programs.

(a) If, at any time during the Agreement Term, either Party acquires a Third Party or a portion of the business of a Third Party (whether by merger, stock purchase or purchase of assets) that is, prior to such acquisition, engaged in discovering, researching, developing or commercializing a Competitive Product within the Field or is engaged in a Competitive Program, in each case that would violate the provisions of ARTICLE 2 if conducted by such Party (such acquired Competitive Product an "***Acquired Competitive Product***" and such acquired Competitive Program an "***Acquired Competitive Program***"), then the limited continuation of the research, development, manufacture or commercialization of the Acquired Competitive Product(s) or Acquired Competitive Programs by the acquiring Party as permitted in this Section 12.5.2(a) in a manner that would have been in the ordinary course of business of such Third Party will not be a violation of such acquiring Party's exclusivity covenants under Section 2.1.1; *provided* that following the closing of such acquisition, the conditions set forth in Sections 12.5.2(a)(i) through 12.5.2(a)(iv) are met:

(i) Such acquiring Party shall promptly provide written notice to the other Party of such acquisition;

(ii) Such acquiring Party shall use reasonable efforts to divest all such Acquired Competitive Products and Acquired Competitive Programs promptly following the closing of such acquisition, and in any event such Party shall complete such divestment within [***] after the closing of such acquisition (the "***Collaboration Divestiture Period***"); *provided* that such Collaboration Divestiture Period shall be extended, and such Party shall not be in breach of this Section 12.5.2(a) if, at the expiration thereof (and any extensions thereto), such Party provides competent evidence of reasonable ongoing efforts to divest such Acquired Competitive Products and Acquired Competitive Programs; *provided further* that such Party shall cease all development and commercialization activities with respect to all such Acquired Competitive Products and Acquired Competitive Programs if such Party has not completed such divestiture within [***] after the closing of such acquisition (it being understood that such Party may thereafter continue its efforts to divest such asset);

(iii) During such divestiture period, the acquiring Party shall comply with Section 12.6 to separate its Development activities under this Agreement from its development activities relating to any Acquired Competitive Product or Acquired Competitive Program; and

(iv) Neither Party nor its Affiliates may acquire a Competitive Product or a Competitive Program on a standalone basis.

(b) If Ionis is the acquiring Party of an Acquired Competitive Product or Acquired Competitive Program, then during the Collaboration Divestiture Period until Ionis [***], Biogen may elect that [***].

(c) In addition, without limiting Section 12.5.2(a)(iv), if at any time during the Agreement Term, (i) Ionis acquires a Third Party or a portion of the business of a Third Party (whether by merger, stock purchase or purchase of assets) that is, prior to such acquisition, engaged (A) in [***] (an "***Associated Product***") or any Competitive Indication Product, or (B) is engaged in [***] (an "***Associated Program***") or a Competitive Indication Program, (ii) Ionis or an Ionis Affiliate [***] or (iii) Ionis or an Ionis Affiliate [***] then, in each case ((i) through (iii)) with respect to any Collaboration Program directed to the Collaboration Target to which the Associated Product, Associated Program, Competitive Product or Competitive Program is directed and with respect to any Collaboration Program intended for the same indication as the Competitive Indication Product or the Competitive Indication Program, Biogen may elect that [***] and Ionis shall comply with the same procedures as under Section 12.6 to separate its Development activities under this Agreement from its development activities relating to any such Associated Product, Associated Program, Competitive Product, Competitive Program, Competitive Indication Product or Competitive Indication Program.

12.6. **Protective Provisions**. At any time while (a) the Party involved in a Change of Control with a Competing Collaboration Acquirer, (b) the Party with an Acquired Competitive Product or Acquired Competitive Program or (c) Ionis (in cases where Ionis otherwise has an Associated Product, Associated Program, Competitive Product, Competitive Program, Competitive Indication Product or Competitive Indication Program) is conducting Development activities under this Agreement, then, in each case ((a) through (c)) such Party (as applicable under clause (a), (b) or (c)) must separate such Development activities from its or its Affiliates' other development activities relating to any such Competitive Product or Competitive Program, and, in the case of Ionis, from any such Associated Product, Associated Program, Competitive Indication Product or Competitive Indication Program, as applicable (such other development activities, "***Competing Development Activities***"). To that end, and subject to the licenses granted to each Party (as applicable) under Section 4.3 or Section 4.4, any such Party will, and (if applicable) will cause the Competing Collaboration Acquirer to, (i) establish separate teams to conduct Development activities under this Agreement and such Competing Development Activities, (ii) prevent any Confidential Information relating to the Development, Manufacture or Commercialization of any applicable Product (including Know-How) from being disclosed to, or used by, individuals performing such Competing Development Activities and (iii) not use or reference in the development, manufacture or commercialization of the Competitive Product any Know-How that is Confidential Information or conduct any activities Covered by any Patent Rights, in each case, Controlled by the Party involved in the Change of Control or the acquisition or its Affiliates prior to the effective date of the Change of Control or the acquisition.

12.7. **Force Majeure**. No Party will be held 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 performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or Laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying 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 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 90 days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

12.8. **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested) electronic mail transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Ionis, addressed to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Executive Officer E-mail: [***]
with a copy to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel E-mail: [***]
If to Biogen, addressed to:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 Attention: Chief Legal Officer E-mail: [***]
with a copy to:	Ropes & Gray LLP Prudential Tower 800 Boylston Street Boston, MA 02199-3600 Attention: Hannah Freeman E-mail: hannah.freeman@ropesgray.com

or to such other address for such Party as it will have specified by like notice to the other Party; *provided* that notices of a change of address will be effective only upon receipt thereof. If delivered personally or by electronic mail transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery will be deemed to be the third Business Day after such notice or request was deposited with the U.S. Postal Service.

12.9. **Export Clause**. Each Party acknowledges that the Laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

12.10. **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

12.11. **Severability**. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, then the Parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

12.12. **Entire Agreement**. This Agreement, together with the Schedules and Appendices hereto (including the [***] Letter), amends and restates the Original Agreement, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties with respect to the subject matter hereof, fully supersedes the Original Agreement for the period commencing on the Amendment Date and continuing thereafter and supersedes and terminates all prior agreements and understanding between the Parties with respect to the subject matter hereof. Without limiting the foregoing, this Agreement supersedes that certain side letter between the Parties, dated as of October 9, 2015, relating to drug substance process development and manufacturing, solely to the extent such side letter relates to Collaboration Programs under this Agreement. For clarity, such side letter shall remain in full force and effect with respect to the Ionis/Biogen Additional Agreements. For the avoidance of doubt, this Agreement in no way supersedes, modifies or otherwise affects any of the Ionis/Biogen Additional Agreements, which will remain in full force and effect in accordance with each of their respective terms. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties with respect to the subject matter hereof other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement will be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

12.13. **Independent Contractors**. Nothing herein will be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party will assume, either directly or indirectly, any liability of or for the other Party. Neither Party will have the authority to bind or obligate the other Party and neither Party will represent that it has such authority.

12.14. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word "including" (in its various forms) means "including without limitation," (c) the words "shall" and "will" have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, "$" is in reference to United States dollars, and (h) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

12.15. **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with U.S. Generally Accepted Accounting Principles (or any successor standard), consistently applied.

12.16. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

12.17. **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

12.18. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

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

12.20. **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant Laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

*** - * - * - ***

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

BIOGEN MA INC.

By:/s/Anabella Villalobos
Name: Anabella Villalobos
Title: Senior Vice President, Biotherapeutics & Medicinal Sciences

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

IONIS PHARMACEUTICALS, INC.

By:/s/Brett Monia
Name: Brett Monia
Title: Chief Executive Officer

List of Appendices and Schedules

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***Accelerated Target***" has the meaning set forth in Section 2.3.

"***Acceptance***" means, with respect to an NDA, MAA or JNDA filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by Biogen of written notice of acceptance by the EMA of such MAA for filing under the centralized European procedure in accordance with any feedback received from EU Regulatory Authorities; *provided* that if the centralized filing procedure is not used, then Acceptance will be determined upon the acceptance of such MAA by the applicable Regulatory Authority in a Major Market in the EU, (c) in any Major Market in Europe that is not a European Union country, receipt by Biogen of written notice of acceptance by the applicable Regulatory Authority of such MAA for filing in such country, and (d) in Japan, receipt by Biogen of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Acquired Competitive Product***" has the meaning set forth in Section 12.5.2(a).

"***Acquired Competitive Program***" has the meaning set forth in Section 12.5.2(a).

"***Action***" has the meaning set forth in Section 12.2.2.

"***Actual Biogen-Approved Costs***" has the meaning set forth in Section 1.8.5.

"***Additional Core IP***" means Third Party intellectual property that is necessary to [***]. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***].

"***Additional Plan Costs***" means [***].

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (a) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (b) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity. For clarity, Regulus Therapeutics Inc. will not be deemed an "*Affiliate*" of Ionis for the purposes of this Agreement under any circumstances.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 10.1.

"***Alliance Manager***" has the meaning set forth in Section 1.11.5.

"***Amendment Date***" has the meaning set forth in the Preamble of this Agreement.

"***ANDA***" means an Abbreviated New Drug Application and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any equivalent agency or governmental authority outside the U.S. (including any supra-national agency such as the EMA in the EU).

"***Annual***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP for a Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means, with respect to a Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing or reimbursement authorizations necessary for the general marketing and sale of such Product in the marketplace, Approval will not be deemed to have occurred if the final approval to market and sell such Product is being withheld because Biogen (or its Affiliate or Sublicensee) and the Regulatory Authority have not yet determined pricing or reimbursement even if all other approvals, licenses, registrations or authorizations necessary for marketing, sale or use of such Product in such jurisdiction have been obtained. "Approval" does not include authorization by a Regulatory Authority to conduct named patient, compassionate use or other similar activities.

"***ASO***" means an Oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target, excluding any double-stranded Oligonucleotide compounds that are designed to act through the RNA-induced silencing complex.

"***Associated Product***" has the meaning set forth in Section 12.5.2(c).

"***Associated Program***" has the meaning set forth in Section 12.5.2(c).

"***Audit Report***" has the meaning set forth in Section 6.10.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.7(b).

"***Biogen***" has the meaning set forth in the Preamble of this Agreement.

"***Biogen Activities***" means, under any Collaboration Program Research Plan or Development Plan, any and all research, pre-clinical and/or clinical activities that Biogen agrees to conduct; *provided* that Biogen will be deemed to have agreed to conduct any activities designated as Biogen Activities under any Collaboration Program Research Plan or Development Plan it approves.

"***Biogen-Approved Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the applicable Development Plan for a Product that are requested by either Party after the Parties have set the initial Cost Estimates for such Development Plan under Section 1.5.2(b), and (i) required by a Regulatory Authority or (ii) agreed to be paid for by Biogen.

"***Biogen-Approved Costs***" has the meaning set forth in Section 1.8.

"***Biogen's FTE Cost***" means the FTE Rate applicable to Biogen, *multiplied* by the applicable number of FTEs.

"***Biogen Full Royalty***" has the meaning set forth in Section 6.6.1.

"***Biogen Know-How***" means any Know-How owned, used, developed by, or licensed to Biogen or its Affiliates, in each case to the extent Controlled by Biogen or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the Biogen Program Know-How.

"***Biogen Manufacturing Program Patent***" has the meaning set forth in Section 4.8.5(a).

"***Biogen Patents***" means any Patent Rights included in the Biogen Technology.

"***Biogen Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to Biogen or its Affiliates, in each case to the extent Controlled by Biogen or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Biogen Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Biogen Program Patents***" has the meaning set forth in Section 7.1.2.

"***Biogen Program Technology***" has the meaning set forth in Section 7.1.2.

"***Biogen-Prosecuted Patents***" has the meaning set forth in Section 7.2.4.

"***Biogen Reduced Participation and Information Obligations***" means solely with respect to the [***] (a) Biogen may [***], (b) Biogen will [***], (c) Biogen may [***] and (d) Biogen's obligation [***], other than (i) reports required by Section 5.2.2, Section 6.9.1 and Section 10.4.3 (if applicable) (ii) upon Ionis' reasonable request, information to the extent required to confirm Biogen's compliance with its obligations under Section 5.1 and (iii) as reasonably required to permit Ionis to perform its obligations under this Agreement. The Biogen Reduced Participation and Information Obligations will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement.

"***Biogen Reduced Royalty***" has the meaning set forth in Section 6.6.2(c).

"***Biogen Results***" has the meaning set forth in Section 4.8.5(a).

"***Biogen Supported Pass-Through Costs***" means [***].

"***Biogen Technology***" means the Biogen Program Technology, Jointly-Owned Program Technology, Biogen Product-Specific Patents and any trademarks described in Section 4.1.5, owned, used, developed by, or licensed to Biogen or its Affiliates that is necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, New York are open for business.

"[***]" means [***], or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***Calendar Quarter***" means a period of three consecutive months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2012, the Effective Date) and ending on December 31.

"***Carryover Development Candidate***" has the meaning set forth in Section 1.7.4.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent Laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control***" means, with respect to a Party, (a) a merger or consolidation of such Party with a Third Party which results in the voting securities of such Party outstanding immediately prior thereto ceasing to represent at least 50% of the combined voting power of the surviving entity immediately after such merger or consolidation, (b) a transaction or series of related transactions in which a Third Party, together with its Affiliates, becomes the owner of 50% or more of the combined voting power of the outstanding securities of such Party, (c) the sale or other transfer to a Third Party of all or substantially all of such Party's business to which the subject matter of this Agreement relates, or (d) the stockholders or equity holders of such Party will approve a plan of complete liquidation of such Party or an agreement for the sale or disposition by such Party of all or a substantial portion of such Party's assets, other than pursuant to the transaction as described above or to an Affiliate. Notwithstanding the foregoing, the sale or issuance of shares in exchange for cash for purposes of a *bona fide* financing will not constitute a Change of Control.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, Phase 3 Trial or Phase 4 Trial, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA or other similar marketing application.

"***Clinical Supplies***" means API and Finished Drug Product for use in a Clinical Study.

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

"***CMO***" means a Third Party contract manufacturer Manufacturing API, Clinical Supplies or Finished Drug Product for any purpose under this Agreement.

"***Collaboration Divestiture Period***" has the meaning set forth in Section 12.5.2(a)(ii).

"***Collaboration Program***" has the meaning set forth in Section 1.2.

"***Collaboration Program Research Plan***" has the meaning set forth in Section 1.5.1(b).

"***Collaboration Target***" means a gene target designated as a Collaboration Target pursuant to Section 1.4.

"***Collaborator IP***" has the meaning set forth in Section 7.1.3(b).

"***Collaborator License***" has the meaning set forth in Section 7.1.3(c).

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Product following receipt of Approval for such Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of such Product and studies to provide improved formulation and Product delivery, and launching and promoting such Product in each country.

"***Commercializing Party***" means (a) Biogen, with respect to a Product that is being Developed and Commercialized by or on behalf of Biogen, its Affiliates or Sublicensees hereunder, and (b) Ionis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Ionis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means the carrying out of discovery, research, development or commercialization activities using good-faith commercially reasonable and diligent efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, Regulatory Authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of Approval and other relevant scientific, technical and commercial factors. Without limiting any of the foregoing, Commercially Reasonable Efforts as it applies to Biogen's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform the "*General Activities*" described in SCHEDULE 5.1.1, and Commercially Reasonable Efforts as it applies to Ionis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to adhere to the activities and timelines set forth in each Collaboration Program Research Plan and Development Plan.

"***Communications Lead***" has the meaning set forth in Section 11.4.1.

"***Competing Collaboration Acquirer***" has the meaning set forth in Section 12.5.1.

"***Competing Development Activities***" has the meaning set forth in Section 12.6.

"***Competitive Indication Product***" means any product intended for use in the same indication as any Development Candidate or Product.

"***Competitive Indication Program***" means any internal research program for which a budget has been established or to which research personnel have been assigned, with the goal of discovering and developing a Competitive Indication Product for which drug discovery activities have been initiated.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Competitive Product***" means any ASO that is designed to bind to or directly modulate the RNA that encodes a High Interest Target or a Collaboration Target, other than a Product that is being pursued under this Agreement.

"***Competitive Program***" means any internal research program for which a budget has been established or to which research personnel have been assigned, with the goal of discovering and developing a Competitive Product for which drug discovery activities have been initiated.

"***Complete***," "***Completed***," or "***Completion***" means, with respect to a Clinical Study, the point in time at which the primary database lock for such study has occurred and, if such study has a statistical analysis plan, the data generated based on that primary database lock under the statistical analysis plan for such study are available.

"***Compound***" means on a Collaboration Program-by-Collaboration Program basis, any ASO that is designed to bind to the RNA that encodes the applicable Collaboration Target, where such ASO is discovered by Ionis prior to or in the performance of the Collaboration Program Research Plan, including each Development Candidate under such Collaboration Program.

"***Confidential Information***" has the meaning set forth in Section 11.1. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(d) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Conflicting Patent Right***" has the meaning set forth in Section 7.2.4(d).

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided*, *however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Ionis Supported Pass-Through Costs in the case of Ionis, and other than Biogen Supported Pass-Through Costs in the case of Biogen), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Cost Estimate***" has the meaning set forth in Section 1.5.2(b).

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CTD***" has the meaning set forth in Section 4.6.

"***Deficiency Notice***" has the meaning set forth in Section 3.1.2.

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to the Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of the Product to seek Approval for additional indications for the Product.

"***Development Candidate***" means a Compound that is reasonably determined by Ionis' RMC in accordance with Ionis' standard procedures for designating development candidates [***] as ready to start IND-Enabling Toxicology Studies. The checklist Ionis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as Appendix 2.

"***Development Candidate Data Package***" means, with respect to a [***], the [***]; *provided* that such package contains the [***]. The checklist Ionis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as Appendix 2.

"***Development Plan***" has the meaning set forth in Section 1.5.2(a).

"***Diagnostic Option***" has the meaning set forth in Section 3.2.1.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means a Product that is the subject of a termination under this Agreement.

"***Dispositive Disagreement Condition***" has the meaning set forth in Section 1.3.2.

"***Dispute***" means any dispute arising between the Parties relating to, arising out of or in any way connected with this Agreement or any term or condition hereof, or the performance by either Party of its obligations hereunder, whether before or after termination of this Agreement that cannot be resolved by the Parties.

"***DMPK Agreement***" means the DMPK Research, Development, Option and License Agreement between the Parties dated June 27, 2012, as amended and/or restated from time to time.

"***DOJ***" has the meaning set forth in Section 3.1.4(a).

"***Drug Development Program***" means the aggregate drug development activities related to each Development Candidate through [***] under a Collaboration Program in accordance with the applicable Development Plan for all Collaboration Programs under this Agreement.

"***Drug Discovery Program***" means the aggregate drug discovery activities including drug screening, identification, characterization, optimization and other necessary activities according to the applicable Collaboration Program Research Plans to achieve Target Sanction status, and then identify a Development Candidate for all Collaboration Programs under this Agreement.

"***Drug Discovery Term***" has the meaning set forth in Section 1.7.1.

"***Effective Date***" has the meaning set forth in the Recitals of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***Enabled Core Program Patents***" means Program Patents Controlled by a Party or any of its Affiliates on the Effective Date or during the Agreement Term claiming (a) methods of dosing (frequency, duration, concentration, volume, etc.) generally applicable to Oligonucleotides to achieve optimal tissue distribution or enhance other properties of an Oligonucleotide; (b) methods of determining an effective human dose based on animal data that are generally applicable to Oligonucleotides; (c) methods of determining an effective dose based on actual or modeled pharmacokinetic data generally applicable to Oligonucleotides; (d) methods of identifying or optimizing predictive biomarkers for diseases; (e) observations about a disease based on data from a natural history study; (f) proprietary disease models; or (g) methods of using radio-labeled ligands with Oligonucleotides in animals.

"***Estimated Lock Date***" has the meaning set forth in Section 3.1.1.

"***Estimated Biogen-Approved Costs***" means Ionis' good faith estimate of the Biogen-Approved Costs it will incur during the applicable Measurement Period.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Excluded Payments***" means (a) royalty or profit sharing payments, or any other type of payment based on periodic sales of a Product; (b) payments made in consideration of Ionis' or Ionis' Affiliate's equity or debt securities at fair market value; (c) payments made to pay for or reimburse Ionis or Ionis' Affiliate for the fully-burdened cost of research and development; (d) payments made to pay for or reimburse Ionis or Ionis' Affiliate for the cost of prosecuting, maintaining or defending Patent Rights; and (e) payments made to Ionis or Ionis' Affiliate to pass-through to a Third Party in satisfaction of a payment obligation Ionis or Ionis' Affiliate has to such Third Party.

"***Executives***" has the meaning set forth in Section 12.1.1.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***Field***" means, except as may be limited under Section 4.1.4, any prophylactic or therapeutic use or form of administration for any indication.

"***Finished Drug Product***" means any drug product containing API as an active ingredient in finished bulk form for the Development or Commercialization by a Party under this Agreement.

"***First Commercial Sale***" means with respect to a Product, the first sale of such Product by Biogen, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of the Product has been obtained in such country.

"***Follow-On Agreement***" has the meaning set forth in Section 2.1.2.

"***Follow-On Compound***" means, with respect to a given Compound for a given Collaboration Target, any ASO (other than the Development Candidate for such Collaboration Target) that is designed to bind to the RNA that encodes such Collaboration Target discovered by or on behalf of Ionis following the License Effective Date for the applicable Collaboration Program.

"***Follow-On Interest Notice***" has the meaning set forth in Section 2.1.2(a).

"***Follow-On Negotiation Notice***" has the meaning set forth in Section 2.1.2.

"***FTC***" has the meaning set forth in Section 3.1.4(a).

"***FTE***" means a total of 47 weeks or 1880 hours per year of work on the Development, Manufacturing or Commercialization of a Product carried out by employees of a Party having the appropriate relevant expertise to conduct such activities.

"***FTE Costs***" has the meaning set forth in Section 1.8.

"***FTE Rate***" means $[***] for the Calendar Year 2012. The FTE Rate will be increased each Calendar Year thereafter by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.6.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Ionis as determined using the methodology set forth in SCHEDULE 4.6.3 fairly applied and as employed on a consistent basis throughout Ionis' operations.

"***Gene-Editing Product***" means an Oligonucleotide that, when introduced into a cell of an organism, (a) is stably integrated within the genome or stable episome of the cell of such organism or (b) causes (or is perceived to cause) a permanent change in the genome of the cell of such organism.

"***Generic Product***" means, with respect to a particular Product, one or more Third Party product(s) (a) having the same active pharmaceutical ingredient as such Product and for which in the U.S. an ANDA has been filed naming such Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to such Product has been asserted, and (b) such Third Party product(s) when taken in the aggregate have a market share (measured in number of prescriptions with the numerator of such fractional share being such Third Party product(s) taken in the aggregate, and the denominator being the total of such Third Party product(s) taken in the aggregate plus such Product taken in the aggregate, as provided by IMS) during the applicable Calendar Quarter in such country of at least [***]%.

"***GLP***" means the then-current good laboratory practice standards promulgated or endorsed by the FDA as defined in 21 C.F.R. Part 58, and comparable foreign regulatory standards.

"***High Interest Target***" has the meaning set forth in Section 1.3.1. For clarity, at any given time, if a gene target is not on the High Interest Target List at such time, then such gene target is not a High Interest Target.

"***High Interest Target Development Candidate***" means an ASO that is discovered by or on behalf of Ionis and designed to bind to the RNA that encodes a High Interest Target that is reasonably determined by Ionis' RMC to be a development candidate in accordance with Ionis' standard procedures for designating development candidates.

"***High Interest Target List***" has the meaning set forth in Section 1.3.1.

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

"***HSR Clearance***" means all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Clearance Date***" means the earliest date on which the Parties have actual knowledge that all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Filing***" means filings by Biogen and Ionis with the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice of a Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) with respect to the matters set forth in this Agreement, together with all required documentary attachments thereto.

"***HSR Termination Royalty***" has the meaning set forth in Section 10.2.3(b)(ii).

"***Incremental Tax Cost***" has the meaning set forth in Section 12.4.

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***Initiation***" or "***Initiate***" means, with respect to any IND-Enabling Toxicology Study, dosing of the first animal subject in such IND-Enabling Toxicology Study and, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Development Plan***" or "***IDP***" has the meaning set forth in Section 5.1.2.

"***Ionis***" has the meaning set forth in the Preamble of this Agreement.

"***Ionis Attribution Language***" has the meaning set forth in Section 11.4.11.

"***Ionis/Biogen Additional Agreement***" means (a) each of the Ionis/Biogen Preexisting Development Agreements, (b) the Neurology II Agreement, (c) the Research Collaboration, Option and License Agreement between the Parties dated December 19, 2017, and (d) the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated April 19, 2018, in each case ((a)-(d)), as amended or restated from time to time.

"***Ionis/Biogen Preexisting Development Agreements***" means the SMN Agreement and the DMPK Agreement.

"***Ionis Breach Event***" has the meaning set forth in Section 10.4.4(a).

"***Ionis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Ionis Product-Specific Patents or Ionis Manufacturing and Analytical Patents. A list of Ionis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(a) attached hereto.

"***Ionis In-License Agreements***" has the meaning set forth in Section 6.8.1(a).

"***Ionis Internal ASO Safety Database***" has the meaning set forth in Section 5.2.2.

"***Ionis Know-How***" means any Know-How, including any Jointly-Owned Program Know-How and Ionis Program Know-How, owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. Ionis Know-How does not include the Ionis Manufacturing and Analytical Know-How.

"***Ionis Manufacturing and Analytical Know-How***" means Know-How, including Jointly-Owned Program Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. Ionis Manufacturing and Analytical Know-How does not include the Ionis Know-How.

"***Ionis Manufacturing and Analytical Patents***" means Patent Rights, including Jointly-Owned Program Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Ionis Manufacturing and Analytical Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(b) attached hereto. Ionis Manufacturing and Analytical Patents do not include the Ionis Product-Specific Patents or the Ionis Core Technology Patents.

"***Ionis Platform Technology***" has the meaning set forth in Section 8.2.4.

"***Ionis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Ionis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(c) attached hereto.

"***Ionis Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Ionis Program Patents***" has the meaning set forth in Section 7.1.2.

"***Ionis Program Technology***" has the meaning set forth in Section 7.1.2.

"***Ionis Results***" has the meaning set forth in Section 4.8.5(a).

"***Ionis Supported Pass-Through Costs***" means [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***JNDA Approval***" means the Approval of a JNDA by the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto) for the applicable Product in Japan.

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 7.1.3(a).

"***Jointly-Owned Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Patents***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Technology***" has the meaning set forth in Section 7.1.2.

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable.

"***Lead Party***" has the meaning set forth in Section 7.4.1.

"***License Effective Date***" means, on an Option-by-Option and Collaboration Program-by-Collaboration Program basis, the date on which Biogen notifies Ionis in writing that it wishes to exercise the Option and pays to Ionis the applicable license fee set forth in Section 6.3 (in the event Biogen wishes to exercise its Option for a Collaboration Program).

"***Licensed Know-How***" means Ionis Manufacturing and Analytical Know-How, and Ionis Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices.

"***Licensed Patents***" means the Ionis Product-Specific Patents, Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents and Ionis' interest in Jointly-Owned Program Patents. For clarity, Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices unless such Patent Rights are included in the Jointly-Owned Program Patents.

"***Licensed Technology***" means, on a Product-by-Product basis, any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 4.1.5, to the extent necessary or useful to Develop, register, Manufacture or Commercialize such Product. Licensed Technology does not include any technology in-licensed by Ionis from [***] under the [***].

"***Losses***" has the meaning set forth in Section 9.1.

"***MAA***" means, with respect to a particular Product, a marketing authorization application filed with the EMA or other European Regulatory Authority after completion of Clinical Studies to obtain Approval for such Product under the centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures in any European Union country or other country in Europe.

"***MAA Approval***" means, with respect to a particular Product, the Approval of an MAA by the EMA for such Product in any European Union country or other country in Europe.

"***Major Market***" means any of the following countries: the United States, Japan, the United Kingdom, Germany, France, Italy and Spain.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical and clinical purposes, of API or a Product in finished form.

"***Manufacturing Process Development Terms***" means Section 4.1.2(c)(ii), Section 4.3.1(a), Section 4.3.1(c), Section 4.4, Section 4.5, Section 4.7.2 and Section 4.8.5 of this Agreement.

"***Measurement Period***" has the meaning set forth in Section 1.8.3 or Section 1.8.4, as applicable.

"***Milestone Event***" means a Pre-Licensing Milestone Event or a Post-Licensing Milestone Event, as the case may be.

"***Minimum Third Party Payments***" means [***].

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***NDA Approval***" means the Approval of an NDA by the FDA for a Product in the U.S.

"***Negotiation Period***" has the meaning set forth in Section 2.1.2.

"***Net Sales***" means the gross amount billed or invoiced on sales of a Product by Biogen, its Affiliates and Sublicensees, less the following:

(a) customary trade, quantity, or cash discounts to non-affiliated brokers or agents to the extent actually allowed and taken;

(b) amounts repaid or credited by reason of rejection or return;

(c) to the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes or other governmental charges levied on the production, sale, transportation, delivery, or use of such Product which is paid by or on behalf of Biogen; and

(d) outbound transportation costs prepaid or allowed and costs of insurance in transit.

In any transfers of a Product between Biogen, its Affiliates and Sublicensees, Net Sales are calculated based on the final sale of such Product to an independent Third Party. If Biogen, its Affilate or a Sublicensee receives non-monetary consideration for a Product, Net Sales are calculated based on the fair market value of that consideration. If Biogen, its Affiliates or Sublicensees uses or disposes of a Product in the provision of a commercial service, the Product is sold and the Net Sales are calculated based on the sales price of the Product to an independent Third Party during the same royalty period or, in the absence of sales, on the fair market value of the Product as determined by the Parties in good faith. Net Sales shall not include any transfers of supplies of the applicable Product for (i) use in clinical trials, pre-clinical studies or other research or development activities, or (ii) a *bona fide* charitable purpose, or (iii) a commercially reasonable sampling program.

With respect to Net Sales as it applies to royalties payable by Ionis, the Parties agree that any reasonable definition of "net sales" that is (x) customarily used in pharmaceutical industry technology licensing or collaboration contracts and (y) consistent with GAAP or International Financial Reporting Standards and is subsequently agreed to by Ionis (or a Third Party acquirer or assignee) and Ionis' Sublicensee or commercialization partner in an arms-length transaction under a particular sublicense or commercialization agreement will replace the definition of Net Sales in this Agreement and will be used in calculating the royalty payment to Biogen on sales of products sold pursuant to such agreement. If Ionis uses such an alternate definition of "net sales" in a particular sublicense, (A) Ionis will include such "net sales" definition in the applicable royalty reports to assist Biogen with verifying royalty payments and (B) if such definition is not consistent with GAAP or International Financial Reporting Standards, upon Biogen's request, Ionis will reconcile the royalties calculated under such definition with GAAP or International Financial Reporting Standards.

"***Neurology II Agreement***" means the Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated October 17, 2018.

"***Neurology JSC***" has the meaning set forth in Section 1.11.1.

"***New Third Party Licenses***" has the meaning set forth in Section 8.3.2.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***[***] Indications***" means therapeutic uses that are not designed to treat [***] diseases or [***] diseases.

"***Oligonucleotide***" means a synthetic compound that comprises or consists of at least five linked nucleosides (including any analog, variant, mimic, or mimetic thereof). For clarity, the [***] of Oligonucleotides [***]. Oligonucleotides [***]. Oligonucleotides may be single-stranded or multi-stranded.

"***Option***" has the meaning set forth in Section 3.1.3.

"***Option Acceleration Deadline***" has the meaning set forth in Section 1.5.2(d).

"***Option Acceleration Notice***" has the meaning set forth in Section 1.5.2(d).

"***Option Deadline***" has the meaning set forth in Section 3.1.3.

"***Option Period***" means, with respect to a Collaboration Program, the period beginning on the Effective Date and ending on the expiration or earlier termination of the Option with respect to such Collaboration Program.

"***Original Agreement***" has the meaning set forth in the Recitals of this Agreement.

"***Panel Decision***" has the meaning set forth in Section 10.4.4(b).

"***Party***" or "***Parties***" means Biogen and Ionis individually or collectively.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (a) licenses granted by Ionis before or after the Effective Date to any Third Party under the Ionis Core Technology Patents, the Ionis Manufacturing and Analytical Patents, or the Ionis Manufacturing and Analytical Know-How (but not under the Ionis Product-Specific Patents) to (i) use Oligonucleotides (or supply Oligonucleotides to end users) solely to conduct pre-clinical research, or (ii) enable such Third Party to manufacture or formulate Oligonucleotides, where (A) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (B) Ionis does not assist such Third Party to identify, discover or make a Compound or Product; and (b) material transfer agreements with academic collaborators or non-profit institutions solely to conduct noncommercial research.

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

"***Pharmacovigilance Agreement***" has the meaning set forth in Section 5.2.1.

"***Phase 1 Trial***" means the first clinical study in human beings Initiated by Ionis under the applicable Development Plan pursuant to an IND that has been filed with a Regulatory Authority in a Major Market or Canada. If Biogen exercises the Option before Ionis Initiates such a Phase 1 Trial, then the definition of "*Phase 1 Trial*" means the first clinical study of the applicable Development Candidate in human beings Initiated by Biogen, its Affiliate or its Sublicensee.

"***Phase 1 Trial Design***" means, with respect to a Collaboration Program, the Phase 1 Trial design set forth in the applicable Development Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the Neurology JSC).

"***Phase 2 Trial***" means, with respect to a Product, a Clinical Study that is intended to explore the feasibility, safety, dose ranging or efficacy of such Product, that is prospectively designed to generate sufficient data (if successful) to commence a Phase 3 Trial (or foreign equivalent) of such Product, as further defined in 21 C.F.R. 312.21(b) or the corresponding regulation in jurisdictions other than the United States.

"***Phase 3 Trial***" means, with respect to a Product, a pivotal Clinical Study in humans performed to gain evidence with statistical significance of the efficacy of such Product in a target population, and to obtain expanded evidence of safety for such Product that is needed to evaluate the overall benefit-risk relationship of such Product, to form the basis for approval of an NDA 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.

"***Phase 4 Trial***" means, with respect to a Product, (a) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain a Regulatory Approval for such Product or (b) any Clinical Study conducted after the first Regulatory Approval in the same disease state for which such Product received Regulatory Approval other than for purposes of obtaining Regulatory Approval.

"***PoC Data Package***" means, with respect to a Product, [***], (d) copies of all filings submitted to Regulatory Authorities regarding such Product, (e) a summary of the patent status relating to such Product, and (f) a summary of any Third Party Obligations Ionis believes relate to the Product.

"***PoC Trial***" means, with respect to a Collaboration Program, the first phase 2a Clinical Study in human patients with a pharmacokinetic or target reduction endpoint or other therapeutic or physiological endpoint.

"***PoC Trial Completion Notice***" has the meaning set forth in Section 3.1.2.

"***PoC Trial Design***" means the PoC Trial design set forth in each Development Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the Neurology JSC).

"***Post-Licensing Milestone Event***" has the meaning set forth in Section 6.4.

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of a Product, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of such Product and whether such Product has a desired effect.

"***Pre-Existing Competitive Product***" has the meaning set forth in Section 12.5.1.

"***Pre-Existing Competitive Program***" has the meaning set forth in Section 12.5.1.

"***Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.2.

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.8 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means, on a Collaboration Program-by-Collaboration Program basis, a finished drug product containing a Compound as an active pharmaceutical ingredient.

"***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date, including any Program Patents, claiming (a) the specific composition of matter of a Product, or (b) methods of using a Product as a prophylactic or therapeutic; *provided*, *however*, that Patent Rights Controlled by Ionis or any of its Affiliates that (i) include claims that are directed to subject matter applicable to ASOs in general, or (ii) include an ASO, the sequence of which targets the RNA that encodes a Collaboration Target and the RNA of a gene that does not encode a Collaboration Target, will not be considered Product-Specific Patents, and in the case of (i) and (ii), such Patent Rights will be considered Ionis Core Technology Patents.

"***Program Patents***" has the meaning set forth in Section 7.1.2.

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "***Prosecution and Maintenance***" or "***Prosecute and Maintain***" will not include any other enforcement actions taken with respect to a Patent Right.

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Reduced Royalty Period***" has the meaning set forth in Section 6.6.2(e).

"***Regulatory Approval***" means the approval necessary for the commercial manufacture, distribution, marketing, promotion, offer for sale, use, import, export, and sale of a pharmaceutical product in a jurisdiction regulated by a Regulatory Authority.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"***Regulatory Materials***" means, with respect to a Product, any regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction, and any other records required by Applicable Law to be maintained that may be necessary or useful to develop, manufacture, market, sell or otherwise commercialize such Product in any such country or jurisdiction.

"***Replacement Limit***" has the meaning set forth in Section 1.3.3.

"***Research***" means conducting the research activities with Compounds as set forth in each Collaboration Program Research Plan, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "*Researching*" means to engage in Research.

"***Results***" has the meaning set forth in Section 4.8.5(a).

"***Reverse Royalties***" has the meaning set forth in Section 6.7.1.

"***RMC***" means Ionis' Research Management Committee, or any successor committee.

"***ROFN Period***" has the meaning set forth in Section 2.1.2.

"***ROFN Termination Event***" has the meaning set forth in Section 2.1.2.

"***Royalty Quotient***" has the meaning set forth in Section 6.6.2(c).

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under the applicable Development Plan.

"***Setoff Amount***" has the meaning set forth in Section 10.4.4(b).

"***Setoff Dispute***" has the meaning set forth in Section 10.4.4(b).

"***Setoff Dispute Notice***" has the meaning set forth in Section 10.4.4(b).

"***SMN Agreement***" means the Development, Option and License Agreement between the Parties dated January 3, 2012, as amended and/or restated from time to time.

"***Specific Performance Milestone Event***" has the meaning set forth in Section 5.1.1.

"***Step-In Party***" has the meaning set forth in Section 7.4.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or Biogen Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Subsequent Deal***" has the meaning set forth in Section 10.2.3(b)(i).

"***Substitution Limit***" has the meaning set forth in Section 1.4.2.

"***Superior Patent Right***" has the meaning set forth in Section 7.2.4(d).

"***Target Related Biogen Program Claim***" has the meaning set forth in Section 4.3.3(a).

"***Target Related Ionis Program Claim***" has the meaning set forth in Section 4.3.2(a).

"***Target Sanction***" means when the therapeutic potential of a Collaboration Target has been demonstrated in pre-clinical disease models and such Collaboration Target has received approval by Ionis' RMC to expend resources to identify a human Development Candidate, all in accordance with Ionis' standard processes.

"[***]" means the [***].

"[***] Letter" means that certain [***].

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between Ionis and a Third Party (including the Ionis In-License Agreements) that relate to a Product or a Collaboration Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transition Services***" has the meaning set forth in Section 10.4.5(b).

"***Trial Court***" has the meaning set forth in Section 10.4.4(b).

"***Trial Master File***" has the meaning set forth in Section 4.8.4.

"***Trial Master File Deficiency Notice***" has the meaning set forth in Section 4.8.4.

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Valid Claim***" means a claim (a) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (b) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (a) above with respect to such application issues.

APPENDIX 2

Development Candidate Checklist

[***]

APPENDIX 3

Form of Side Letter

[*Date*]

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Executive Officer
E-mail: [***]

Re: Establishment of Cost Estimates and Milestone Payments

Dear [*Chief Executive Officer*]:

Reference is hereby made to that certain Amended and Restated Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis and Biogen dated _____ ___, [2020] (the "***Neurology I Agreement***"), as supplemented and/or amended to date. Any capitalized terms not defined herein will have the meaning set forth in the Neurology I Agreement.

This letter memorializes the Cost Estimates and corresponding milestone payments set forth on the exhibit attached hereto as Exhibit A for the Collaboration Program and Development Candidate specified on Exhibit A, which Cost Estimates and corresponding milestone payments have been agreed by the Neurology JSC in accordance with Section 1.5.2(b) of the Neurology I Agreement. Exhibit A hereto supersedes and replaces any previously approved Cost Estimates and corresponding milestone payments for the Collaboration Program and Development Candidate set forth on Exhibit A.

Please indicate your concurrence with the accuracy of Exhibit A as agreed to by the Neurology JSC by executing a copy of this letter and returning it to Biogen. This letter may be executed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from electronic transmission, store and printing of copies of this letter from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[*The remainder of this page is intentionally left blank.*]

Sincerely,

[*VP of Corporate Development*]
Vice President, Corporate Development
Biogen MA Inc.

CONFIRMED ON BEHALF OF IONIS PHARMACEUTICALS, INC.:

By:

Name:

Title:

Date:

Cc: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Email: [***]

Exhibit A

Collaboration Program: _____

Development Candidate: _____

[***]

[*Date*]

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Executive Officer
E-mail: [***]

Re: Establishment of Biogen-Approved Costs

Dear [*Chief Executive Officer*]:

Reference is hereby made to that certain Amended and Restated Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis and Biogen dated _____ ___, [2020] (the "***Neurology I Agreement***"), as supplemented and/or amended to date. Any capitalized terms not defined herein will have the meaning set forth in the Neurology I Agreement.

This letter memorializes certain Biogen-Approved Costs set forth on the exhibit attached hereto as Exhibit A for the Collaboration Program and Development Candidate specified on Exhibit A, which Biogen-Approved Costs have been mutually agreed by the Parties (including, if applicable, through the Neurology JSC) in accordance with Section 1.8 of the Neurology I Agreement.

Please indicate your concurrence with the accuracy of Exhibit A as agreed to by the Parties by executing a copy of this letter and returning it to Biogen. This letter may be executed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from electronic transmission, store and printing of copies of this letter from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[*The remainder of this page is intentionally left blank.*]

Sincerely,

[*VP of Corporate Development*]
Vice President, Corporate Development
Biogen MA Inc.

CONFIRMED ON BEHALF OF IONIS PHARMACEUTICALS, INC.:

By: _____

Name: _____

Title: _____

Date: _____

Cc: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
E-mail: [***]

Exhibit A

Collaboration Program: _____

Development Candidate: _____

[***]	Biogen-Approved Costs	Apportionment of Biogen-Approved Costs under Section 1.8.1 [***]

APPENDIX 4

[***] Letter

(*See attached*)

SCHEDULE 1.5.2(b)

Apportionment of Certain Milestone Payments and Biogen-Approved Costs

[***]

Neurology JSC Governance

(a) The Neurology JSC will determine the Neurology JSC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The Neurology JSC will codify these operating procedures in the written minutes of the first meeting.

(b) The Neurology JSC may hold meetings in person or by audio or video conference as determined by the Neurology JSC; but at least two meetings per year will be in person (one held at Ionis' facilities, and the other held at Biogen's facilities in the U.S.). Alliance Managers will attend Neurology JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend Neurology JSC meetings, including any subject matter expert(s) with valuable knowledge of Collaboration Targets or the diseases associated with such Collaboration Targets.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JSC meetings occur, Neurology JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.11.3, Section 7.1.3 and Section 12.1, as applicable.

(d) The Neurology JSC members from the same Party will collectively have one vote. The Neurology JSC will strive to make recommendations with approval of both Ionis members and Biogen members, and record such recommendations in the minutes of the applicable Neurology JSC meeting.

(e) The Neurology JSC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the Neurology JSC dissolves.

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(b) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first 100 days after the Effective Date to support the Collaboration Programs;

(c) Organizing Neurology JSC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the Neurology JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(e) Preparing status and progress reports on the above as determined necessary by the Neurology JSC;

(f) Ensuring compliance in maintaining the Ionis Internal ASO Safety Database as outlined in Section 5.2;

(g) Ensuring proper approval of publications prior to submission as required in Section 11.4; and

(h) Understanding and communicating the components contained in the relationship-management document provided by Ionis to Biogen, to assist Biogen in understanding and complying with the contractual obligations under the Ionis In-License Agreements after the License Effective Date with respect to a Collaboration Program.

SCHEDULE 4.6.3

Ionis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram
(OOO's)

[***]

SCHEDULE 5.1.1

Biogen's Development and Commercialization Activities

[***]

SCHEDULE 6.6.2(f)

Royalty Calculation Examples

[***]

SCHEDULE 6.6.2(g)

Allocation of Net Sales

[***]

SCHEDULE 6.8.1

Certain Ionis In-License Agreements

(Relevant to the Collaboration Programs and High Interest Targets as of the Effective Date)

[***]

SCHEDULE 8.2.4(a)

Ionis Core Technology Patents

[***]

SCHEDULE 8.2.4(b)

Ionis Manufacturing and Analytical Patents

[***]

SCHEDULE 8.2.4(c)

Ionis Product-Specific Patents

[***]

SCHEDULE 8.2.8

Prior Agreements

[***]

SCHEDULE 10.4.4(b)

Advisory Panel Regarding Setoff Disputes

[***]

SCHEDULE 10.4.5

Transition Services

[***]

SCHEDULE 12.1.2

Mediation

1. Mediation.

1.1 If a Dispute cannot be resolved pursuant to Section 12.1.1 of the Agreement (Escalation), the Parties agree to try in good faith to resolve any such Dispute by non-binding mediation administered by the American Arbitration Association (the "***AAA***") in accordance with its Commercial Mediation Procedures then in effect (the "***Procedures***"), as modified by this Section 1.1 of this SCHEDULE 12.1.2. The mediation will be conducted by a single mediator appointed by agreement of the Parties, within 15 days after either Party notifies the other Party of its intention to mediate such Dispute, or failing such agreement, appointed by the AAA in accordance with the Procedures; *provided* that in either case the mediator will be a retired Delaware state or federal judge. Unless otherwise mutually agreed upon by the Parties, the mediation proceedings will be conducted in Dover, Delaware. The Parties agree that they will share equally the costs and expenses of the mediation; *provided* that each Party will bear its own attorneys' fees and associated costs and expenses. The mediation conference will be held within [***] days after appointment of the mediator, and will last no more than two consecutive days unless otherwise mutually agreed upon by the Parties. Any resolution of a Dispute by mediation pursuant to this Section 1.1 of these mediation procedures will be in writing and signed by duly authorized representatives of both Parties.

1.2 If the Parties cannot resolve a Dispute in accordance with Section 1.1 of this SCHEDULE 12.1.2, then such Dispute will be resolved by the Parties in accordance with Section 12.2 of the Agreement (Governing Law; Jurisdiction; Venue; Service of Process).

Exhibit 10.2

Confidential
Execution Version

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

COLLABORATION AND LICENSE AGREEMENT

between

BICYCLETX LIMITED

and

IONIS PHARMACEUTICALS, INC.

Dated as of July 9, 2021

TABLE OF CONTENTS

COLLABORATION AND LICENSE AGREEMENT

This **Collaboration and License Agreement** (the "**Agreement**") is made and entered into effective as of July 9, 2021 (the "**Effective Date**") by and between **BicycleTx Limited**, a company incorporated in England and Wales with a place of business at Building 900, Babraham Research Campus, Cambridge CB22 3AT, UK ("**BicycleTx**"), and Ionis Pharmaceuticals, Inc., a Delaware corporation with a principal place of business at 2855 Gazelle Court, Carlsbad, California 92010, USA ("**Ionis**"). BicycleTx and Ionis are referred to herein individually as a "**Party**" and collectively as the "**Parties**".

RECITALS

Whereas, BicycleTx, a biopharmaceutical company, has developed certain proprietary technology relating to the use of Bicycles directed to transferrin receptors;

Whereas, Ionis, a biotechnology company, has expertise in the research and development of pharmaceutical products, and is working to create and develop novel pharmaceutical products;

Whereas, BicycleTx and Ionis entered into that certain Evaluation and Option Agreement dated as of December 31, 2020 (the "**Option Agreement**") pursuant to which BicycleTx granted to Ionis an exclusive option to obtain an exclusive license under BicycleTx's relevant technology to research, develop, manufacture, and commercialize products incorporating TfR1 Bicycles (as defined below) and Ionis has exercised such option in accordance with the terms of the Option Agreement;

Whereas, subject to the terms and conditions of this Agreement, BicycleTx will exclusively partner with Ionis with respect to Compounds in the Field; and

Whereas, in connection with this transaction, Bicycle Therapeutics plc, an Affiliate of BicycleTx, and Ionis are entering into a stock purchase agreement on even date herewith (the "**Stock Purchase Agreement**") pursuant to which Ionis is purchasing shares of Bicycle Therapeutics plc in accordance with the terms thereof.

Now Therefore, in consideration of the foregoing premises and the mutual promises, covenants, and conditions set forth herein and other valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, hereby agree as follows:

ARTICLE 1
DEFINITIONS

Unless otherwise specifically provided herein, the following terms shall have the following meanings:

1.1 "**Accounting Standards**" means, with respect to a Party and its Affiliates, either (a) International Financial Reporting Standards ("**IFRS**") or (b) United States generally accepted accounting principles ("**GAAP**"), in either case ((a) or (b)) that are used at the applicable time, and as consistently applied, by such Party or any of its Affiliates.

1.2 "**Adverse Ruling**" has the meaning set forth in Section 11.3.2.

1.3 "**Affiliate**" means, with respect to a Party, any Person that, directly or indirectly, through one (1) or more intermediaries, controls, is controlled by, or is under common control with such Party, for so long as such control exists. For purposes of this definition, "control" and, with correlative meanings, the terms "controlled by" and "under common control with" means (a) the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract relating to voting rights or corporate governance, or otherwise; or (b) the ownership, directly or indirectly, of more than fifty percent (50%) of the voting securities or other ownership interest of a Person (or, with respect to a limited partnership or other similar entity, its general partner or controlling entity).

1.4 "**Agreement**" has the meaning set forth in the preamble hereto.

1.5 "**Alliance Manager**" has the meaning set forth in Section 3.5.

1.6 "**Applicable Law**" means federal, state, local, national, and supra-national laws, statutes, rules, and regulations, including any rules, regulations, guidelines, or other requirements enacted by a government authority, including Regulatory Authorities, major national securities exchanges or major securities listing organizations, that may be in effect from time to time during the Term and applicable to the performance by a Party of its obligations, or exercise of its rights, under this Agreement.

1.7 "**ASO**" means a compound comprising one or more Oligonucleotides [***]. The Parties acknowledge that [***].

1.8 "**ASO-Related Claim**" has the meaning set forth in Section 7.2.1(b).

1.9 "**ASO-Related Claim Application**" has the meaning set forth in Section 7.2.1(b).

1.10 "**Auditor**" has the meaning set forth in Section 6.11.

1.11 "**Available Target(s)**" means:

(a) with respect to a request by Ionis, any Target that as of the date the Gatekeeper (or BicycleTx, as applicable) receives a Target Nomination Notice from Ionis for such Target, or Ionis initiates a request with the Gatekeeper pursuant to Sections 4.8.2 or 4.8.4, as applicable, is not (i) a BicycleTx Excluded Target, (ii) [***], (A) a Target that was placed on the Gatekeeper List during the BicycleTx Initial Target Designation Period pursuant to Section 4.8.3, or (B) a Target placed on the Gatekeeper List by BicycleTx pursuant to Section 4.8.6; and

(b) with respect to a request by BicycleTx under Section 4.8.3 or Section 4.9 following the termination of Oligo Exclusivity, any Target that as of the date BicycleTx makes a BicycleTx Target Request, is not a Collaboration Target, including, for clarity, any Target placed on the Gatekeeper List by Ionis pursuant to Section 4.8.4 (subject to the limitations set forth therein).

1.12 "**Bankruptcy Code**" has the meaning set forth in Section 11.5.1.

1.13 "**Bicycle**" means a monomeric peptide or peptide derivative crosslinked via a central scaffold to form a conformationally constrained structure with more than one cyclic component.

1.14 "**BicycleTx**" has the meaning set forth in the preamble hereto.

1.15 "**BicycleTx Excluded Targets**" means Targets with respect to which BicycleTx has granted exclusive rights to a Third Party under the BicycleTx Existing Third Party Agreements.

1.16 "**BicycleTx Existing Third Party Agreements**" means (a) that certain agreement between [***], and (b) that certain agreement between [***], in each case as such agreements are in effect on the Effective Date. For clarity, during the Term when Oligo Exclusivity applies, BicycleTx [***].

1.17 "**BicycleTx Indemnitees**" has the meaning set forth in Section 10.1.

1.18 "**BicycleTx Initial Target Designation Period**" has the meaning set forth in Section 4.8.3.

1.19 "**BicycleTx Intellectual Property**" means the BicycleTx Know-How, BicycleTx Patents, and BicycleTx's interest in any Joint Inventions and Joint Patents.

1.20 "**BicycleTx Know-How**" means all Know-How that (a) is Controlled by BicycleTx or any of its Affiliates on the Effective Date or during the Term and (b) (i) with respect to all Know-How other than the Know-How included in the [***], and (ii) with respect to [***], in each case of (i) and (ii), for the Research and Exploitation of Compounds and Licensed Products in the Field. For clarity, "BicycleTx Know-How" includes any TfR1 BicycleTx Inventions and BicycleTx Product Inventions.

1.21 "**BicycleTx Patents**" means all Patents that (a) are Controlled by BicycleTx or any of its Affiliates on the Effective Date or during the Term and (b) Cover BicycleTx Know-How. For clarity, "BicycleTx Patents" includes any BicycleTx Product Patents. Without limiting the foregoing, an exemplary list of BicycleTx Patents is attached hereto as Schedule 9.2.1.

1.22 "**BicycleTx Platform IP**" means Know-How and Patents that are Controlled by BicycleTx or any of its Affiliates on the Effective Date or during the Term solely to the extent such Know-How and Patents Cover or specifically relate to [***]. The list of Patents included in the BicycleTx Platform IP (the "**BicycleTx Platform Patents**") is attached hereto as Schedule 1.22.

1.23 "**BicycleTx Product Invention**" means a Product Invention solely invented by employees, agents, or independent contractors of BicycleTx or its Affiliates.

1.24 "**BicycleTx Product Patents**" means all Patents that Cover BicycleTx Product Inventions.

1.25 "**BicycleTx Relevant Patent**" has the meaning set forth in Section 7.2.1(b).

1.26 "**BicycleTx Research Stage Target**" has the meaning set forth in Section 4.8.6(a).

1.27 "**BicycleTx Target**" has the meaning set forth in Section 4.9.

1.28 "**BicycleTx Target Request**" has the meaning set forth in Section 4.9.

1.29 "**Breach Cure Period**" has the meaning set forth in Section 11.3.1.

1.30 "**Breach Notice**" has the meaning set forth in Section 11.3.1.

1.31 "**Breaching Party**" has the meaning set forth in Section 11.3.1.

1.32 "**Business Day**" means a day other than a Saturday or Sunday on which banking institutions in San Diego, California and London, England are open for business.

1.33 "**Calendar Quarter**" means each successive period of three calendar months commencing on January 1, April 1, July 1, and October 1, except that the first Calendar Quarter of the Term shall commence on the Effective Date and end on the day immediately prior to the first to occur of January 1, April 1, July 1 or October 1 after the Effective Date, and the last Calendar Quarter shall end on the last day of the Term.

1.34 "**Calendar Year**" means each successive period of twelve (12) calendar months commencing on January 1 and ending on December 31, except that the first Calendar Year of the Term shall commence on the Effective Date and end on December 31 of the year in which the Effective Date occurs and the last Calendar Year of the Term shall commence on January 1 of the year in which the Term ends and end on the last day of the Term.

1.35 "**Clinical Trial**" means a human clinical study (a) in which a pharmaceutical product is administered to human subjects and (b) that is designed to (i) establish that a pharmaceutical product is reasonably safe for continued testing; (ii) investigate the safety and efficacy of the pharmaceutical product for its intended use, and to define warnings, precautions and adverse reactions that may be associated with the pharmaceutical product in the dosage range to be prescribed; (iii) support Regulatory Approval of such pharmaceutical product or label expansion of such pharmaceutical product; or (iv) obtain or maintain marketing approval and for a purpose other than to obtain, support or maintain Regulatory Approval, including any and all post-marketing commitments.

1.36 "**Collaboration Target**" has the meaning set forth in Section 4.8.1.

1.37 "**Combination Product**" means (a) a single pharmaceutical formulation containing as its active ingredients both (i) a Compound and (ii) one or more other therapeutically or prophylactically active ingredients that are not Compounds (each such other therapeutically or prophylactically active ingredient, a "**Non-Compound Active Agent**") or (b) a combination therapy comprised of (i) a Compound and (ii) one or more other therapeutically or prophylactically active products containing at least one Non-Compound Active Agent, whether priced and sold together in a single package containing such multiple products or packaged separately but sold together for a single price, in each case (a) and (b), including all dosage forms, formulations, presentations, line extensions, and package configurations.

1.38 "**Commercialization**" means any and all activities directed to the preparation for sale of, offering for sale of, or sale of a pharmaceutical product, including activities related to marketing, promoting, selling, distributing, importing, and exporting such product, and interacting with Regulatory Authorities regarding any of the foregoing. When used as a verb, "**to Commercialize**" and "**Commercializing**" means to engage in Commercialization, and "**Commercialized**" has a corresponding meaning.

1.39 "**Commercially Reasonable Efforts**" means, with respect to the performance of Research, Development, Commercialization, or Manufacturing activities with respect to a Compound or a Licensed Product, the carrying out of such activities using efforts and resources comparable to the efforts and resources [***], taking into account issues of safety and efficacy, [***].

1.40 "**Compound**" means a TfR1 Bicycle conjugated to an ASO, where such ASO is directed to a Target that is not a BicycleTx Excluded Target.

1.41 "**Confidential Information**" means any information provided orally, visually, in writing or other form by or on behalf of one (1) Party (or an Affiliate or representative of such Party) to the other Party (or to an Affiliate or representative of such other Party) in connection with this Agreement, whether prior to, on, or after the Effective Date, including information relating to the terms of this Agreement, the identities of Collaboration Targets and Available Targets, any Research or Exploitation of any Licensed Product, any Know-How with respect thereto developed by or on behalf of the disclosing Party or its Affiliates, or the scientific, regulatory, or business affairs or other activities of either Party. In addition, all information disclosed by a Party to the other under the Option Agreement shall be deemed to be such Party's Confidential Information disclosed under this Agreement.

1.42 "**Control**" means, with respect to any Know-How, Regulatory Documentation, material, Patent, or other property right, the possession of the right, whether directly or indirectly, and whether by ownership, license, covenant not to sue, or otherwise (other than by operation of the license and other grants in Sections 2.1 and 2.2), to grant a license, sublicense, or other right to or under such Know-How, Regulatory Documentation, material, Patent, or other property right, as provided for herein without violating the terms of any agreement or other arrangement with any Third Party; provided that with respect to any Know-How, Regulatory Documentation, material, Patent, or other property right obtained by BicycleTx from a Third Party after the Effective Date, BicycleTx shall be deemed to Control such Know-How, Regulatory Documentation, material, Patent, or other property right, as applicable, only if it possesses the right to grant such license, sublicense, or other right thereto without being obligated to pay any royalties or other consideration therefor, unless Ionis agrees to (a) pay such royalties or other consideration arising as a result of Ionis' or its Affiliate's or Sublicensee's use or practice of such Know-How, Regulatory Documentation, material, Patent, or other property right under this Agreement and (b) comply with the terms and conditions of such agreement as it relates to Ionis and this Agreement.

1.43 "**Cover**" means, with respect to a particular subject matter at issue and a relevant Patent, that, in the absence of a license under or ownership of such Patent, the developing, making, using, offering for sale, promoting, selling, exporting, or importing of such subject matter would infringe one or more Valid Claims of such Patent (considering any pending claim included in such Patent as if such pending claim were to issue in an issued Patent).

1.44 "**CRO**" shall have the meaning set forth in Section 4.2.3.

1.45 [***].

1.46 "**Development**" means all activities related to (i) human clinical lead optimization with the goal of identifying a Development Candidate (as defined below), test method development and stability testing, toxicology, formulation, process development, manufacturing scale-up, qualification and validation, quality assurance/quality control, (ii)IND-Enabling Toxicology Studies, (iii) Clinical Trials, including Manufacturing in support thereof, (iv) statistical analysis and report writing, (v) the preparation and submission of Drug Approval Applications, regulatory affairs with respect to the foregoing and all other activities necessary or reasonably useful or otherwise requested or required by a Regulatory Authority as a condition or in support of obtaining or maintaining a Regulatory Approval. When used as a verb, "**Develop**" means to engage in Development. For purposes of clarity, Development shall include any submissions and activities required in support thereof required by Applicable Laws or a Regulatory Authority as a condition or in support of obtaining a pricing or reimbursement approval for a Compound or Licensed Product.

1.47 "**Development Candidate**" with respect to Ionis means a Compound that is [***] for further Development and Commercialization in accordance with Ionis' [***]. With respect to BicycleTx, Development Candidate means an active pharmaceutical ingredient [***] for further Development and Commercialization in accordance with BicycleTx's [***].

1.48 "**Diligence Extension Fee**" has the meaning set forth in Section 4.5.3(b).

1.49 "**Dispute**" has the meaning set forth in Section 12.2.

1.50 "**Dollars**" or "**$**" means United States Dollars.

1.51 "**Drug Approval Application**" means an NDA and any corresponding foreign application in the Territory, including, with respect to the European Union, a Marketing Authorization Application (a "**MAA**") filed with the EMA or with the applicable Regulatory Authority of a country in Europe with respect to the mutual recognition or any other national approval procedure.

1.52 "**Effective Date**" means the effective date as set forth in the preamble hereto.

1.53 "**EMA**" means the European Medicines Agency and any successor agency(ies) or authority having substantially the same function.

1.54 "**European Major Market**" means each of the United Kingdom, France, Germany, Italy, and Spain.

1.55 "**Exclusivity Obligations**" has the meaning set forth in Section 2.7.1.

1.56 "**Existing Collaboration Target**" has the meaning set forth in Section 4.8.2.

1.57 "**Existing Patents**" has the meaning set forth in Section 9.2.1.

1.58 "**Exploit**" or "**Exploitation**" means to Develop, use, make, have made, Manufacture, sell, have sold, offer for sale, import, and Commercialize.

1.59 "**Extension Notice**" has the meaning set forth in Section 4.5.3(c).

1.60 "**FDA**" means the United States Food and Drug Administration and any successor agency(ies) or authority having substantially the same function.

1.61 "**FFDCA**" means the United States Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., as amended from time to time, together with any rules, regulations and requirements promulgated thereunder (including all additions, supplements, extensions, and modifications thereto).

1.62 "**Field**" means all diagnostic, therapeutic, prophylactic, and preventative uses in humans.

1.63 "**First Commercial Sale**" means, with respect to a Licensed Product and a country, the first sale for monetary value for use or consumption by the end user of such Licensed Product in such country after Regulatory Approval for such Licensed Product has been obtained in such country.

1.64 "**FTE**" means a full-time equivalent person-year, based upon a total of no less than [***] working hours per year, pro-rated as necessary, undertaken in connection with the conduct of research in a Research Plan. In no circumstance can the work of any given person exceed one (1) FTE.

1.65 "**Gatekeeper**" has the meaning set forth in Section 2.2.1.

1.66 "**Gatekeeper List**" has the meaning set forth in Section 2.2.1.

1.67 "**Generic Product**" means, with respect to a particular Licensed Product that has received Regulatory Approval in a regulatory jurisdiction in the Territory and is being marketed and sold by Ionis or any of its Affiliates or Sublicensees in such jurisdiction, a pharmaceutical product that (a) is sold in such jurisdiction by a Third Party that is not an Affiliate or Sublicensee of Ionis, and did not purchase or acquire such product in a chain of distribution that included Ionis or any of its Affiliates or Sublicensees, (b) has received Regulatory Approval in such jurisdiction for at least one of the same indications as such Licensed Product as a "generic drug", "generic medicinal product", "bioequivalent", or similar designation of interchangeability by the applicable Regulatory Authority in such jurisdiction pursuant to an expedited, abbreviated, or bibliographic approval process in accordance with the then-current rules and regulations in such jurisdiction, where such approval referred to or relied on (i) the approved Drug Approval Application for such Licensed Product held by Ionis, its Affiliate, or a Sublicensee in such jurisdiction or (ii) the data contained or incorporated by reference in such approved Drug Approval Application for such Licensed Product in such jurisdiction.

1.68 "**GLP**" means current good laboratory practice standards promulgated or endorsed by the FDA, as defined in U.S. 21 C.F.R. Part 58 (or such other comparable regulatory standards in jurisdictions outside the U.S.), as updated from time to time.

1.69 "**IND**" means an application filed with a Regulatory Authority for authorization to commence Clinical Trials, including (a) an Investigational New Drug Application as defined in the FFDCA or any successor application or procedure filed with the FDA, (b) any equivalent thereof in other countries or regulatory jurisdictions, (e.g., a Clinical Trial Application (CTA) in the European Union), and (c) all supplements, amendments, variations, extensions, and renewals thereof that may be filed with respect to the foregoing.

1.70 "**IND Acceptance**" means, with respect to a Licensed Product, the earliest of (a) receipt of notice of acceptance by the FDA or the EMA of the filing of an IND for such Licensed Product, (b) the passage of any period of time determined by Applicable Law by the end of which the FDA or EMA, as applicable, is supposed to comment on such filing, extended if any such comments were made by the period of time necessary to address such comments to the reasonable satisfaction of the FDA or EMA, as applicable, or (c) the first dose of such Licensed Product in a Clinical Trial in the U.S. or in any country in the European Union.

1.71 "**IND Acceptance Credit**" shall have the meaning set forth in Section 6.3.

1.72 "**IND Acceptance Fee**" shall have the meaning set forth in Section 6.3.

1.73 "**IND-Enabling Toxicology Study**" means, with respect to a Licensed Product, an in vivo toxicology study conducted under conditions of GLP that is required for filing an IND for such Licensed Product with the FDA or EMA.

1.74 "**Indemnification Claim Notice**" has the meaning set forth in Section 10.3.

1.75 "**Indemnified Party**" has the meaning set forth in Section 10.3.

1.76 "**Indemnifying Party**" has the meaning set forth in Section 10.3.

1.77 "**Initiation**" means, with respect to a Licensed Product and a Clinical Trial, the first dosing of the first patient with such Licensed Product in such Clinical Trial.

1.78 "**Intellectual Property**" has the meaning set forth in Section 11.5.1.

1.79 "**Interim Gatekeeper**" has the meaning set forth in Section 2.2.2.

1.80 "**Internal Development Program**" means on a Target-by-Target basis, a [***] internal program of BicycleTx, pursuant to which BicycleTx is conducting Research, development and/or commercialization activities in connection with compounds or products directed to such Target [***].

1.81 "**Invention**" means any invention, process, method, utility, formulation, composition of matter, article of manufacture, material, creation, discovery, development, or finding, or any improvement thereto, whether or not patentable, including all intellectual property rights therein.

1.82 "**Ionis**" has the meaning set forth in the preamble hereto.

1.83 "**Ionis Indemnitees**" has the meaning set forth in Section 10.2.

1.84 "**Ionis Initial Target Designation Period**" has the meaning set forth in Section 4.8.2.

1.85 "**Ionis Intellectual Property**" means the Ionis Know-How, Ionis Patents, and Ionis' interest in any Joint Inventions and Joint Patents.

1.86 "**Ionis Know-How**" means all Know-How that (a) is Controlled by Ionis or any of its Affiliates on the Effective Date or during the Term and (b) is necessary or reasonably useful for the Exploitation of Compounds and Licensed Products in the Field. For clarity, "Ionis Know-How" includes any Ionis Product Inventions.

1.87 "**Ionis Patents**" means all Patents that (a) are Controlled by Ionis or any of its Affiliates on the Effective Date or during the Term and (b) Cover Ionis Know-How. For clarity, "Ionis Patents" includes any Ionis Product Patents.

1.88 "**Ionis Product Invention**" means a Product Invention solely invented by employees, agents, or independent contractors of Ionis or its Affiliates.

1.89 "**Ionis Product Patents**" means all Patents that Cover Ionis Product Inventions.

1.90 "**Ionis Research Stage Target**" has the meaning set forth in Section 4.8.4.

1.91 "**Ionis Withholding Tax Action**" has the meaning set forth in Section 6.9.3.

1.92 "**Joint Inventions**" has the meaning set forth in Section 7.1.2(b).

1.93 "**Joint Patents**" means all Patents that Cover Joint Inventions.

1.94 "**Joint Product Patents**" means all Joint Patents that Cover [***] developed jointly by employees, agents, or independent contractors of one Party and its Affiliates together with employees, agents, or independent contractors of the other Party and its Affiliates.

1.95 "**JSC**" has the meaning set forth in Section 3.1.1.

1.96 "**Know-How**" means all commercial, technical, scientific, and other know-how and information, Inventions, discoveries, trade secrets, knowledge, technology, methods, processes, practices, formulae, amino acid sequences, nucleotide sequences, instructions, skills, techniques, procedures, ideas, designs, drawings, computer programs, specifications, data and results (including biological, chemical, pharmacological, toxicological, pharmaceutical, physical and analytical, preclinical, clinical, safety, manufacturing and quality control data (including regulatory data, study designs, and protocols), reagents and materials (including assays and compounds) in all cases, whether or not confidential, proprietary, or patentable, in written, electronic, or any other form now known or hereafter developed, but expressly excluding all Patents.

1.97 "**Licensed Product**" means any product that contains or incorporates a Compound, whether alone or in combination with other active ingredients, in any form, formulation, presentation, or dosage, and for any mode of administration.

1.98 "**Losses**" has the meaning set forth in Section 10.1.

1.99 "**MAA**" has the meaning set forth in Section 1.51.

1.100 "**Major Market**" means each of the United States, the European Major Markets, and Japan.

1.101 "**Manufacture**", "**Manufactured**", and "**Manufacturing**" means all activities related to the synthesis, making, production, processing, analysis, purifying, formulating, filling, finishing, packaging, labeling, shipping, and holding of a pharmaceutical product, or any raw materials, intermediate thereof, including process development, process qualification and validation, scale-up, pre-clinical, clinical and commercial production and analytic development, product characterization, stability testing, quality assurance, and quality control, whether by a Party itself or through a Third Party. For clarity, Manufacture of a Compound or Licensed Product will include activities related to the synthesis, making, production, processing, formulating, analyzing for manufacturing purposes and purifying of the TfR1 Bicycle that is incorporated into the applicable Compound or Licensed Product.

1.102 "**Market Exclusivity**" means any exclusive marketing rights or data exclusivity rights conferred by any Regulatory Authority with respect to a Licensed Product other than Patents, including rights conferred in the U.S. under the Hatch-Waxman Act or the FDA Modernization Act of 1997 (including pediatric exclusivity), or rights similar thereto outside the U.S., such as Directive 2001/83/EC (as amended) in the EU.

1.103 "**MHRA**" means the United Kingdom's Medicines and Healthcare products Regulatory Agency and any successor agency(ies) or authority having substantially the same function.

1.104 "**Mono Product**" has the meaning set forth in Section 1.107.

1.105 "**NDA**" means a "**New Drug Application**", as defined in the FFDCA, as amended, and applicable regulations promulgated thereunder by the FDA and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any Regulatory Authority, including all documents, data, and other information concerning a pharmaceutical product, which are necessary for gaining Regulatory Approval to market and sell such pharmaceutical product in the relevant jurisdiction.

1.106 "**Naked Sublicense**" means a sublicense to a Third Party that [***].

1.107 "**Net Sales**" means, with respect to any Licensed Product, the gross amounts invoiced for sales or other dispositions of such Licensed Product by or on behalf of Ionis or its Affiliates or Sublicensees to Third Parties, less the following deductions to the extent included in the gross invoiced sales price for such Licensed Product and determined in accordance with Accounting Standards or otherwise directly paid or incurred by Ionis or its Affiliates or Sublicensees, as applicable, with respect to the sale or other disposition of such Licensed Product:

1.107.1 [***];

1.107.2 [***];

1.107.3 [***];

1.107.4 [***];

1.107.5 [***]; and

1.107.6 [***].

In no event will any particular amount identified above be deducted more than once in calculating Net Sales. Sales of a Licensed Product between Ionis and its Affiliates or Sublicensees for resale shall be excluded from the computation of Net Sales, but the subsequent resale of such Licensed Product to a Third Party shall be included within the computation of Net Sales.

The supply of Licensed Product for no charge or at cost as samples for charitable or promotional purposes, for use in non-clinical or clinical trials or any test or other studies reasonably necessary to comply with Applicable Laws shall not be included in the computation of Net Sales.

If a Licensed Product is sold as part of a Combination Product in a country, the Net Sales with respect to the Combination Product in such country shall be determined as follows:

If a Licensed Product is a Combination Product, the Net Sales for such Combination Product shall be calculated as follows: [***].

Notwithstanding the foregoing, the definition of net sales that [***]; provided that [***]. Ionis shall promptly notify BicycleTx of any [***], including the details thereof.

1.108 "**Nominated Target**" has the meaning set forth in Section 4.8.5.

1.109 "**Non-Breaching Party**" has the meaning set forth in Section 11.3.1.

1.110 "**Non-Compound Active Agent**" has the meaning set forth in Section 1.37.

1.111 "**Oligo Exclusivity**" has the meaning set forth in Section 2.7.1.

1.112 "**Oligonucleotide**" means [***].

1.113 "**Oxford**" shall have the meaning set forth in Section 8.3.3(g).

1.114 "**Party**" and "**Parties**" has the meaning set forth in the preamble hereto.

1.115 "**Patents**" means (a) all national, regional and international patents and patent applications, including provisional patent applications, (b) all patent applications filed either from such patents, patent applications or provisional applications or from an application claiming priority from either of these, including divisionals, continuations, continuations-in-part, provisionals, converted provisionals and continued prosecution applications, (c) any and all patents that have issued or in the future issue from the foregoing patent applications ((a) and (b)), including utility models, petty patents and design patents and certificates of invention, (d) any and all extensions or restorations by existing or future extension or restoration mechanisms, including revalidations, reissues, re-examinations and extensions (including any pediatric exclusivity and other such exclusivities that are attached to patents, patent term extensions, supplementary protection certificates and the like) of the foregoing patents or patent applications ((a), (b), and (c)), and (e) any similar rights, including so-called pipeline protection or any importation, revalidation, confirmation or introduction patent or registration patent or patent of additions to any of such foregoing patent applications and patents.

1.116 "**Person**" means an individual, sole proprietorship, partnership, limited partnership, limited liability partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture or other similar entity or organization, including a government or political subdivision, department, or agency of a government.

1.117 "**Pivotal Trial**" means a human clinical trial of a Licensed Product that (a) satisfies the requirements of 21 C.F.R. section 312.21(c), or its foreign equivalent or (b) is a registration trial designed to establish statistically significant efficacy and safety of such Licensed Product for the purpose of enabling the preparation and submission of a Drug Approval Application, as evidenced by (i) an agreement with or statement from the FDA on a Special Protocol Assessment or equivalent in another country, or (ii) other guidance or minutes issued by the FDA for such registration trial or equivalent in another country, in each case ((i) and (ii)) where the results of such clinical trial are intended 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 in such country. For clarity, [***].

1.118 "**PMDA**" means Japan's Pharmaceuticals and Medical Devices Agency and any successor agency(ies) or authority having substantially the same function.

1.119 "**Product Invention**" means, on a Compound-by-Compound and Licensed Product-by-Licensed Product basis, an Invention that (a) is generated in the performance of activities under this Agreement and (b) specifically relates to a Compound or Licensed Product.

1.120 "**Product Patents**" means all Patents that Cover any Product Invention.

1.121 "**Publishing Notice**" has the meaning set forth in Section 8.6.

1.122 "**Publishing Party**" has the meaning set forth in Section 8.6.

1.123 "**Redacted Agreement**" shall have the meaning set forth in Section 8.3.2.

1.124 "**Regulatory Approval**" means, with respect to a country or other jurisdiction in the Territory, all approvals (including Drug Approval Applications), licenses, registrations, or authorizations of any Regulatory Authority necessary to Commercialize a Compound or Licensed Product in such country or other jurisdiction, and including pricing or reimbursement approval in such country or other jurisdiction where such pricing and reimbursement approval is legally required for the sale of such Compound or Licensed Product.

1.125 "**Regulatory Authority**" means any applicable supra-national, federal, national, regional, state, provincial, or local governmental or regulatory authority, agency, department, bureau, commission, council, or other entities (e.g., the FDA, EMA, MHRA, and PMDA) regulating or otherwise exercising authority with respect to activities contemplated in this Agreement, including the Exploitation of the Licensed Products in the Territory.

1.126 "**Regulatory Documentation**" means all (a) applications (including all INDs and Drug Approval Applications), registrations, licenses, authorizations, and approvals (including Regulatory Approvals), (b) correspondence and reports submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority) and all supporting documents with respect thereto, including all regulatory drug lists, advertising and promotion documents, adverse event files, and complaint files, and (c) data contained or relied upon in any of the foregoing, in each case ((a), (b), and (c)) to the extent relating to a Compound or Licensed Product.

1.127 "**Research**" means preclinical research and other non-clinical testing, including gene function, gene expression, target validation research, and investigating inhibition of a target in therapeutic models, but specifically excludes Development (including, for the avoidance of doubt, all IND-Enabling Toxicology Studies), Exploitation, or Commercialization.

1.128 "**Research Activities**" has the meaning set forth in Section 4.2.

1.129 "**Research Plan**" has the meaning set forth in Section 4.2.

1.130 "**Research Term**" means the period of time commencing on the Effective Date and ending upon the completion of all activities under the Research Plan.

1.131 "**Reserved Target**" has the meaning set forth in Section 2.2.3.

1.132 "**Royalty Floor Country**" means each of the [***].

1.133 "**Royalty Term**" means, with respect to each Licensed Product and each country in the Territory, the period beginning on the date of the First Commercial Sale of such Licensed Product in such country and ending on the latest to occur of (a) the [***] anniversary of the First Commercial Sale of such Licensed Product in such country or other jurisdiction, (b) the expiration date of the last-to-expire Valid Claim of [***] that [***] such Licensed Product in such country, and (c) the expiration of all Market Exclusivity for such Licensed Product in such country.

1.134 "**Senior Officer**" means, with respect to BicycleTx, its [***] or his/her designee, and with respect to Ionis, its [***] or his/her designee.

1.135 "**SOFR**" has the meaning set forth in Section 6.10.

1.136 "**Stock Purchase Agreement**" has the meaning set forth in the Recitals.

1.137 "**Sublicensee**" means a Person, other than an Affiliate, that is granted a sublicense by Ionis under the license grant in Section 2.1 as provided in Section 2.4.

1.138 "**Target**" means (a) [***]. Such Target shall be deemed to include [***].

1.139 "**Target Acceptance Date**" has the meaning set forth in Section 4.8.5.

1.140 "**Target Availability Notice**" has the meaning set forth in Section 4.8.5.

1.141 "**Target Exclusivity**" has the meaning set forth in Section 4.8.1.

1.142 "**Target Nomination Notice**" has the meaning set forth in Section 4.8.5.

1.143 "**Target Sanction**" means with respect to Ionis, [***], all in accordance with Ionis' standard procedures consistently applied.

1.144 "**Term**" has the meaning set forth in Section 11.1.

1.145 "**Terminated Asset**" means, with respect to a Target that is terminated by either Party under ARTICLE 11, each Compound and Licensed Product directed to such Terminated Target.

1.146 "**Terminated Target**" has the meaning set forth in Section 11.6.

1.147 "**Territory**" means worldwide.

1.148 "**TfR1 Bicycle**" means a Bicycle that is directed to a Transferrin Transporter, including any such composition provided by BicycleTx to Ionis under the Option Agreement and any such composition that is synthesized by the Parties under the Evaluation Studies (as defined in the Option Agreement) under the Option Agreement or the Research Plan.

1.149 "**TfR1 BicycleTx Invention**" means an Invention that [***]. For clarity, [***].

1.150 [***].

1.151 "**Third Party**" means any Person other than BicycleTx, Ionis, and their respective Affiliates.

1.152 "**Third Party Claims**" has the meaning set forth in Section 10.1.

1.153 "**Transferrin Transporter**" means the protein coded by the gene TFRC1 (transferrin receptor), a cell surface protein important for the cellular iron uptake through the process of receptor-mediated endocytosis, which has also been proposed as a mechanism for transporting other molecules across the blood-brain barrier by the same process.

1.154 "**Ultra-Rare Disease Product**" means a Licensed Product with an estimated target patient population that is less than [***] patients in the U.S.

1.155 "**United States**" or "**U.S.**" means the United States of America and its territories and possessions (including the District of Columbia and Puerto Rico).

1.156 "**United States – United Kingdom Income Tax Convention**" means the Convention between the government of the United States of America and the government of the United Kingdom of Great Britain and Northern Ireland for the Avoidance of Double Taxation and the Prevention of Fiscal Evasion with Respect to Taxes on Income and Capital Gains.

1.157 "**Valid Claim**" means (a) a claim of any issued and unexpired Patent that has not been revoked or held unenforceable, unpatentable, or invalid by a decision of a court or other governmental agency of competent jurisdiction that is not appealable or has not been appealed within the time allowed for appeal, and that has not been abandoned, disclaimed, denied, or admitted to be invalid or unenforceable through reissue, re-examination, or disclaimer or otherwise and (b) a claim of a pending patent application that has not been cancelled, withdrawn, or abandoned or finally rejected by an administrative agency action from which no appeal can be taken and that has not been pending for more than [***].

ARTICLE 2
GRANT OF RIGHTS

2.1 Grant to Ionis.

2.1.1 Subject to the terms and conditions of this Agreement, BicycleTx (on behalf of itself and its Affiliates) hereby grants to Ionis a license (with the right to grant sublicenses in accordance with Section 2.4), under the BicycleTx Intellectual Property to Research Compounds and Licensed Products in the Field in the Territory. This license under Section 2.1.1 is exclusive (including with regard to BicycleTx and its Affiliates, except as provided in Section 2.5) so long as Ionis maintains Oligo Exclusivity and non-exclusive if Ionis loses Oligo Exclusivity.

2.1.2 Subject to the terms and conditions of this Agreement, including Section 4.5.4, BicycleTx (on behalf of itself and its Affiliates) hereby grants to Ionis an exclusive (including with regard to BicycleTx and its Affiliates, except as provided in Section 2.5) license (with the right to grant sublicenses in accordance with Section 2.4) under the BicycleTx Intellectual Property to Exploit Compounds and Licensed Products in the Field in the Territory for so long as Ionis maintains Oligo Exclusivity. For clarity, upon the termination of Oligo Exclusivity, the license granted in this Section 2.1.2 shall automatically terminate, and the license grant set forth in Section 2.1.3 shall apply.

2.1.3 On a Collaboration Target-by-Collaboration Target basis, and subject to the terms and conditions of this Agreement, BicycleTx (on behalf of itself and its Affiliates) hereby grants to Ionis an exclusive (including with regard to BicycleTx and its Affiliates, except as provided in Section 2.5) license (with the right to grant sublicenses in accordance with Section 2.4), under the BicycleTx Intellectual Property to Exploit Compounds and Licensed Products directed to such Collaboration Target in the Field in the Territory.

2.2 Excluded Targets; Reserved Targets; Gatekeeper. The Parties acknowledge and agree that the BicycleTx Excluded Targets are excluded from Ionis' licenses under Section 2.1. To enable the Parties to effectively manage their respective rights and obligations under this Agreement, the Parties hereby agree as follows:

2.2.1 Gatekeeper. Promptly following the Effective Date, BicycleTx shall engage an independent Third Party mutually agreeable to the Parties (the "**Gatekeeper**") for the purposes of performing the applicable functions set forth in this Section 2.2, including (a) maintaining the list of BicycleTx Excluded Targets, and (b) maintaining the list of Reserved Targets ((a) and (b) together, the "**Gatekeeper List**"). [***]. Such engagement shall be on terms consistent with this Agreement and mutually agreeable to the Parties, including provisions relating to confidentiality.

2.2.2 Managing BicycleTx Excluded Targets. In conjunction with or immediately following the appointment of the Gatekeeper, BicycleTx shall provide the Gatekeeper with a current list of BicycleTx Excluded Targets. Until the appointment of the Gatekeeper, the list of BicycleTx Excluded Targets shall be held by an independent Third Party that has been mutually agreed by the Parties (the "**Interim Gatekeeper**"). The identity of the BicycleTx Excluded Targets shall be deemed the Confidential Information of BicycleTx. Following the appointment of a Gatekeeper, BicycleTx shall notify the Gatekeeper promptly of [***].

2.2.3 Reserved Targets. Ionis may designate up to [***] Targets that Ionis wishes to reserve to be potentially the subject of its Research and Development efforts under this Agreement, and that are not BicycleTx Excluded Targets ("**Reserved Targets**") as further described in this Section 2.2.3. The Parties acknowledge and agree that as of the Effective Date, BicycleTx has provided the Interim Gatekeeper with the current list of BicycleTx Excluded Targets, and Ionis has provided the Interim Gatekeeper with its current list of Reserved Targets. During the Term when Oligo Exclusivity applies, [***]. Ionis may not [***] without BicycleTx's prior written consent. Each Reserved Target shall remain on the Gatekeeper List until [***] directed to such Reserved Target and notifies BicycleTx in writing of the applicable Target. Upon the termination of Oligo Exclusivity, if applicable, all Reserved Targets shall be removed from the Gatekeeper List. The identity of the Reserved Targets shall be the Confidential Information of Ionis. BicycleTx agrees that it will not take any action that would cause a Reserved Target to become BicycleTx Excluded Target.

2.2.4 Targets [***]. Ionis acknowledges and agrees that no rights are granted by BicycleTx to Ionis under this Agreement to conduct Research or Development activities in connection with any BicycleTx Excluded Target, or any compound or product directed thereto. [***]. Notwithstanding the foregoing, if such Target later ceases to be a BicycleTx Excluded Target, and [***], and Ionis will have the right to deliver a Target Nomination Notice for such Target in accordance with Section 4.8.5.

2.3 Grants to Bicycle. Subject to the terms and conditions of this Agreement, Ionis hereby grants to BicycleTx, during the Research Term, a non-exclusive, royalty-free license, without the right to grant sublicenses (other than to permitted subcontractors of BicycleTx in accordance with Section 4.10), under the Ionis Intellectual Property solely for purposes of performing BicycleTx's obligations under, and as set forth in, the Research Plan.

2.4 Sublicenses. Ionis shall have the right to grant sublicenses, through multiple tiers of sublicensees, under the licenses granted in Section 2.1, to its Affiliates and Third Parties; provided that (a) any sublicense by Ionis or its Affiliates of the rights granted pursuant to Section 2.1.1 to a Third Party shall only permit such Sublicensee to grant further sublicenses (i) [***], (b) each such sublicense shall be consistent with the terms and conditions of this Agreement, including terms of confidentiality and non-use no less restrictive than those set forth in this Agreement, (c) Ionis may not grant to any Third Party any rights to prosecute or enforce any BicycleTx Patents, (d) Ionis shall remain directly liable to BicycleTx with respect to its obligations under this Agreement and for the performance and acts and omissions of all Sublicensees, and (e) Ionis will [***]. As soon as reasonably practicable (but in any case, within [***]) after the execution of any such sublicense agreement, Ionis shall [***].

2.5 Retained Rights. Notwithstanding the exclusive license granted to Ionis pursuant to Section 2.1 during the Term and without limiting Section 2.7, BicycleTx shall retain all rights under the BicycleTx Intellectual Property (a) to perform, and to subcontract pursuant to Section 4.10, its obligations under this Agreement, (b) [***], and (c) for any purpose outside the scope of the license and rights granted under Section 2.1. For clarity, BicycleTx shall have the right to collaborate with academic institutions and non-profit organizations with respect to the use of TfR1 Bicycles for the delivery of ASOs for Research purposes, except with respect to [***].

2.6 No Implied Licenses. Except as expressly provided herein, BicycleTx grants no other right or license to Ionis hereunder, including any rights or licenses to the BicycleTx Intellectual Property not expressly granted herein. Except as expressly provided herein, Ionis grants no other right or license to BicycleTx hereunder, including any rights or licenses to the Ionis Intellectual Property not expressly granted herein.

2.7 Exclusivity.

2.7.1 During the Term, except with respect to BicyleTx's conduct of Research Activities under this Agreement, and subject to Section 4.5.4, BicycleTx shall not, on its own, with its Affiliates, or with a Third Party (including by the grant of any license, but subject to BicycleTx's rights under Section 2.5), [***] in the Field in the Territory, and during such period, Ionis shall have the exclusive right to perform the foregoing activities ("**Oligo Exclusivity**"). Notwithstanding the foregoing, Oligo Exclusivity shall apply only to Compounds directed to Targets that are not BicycleTx Excluded Targets.

2.7.2 BicycleTx shall not, on its own, with its Affiliates, or with a Third Party (including the grant of any license) [***]. To enable BicycleTx to comply with its obligations in the foregoing sentence, Ionis shall [***].

2.7.3 If BicycleTx terminates Oligo Exclusivity in accordance with Section 4.5.4, then BicycleTx's obligations under Section 2.7.1 shall terminate, and in lieu of such obligations, BicycleTx shall not, on its own, with its Affiliates, or with a Third Party (including the grant of any license, but subject to BicycleTx's rights under Section 2.5) [***].

ARTICLE 3
COLLABORATION MANAGEMENT

3.1 Joint Steering Committee.

3.1.1 Formation. Within [***] days after the Effective Date, the Parties shall establish a joint steering committee (the "**JSC**"). The JSC shall consist of two representatives from each of the Parties (with the number of such representatives at each Party's election, but with each Party collectively having one vote). Each representative shall have the requisite experience and seniority to enable such person to make decisions on behalf of the applicable Party with respect to the issues falling within the decision making authority of the JSC. From time to time, each Party may substitute one or more of its representatives to the JSC on written notice to the other Party. Each Party shall select from its representatives a representative who will chair the JSC jointly with the selected representative from the other Party. Each Party may replace its co-chairperson from time to time by informing the other Party in writing.

3.1.2 Specific Responsibilities. The JSC shall oversee the performance of the Research Plan and serve as a consultative and information-exchange body for the Development of Licensed Products. In particular, the JSC shall:

(a) review and discuss the Research Plan, and review and approve any amendments thereto;

(b) set timelines for implementing the Research Plan and measurables for the conduct and progress of the Research Plan;

(c) oversee the conduct and progress of the Research Plan and serve as a forum for discussion of results generated under the Research Plan;

(d) serve as a forum for discussion of Development activities with respect to Compounds and Licensed Products, including results arising from such activities;

(e) establish secure access methods (such as secure databases) for the exchange of Know-How and other information as contemplated under this Agreement;

(f) monitor and implement the technology transfer to Ionis pursuant to Section 4.7; and

(g) perform such other functions as are set forth herein or as the Parties may mutually agree in writing, except where in conflict with any provision of this Agreement.

3.2 General Provisions Applicable to the JSC.

3.2.1 Meetings and Minutes. The JSC shall meet [***], or at such frequency as otherwise agreed to by the Parties, either in person or by tele-/videoconference with the venue of the in-person meetings alternating between locations designated by BicycleTx and locations designated by Ionis. The Alliance Manager shall be permitted to attend the JSC meetings. The chairperson of the JSC shall be responsible for calling meetings on no less than [***] notice. Each Party shall make all proposals for agenda items and shall provide all appropriate information with respect to such proposed items at least [***] in advance of the applicable meeting; provided that under exigent circumstances requiring input by the JSC, a Party may provide its agenda items to the other Party within a shorter period of time in advance of the meeting, or may propose that there not be a specific agenda for a particular meeting, so long as the other Party consents to such later addition of such agenda items or the absence of a specific agenda for such meeting. The chairpersons of the JSC (or their designee) shall prepare and circulate minutes of each meeting within [***] after the meeting for the Parties' review and approval. The Parties shall agree on the minutes of each meeting promptly, but in no event later than within [***] following circulation of the draft minutes.

3.2.2 Procedural Rules. The JSC shall have the right to adopt such standing rules as necessary for its work, so long as such rules are not inconsistent with this Agreement. A quorum of the JSC shall exist whenever there is present at a meeting at least [***] appointed by each Party. Representation by proxy shall be allowed. The JSC shall take action by consensus of the representatives present at a meeting at which a quorum exists, with each Party having a single vote irrespective of the number of representatives of such Party in attendance, or by a written resolution signed by at least [***] appointed by each Party.

3.2.3 Non-Member Attendance. Each Party may from time to time invite a reasonable number of participants, in addition to its representatives, to attend JSC meetings in a non-voting capacity; provided that if either Party intends to have any Third Party (including any consultant) attend such a meeting, such Party shall provide reasonable prior written notice to the other Party and obtain the other Party's approval for such Third Party to attend such meeting, which approval shall not be unreasonably withheld, conditioned, or delayed. Such Party shall ensure that such Third Party is bound by written confidentiality and non-use obligations consistent with the terms of ARTICLE 8.

3.3 Decisions.

3.3.1 Decision Making Authority. The JSC shall decide matters within its responsibilities pursuant to Section 3.1.2.

3.3.2 Consensus; Good Faith. The members of the JSC shall in good faith cooperate with one another and shall endeavor to seek agreement with respect to issues to be decided by the JSC.

3.3.3 Final Decision Right; Dispute Resolution. If the JSC cannot, or does not, reach consensus on an issue, then (a) BicycleTx shall have final say on [***]; (b) subject to Section 3.3.3(c), Ionis shall have final say on [***]; and (c) neither Party shall have final say on [***]. Notwithstanding the foregoing, neither Party shall use its final decision-making authority to (i) impose any requirement on the other Party to undertake obligations beyond those for which it is responsible or to forgo any of its rights under this Agreement, (ii) require the other Party to violate any Applicable Law, ethical requirement, or any agreement it may have with any Third Party, or (iii) amend the terms and conditions of this Agreement. Disputes arising between the Parties in connection with or relating to this Agreement or any document or instrument delivered in connection herewith, and that are outside of the decision-making authority of the JSC, shall be finally resolved pursuant to Section 12.2.

3.4 Limitations on Authority. Each Party shall retain the rights, powers, and discretion granted to it under this Agreement and no such rights, powers, or discretion shall be delegated to or vested in the JSC unless such delegation or vesting of rights is expressly provided for in this Agreement or the Parties expressly so agree in writing. The JSC shall not have the power to amend, modify, or waive compliance with this Agreement, which may only be amended or modified as provided in Section 12.3 or compliance with which may only be waived as provided in Section 12.5.

3.5 Alliance Manager. Each Party shall appoint a person who shall oversee contact between the Parties for all matters between meetings of the JSC and shall have such other responsibilities as the Parties may agree in writing after the Effective Date (each, an "**Alliance Manager**"). If not already a member of the JSC, each Alliance Manager shall be permitted to attend JSC meetings as appropriate as a non-voting participant. Each Party may replace its Alliance Manager at any time by notice in writing to the other Party.

3.6 Discontinuation of the JSC. The activities to be performed by the JSC shall solely relate to governance under this Agreement and are not intended to be or involve the delivery of services. Upon the date of First Commercial Sale of a Licensed Product in the Field in the Territory, or such earlier date agreed by the Parties in writing, the JSC shall have no further responsibilities or authority under this Agreement and, unless otherwise agreed by the Parties in writing, will be considered fully dissolved by the Parties. Thereafter, each Party shall designate, to the extent necessary, a contact person for the exchange of information under this Agreement or such exchange of information shall be made through the Alliance Managers, and decisions of the JSC, if any, shall be decisions as between the Parties, subject to the other terms and conditions of this Agreement.

3.7 Expenses. Each Party shall be responsible for all travel and related costs and expenses of its Alliance Manager and of its members and other representatives to attend meetings of, and otherwise participate on, the JSC.

ARTICLE 4
RESEARCH AND DEVELOPMENT

4.1 Collaboration Overview Subject to the terms and conditions of this Agreement, the Parties shall collaborate in connection with the performance of activities under the Research Plan. Following the completion of the Research Plan, subject to Section 4.5.4, Ionis shall have the sole and exclusive right and responsibility, at its own expense, for the Development of the Compounds and Licensed Products in the Territory

4.2 Research Plan. BicycleTx and Ionis will conduct certain activities to optimize TfR1 Bicycles for use in Compounds, and such other research and discovery activities relating to TfR1 Bicycles as the Parties may agree through the JSC from time to time as reflected by the written minutes of the JSC (the "**Research Activities**"), which activities will be set forth in a mutually agreed research plan (the "**Research Plan**"). The Parties will work together during the [***] following the Effective Date to prepare and finalize the Research Plan. The Research Plan will include [***], which period may be extended upon mutual agreement of the Parties, the cost of which will be borne by BicycleTx. With respect to the Research Activities:

4.2.1 BicycleTx will conduct the Research Activities at no additional cost to Ionis as set forth in the Research Plan including by way of example and without limitation, X-ray crystallography.

4.2.2 Any work by BicycleTx requested by Ionis over and above the [***] annually will be discussed in good faith by the parties with a view to agreeing upon an allocation of costs to the applicable activities. In the event that internal BicycleTx resources are required, the Parties will agree on a commercially reasonable rate payable to BicycleTx.

4.2.3 BicycleTx may utilize a contract research organization or other subcontractor ("**CRO**") to conduct such activities under the Research Plan, provided that the Parties shall discuss and agree upon the scope of such CRO activities at the JSC and Ionis shall be responsible for the out of pocket costs incurred in connection with such CRO activities, on a pass-through basis without mark-up. Subject to Section 3.3, the Parties may amend the Research Plan upon the JSC's written agreement. If the Parties (via the JSC) amend the Research Plan to include additional Research or Development work to be conducted by BicycleTx in respect of the TfR1 Bicycles or any Compounds, the Parties will negotiate in good faith to agree upon a commercially reasonable FTE rate payable to BicycleTx for the conduct of such additional activities.

4.2.4 Notwithstanding the extent of what is set forth in the Research Plan at any given time, all Research Activities that the Parties agree to conduct under this Agreement that are reflected in the written minutes of the JSC will be deemed to have been conducted under the Research Plan (whether or not specifically set forth therein).

4.3 Research Activities. BicycleTx shall carry out the Research Activities assigned to it in the Research Plan in good scientific manner, in accordance with this Agreement, and in compliance with all Applicable Law. Through the JSC, Ionis shall provide reasonable assistance requested by BicycleTx in connection with BicycleTx's performance of the Research Activities. Following the completion of the Research Activities, BicycleTx shall deliver to Ionis, through the JSC, the results and data arising from such Research Activities and set forth to be delivered to the JSC in the Research Plan.

4.4 Development of Licensed Products. Following completion of the Research Plan, Ionis shall have the sole right and responsibility to Develop and Manufacture, including seeking Regulatory Approvals for, Compounds and Licensed Products in the Field in the Territory, in each case at Ionis' sole expense. If BicycleTx terminates Oligo Exclusivity in accordance with Section 4.5.4, such rights and responsibilities shall be limited to Compounds and Licensed Products directed to Collaboration Targets.

4.5 Diligence.

4.5.1 General.

(a) BicycleTx shall use Commercially Reasonable Efforts to perform the Research Activities assigned to it under the Research Plan.

(b) With respect to [***], Ionis shall use Commercially Reasonable Efforts to Develop and obtain Regulatory Approval for a Licensed Product directed to such Target in at least [***] for use in [***]. Ionis shall have the right to satisfy its diligence obligations under this Section 4.5 through its Affiliates and Sublicensees.

4.5.2 Diligence Milestones. Without limiting the generality of the foregoing Section 4.5.1(b), and subject to Section 4.5.3, Ionis shall:

(a) [***];

(b) [***];

(c) [***]; and

(d) [***].

Notwithstanding anything to the contrary herein, [***].

4.5.3 Diligence Milestone Extensions. The deadlines set forth in Section 4.5.2 may be extended as follows:

(a) to the extent of [***]; or

(b) on a one-time basis [***] the following subsections ((i) – (iv)) by a period of [***] upon payment to BicycleTx of a non-refundable, non-creditable payment of [***] per subsection (the "**Diligence Extension Fee**"):

(i) [***];

(ii) [***];

(iii) [***]; and

(iv) [***].

(c) Ionis will have the right to extend any deadline set forth in Section 4.5.2 pursuant to Section 4.5.3(a) or 4.5.3(b) by (i) providing BicycleTx with a written notice therefor prior to the date on which such milestone is required to be performed (an "**Extension Notice**") and (ii) if such extension is pursuant to (A) Section 4.5.3(a), [***], or (B) Section 4.5.3(b), paying to BicycleTx the Diligence Extension Fee, in each case ((A) and (B)) concurrently with the delivery of such notice provided that any further extensions pursuant to Section 4.5.3(a) will require the Parties to [***]. For clarity, the maximum amount payable to BicycleTx pursuant to Section 4.5.3(b) is [***] (i.e. the milestones could be extended pursuant to the application of all of subclauses (i), (ii) and (iv), or by the application of all of subclauses (ii), (iii) and (iv)). For example, [***].

4.5.4 Failure to Achieve Milestones; Termination of Oligo Exclusivity.

(a) If Ionis fails to meet one or more of the diligence milestones set forth in Section 4.5.2 (as the dates for achievement of such diligence milestones may be extended pursuant to Section 4.5.3), and does not elect to extend such diligence milestones as provided under Section 4.5.3 (or no further extension is available to Ionis), then subject to Section 4.5.4(b), BicycleTx shall have the right, by written notice to Ionis at any time after such failure, to terminate the Oligo Exclusivity effective as of the date of such written notice.

(b) If, before BicycleTx provides written notice to Ionis terminating the Oligo Exclusivity under Section 4.5.4(a), Ionis [***], then BicycleTx shall [***].

(c) Following the termination of Oligo Exclusivity as provided in Section 4.5.4(a), (1) BicycleTx shall continue to be subject to its obligations under Section 2.7, and (2) Ionis' license under Section 2.1.2 shall terminate but Ionis' licenses under Sections 2.1.1 and 2.1.3 shall continue without any further action by either Party.

4.6 Updates.

4.6.1 BicycleTx Updates. At each regularly scheduled JSC meeting during the performance of the Research Plan, BicycleTx shall provide the JSC with a report detailing its activities under the Research Plan, to the extent then-ongoing, and the results of such activities. The Parties shall discuss the status, progress, and results of such activities at such JSC meetings.

4.6.2 Ionis Updates. For each Target for which Ionis reaches Target Sanction, Ionis shall notify BicycleTx or the Gatekeeper of the Target within [***] of the Target Sanction decision by Ionis' RMC. For each Target for which Ionis is Developing a Licensed Product, on an annual basis during the Term until the grant of Regulatory Approval for a Licensed Product directed to such Target in each of [***], Ionis will provide to BicycleTx annual reports, within [***] after the start of each Calendar Year, summarizing, with respect to activities by Ionis, its Affiliates and Sublicensees: (a) the significant Development activities undertaken and the results achieved with respect to the applicable Licensed Products during the preceding 12-month period and (b) the significant Development activities planned for the applicable Licensed Products during the following 12-month period, provided however that such reports need not be specifically generated in compliance with this section and Ionis may rely on existing reports and internal communications to its Research Management Committee or other executive management, as long as such reports reasonably provide the information set forth the foregoing (a) and (b). Following the delivery of each report, Ionis will make appropriate personnel reasonably available to BicycleTx during business hours and on reasonable advanced notice to answer questions regarding the information contained in such report in order for BicycleTx to obtain a reasonable understanding regarding the Development status of the applicable Licensed Products.

4.7 Technology Transfer.

4.7.1 Know-How. As soon as reasonably practicable following the completion of the Research Plan (and in any event not more than [***] after), BicycleTx shall, and shall cause its Affiliates to, [***], disclose and make available to Ionis (which obligation may include granting personnel designated by Ionis controlled access to an electronic data room), in such form as maintained by BicycleTx in the ordinary course of business, a copy of the BicycleTx Know-How and jointly owned Know-How (to the extent such jointly owned Know-How is in BicycleTx's possession). The Parties shall reasonably cooperate to provide a smooth and prompt provision of all such Know-How.

4.7.2 Technical Assistance. BicycleTx shall reasonably assist Ionis and its designee(s) in the use and understanding of the BicycleTx Know-How and jointly owned Know-How provided pursuant to Section 4.7.1 and with respect to such BicycleTx Know-How and jointly owned Know-How, shall provide reasonable technical assistance and make its technical personnel reasonably available to Ionis as necessary for Ionis to Exploit the Compounds and Licensed Products, provided that such technical assistance at BicycleTx's cost shall not be required to exceed, in the aggregate, a total of [***]. For any assistance requested by Ionis and provided by BicycleTx in excess of [***], Ionis shall reimburse BicycleTx for all reasonable internal costs, at an agreed FTE rate, and out-of-pocket costs incurred by BicycleTx in providing such additional assistance.

4.8 Target Exclusivity; Collaboration Targets.

4.8.1 Following termination of Oligo Exclusivity by BicycleTx pursuant to Section 4.5.4, Ionis shall retain exclusivity with respect to TfR1 Bicycles for the delivery of ASOs directed to each Collaboration Target (such residual exclusivity, "**Target Exclusivity**"). A "**Collaboration Target**" is each Target that is (a) an Existing Collaboration Target under Section 4.8.2, or (b) designated by Ionis as a Collaboration Target in accordance with Section 4.8.4, and in each case of (a) and (b), is not a Terminated Target.

4.8.2 Within [***] following termination of Oligo Exclusivity (such period, the "**Ionis Initial Target Designation Period**"), Ionis shall provide to BicycleTx and the Gatekeeper written notice specifying the Targets (that are not BicycleTx Excluded Targets) with respect to which Ionis was conducting (a) Research that has [***], or (b) [***] (each, subject to [***], an "**Existing Collaboration Target**"). The Gatekeeper shall update the list of Collaboration Targets by the end of the Ionis Initial Target Designation Period.

4.8.3 During the [***] period following the expiration of the Ionis Initial Target Designation Period (the "**BicycleTx Initial Target Designation Period**"), BicycleTx may make a BicycleTx Target Request under Section 4.9, and may place on the Gatekeeper List (i.e. in addition to any BicycleTx Excluded Targets already on the Gatekeeper List) any Target (a) for which BicycleTx commences, during the BicycleTx Initial Target Designation Period, an Internal Development Program (meeting the criteria set forth in Section 1.79(a) and (b)), or (b) that is the subject of [***].

4.8.4 At any time after expiration of the BicycleTx Initial Target Designation Period, Ionis may nominate as Collaboration Targets (a) up to [***] additional Targets (in addition to any Targets already designated by Ionis under Section 4.8.2) for which Ionis has [***], (in each case of (i) and (ii) in accordance with the terms of this Agreement and without, for clarity, any requirement that [***]) (each, an "**Ionis Research Stage Target**"), and/or (b) any Target [***] for which Ionis (or any Third Party to whom Ionis has granted rights in such Target) [***], in each case of (a) and/or (b) by following the procedure set forth in Section 4.8.5. For clarity, there may be no more than [***] Ionis Research Stage Targets nominated or placed on the Gatekeeper List at any given time, provided that upon Ionis designating a Development Candidate directed to an Ionis Research Stage Target, Ionis may notify the Gatekeeper, and such Target shall thereafter remain a Collaboration Target, but shall no longer be an Ionis Research Stage Target, and Ionis may nominate an additional Ionis Research Stage Target to the Gatekeeper List, subject to (A) any such Target being Available, (B) pre-payment of the IND Acceptance Fee, and (C) the foregoing limit of [***] Ionis Research Stage Targets in total at any time.

4.8.5 To nominate an additional Target as a Collaboration Target under Section 4.8.4 subject to Target Exclusivity, Ionis shall provide the Gatekeeper with a confidential written description of the applicable Target (the "**Nominated Target**"), including, to the extent available, [***] for such Target (the "**Target Nomination Notice**"). Within [***] following the Gatekeeper's receipt of the Target Nomination Notice with respect to a Nominated Target, the Gatekeeper shall verify whether such Nominated Target is an Available Target and notify Ionis in writing ("**Target Availability Notice**"). If the Nominated Target is an Available Target on the date that the Gatekeeper receives the applicable Target Nomination Notice, then such Nominated Target shall be designated as a Collaboration Target and shall be subject to Target Exclusivity as of the date of the Gatekeeper's receipt of the Target Nomination Notice for such Target (the "**Target Acceptance Date**") so long as Ionis pre-pays the IND Acceptance Fee for such Target within [***] of receipt of an invoice therefor. Effective as of the Target Acceptance Date for a Collaboration Target nominated pursuant to this Section 4.8.5, the Parties will have all rights and obligations hereunder in connection with such Collaboration Target (including each Party's respective rights and obligations under Sections 2.1, 2.5, and 2.7). For clarity, if Ionis elects, at its discretion, to provide a Target Nomination Notice directly to BicycleTx, rather than to the Gatekeeper, then this Section 4.8.5 shall be deemed to refer to provision of such Target Nomination Notice to BicycleTx, *mutatis mutandis*.

4.8.6 At any time after the expiration of the BicycleTx Initial Target Designation Period, BicycleTx may place on the Gatekeeper List:

(a) up to [***] additional Targets (in addition to the then-current BicycleTx Excluded Targets and any Targets already designated by BicycleTx during the BicycleTx Initial Target Designation Period under Section 4.8.3) for which BicycleTx [***] (each, a "**BicycleTx Research Stage Target**");

(b) any Target (without any cap on number) [***]; and/or

(c) any Target that is the subject of [***].

in each case of (a) through (c), subject to BicycleTx first confirming with the Gatekeeper that any such Target is Available in accordance with Section 4.9. For clarity, (A) any Target placed on the Gatekeeper list pursuant to Section 4.8.6(c) shall not be counted as a BicycleTx Research Stage Target or against the associated limit of [***], regardless of the stage of Research or Development at which rights in such Target are granted to a Third Party, and (B) there may be no more than [***] BicycleTx Research Stage Targets nominated or placed on the Gatekeeper List at any given time, provided that upon BicycleTx designating a Development Candidate directed to an BicycleTx Research Stage Target, BicycleTx may notify the Gatekeeper, and such Target shall remain on the Gatekeeper List but shall no longer be an BicycleTx Research Stage Target, and BicycleTx may nominate an additional BicycleTx Research Stage Target to the Gatekeeper List, subject to (1) any such Target being Available, and (2) the foregoing limit of [***] BicycleTx Research Stage Targets in total at any time.

4.8.7 Expanded Role of Gatekeeper. Promptly following the termination of Oligo Exclusivity, BicycleTx shall expand the engagement of the Gatekeeper for the purposes of performing the applicable functions set forth in this Section 4.8, to include (in addition to the duties set forth in Section 2.2.1): (a) maintaining a list of Targets that are not Available Targets, (b) issuing the Target Availability Notice, (c) maintaining the list of Collaboration Targets, and (d) performing the functions with respect to Bicycle that are set forth in Section 4.9. [***]. Such engagement shall be on terms consistent with this Agreement and mutually agreeable to the Parties, including provisions relating to confidentiality.

4.8.8 Unavailable Targets. Following the termination of Oligo Exclusivity, if applicable, BicycleTx shall notify the Gatekeeper of any Targets that are not Available Targets (i.e. those falling within Section 4.8.6) promptly, but in no event later than [***] after the Gatekeeper notifies BicycleTx that it has received any Target Nomination Notice, to enable the Gatekeeper to comply with its obligations to Ionis under Section 4.8. Upon receipt of such notification, the Gatekeeper shall update the Gatekeeper List accordingly. If any Nominated Target that was not an Available Target at the time of the Target Nomination Notice later becomes an Available Target, the Gatekeeper shall notify Ionis of the Available Target within [***] of the Gatekeeper receiving notice that such Available Target is available and Ionis shall have sole discretion whether such Available Target becomes a Collaboration Target under this Agreement.

4.9 BicycleTx Use of Gatekeeper to Clear Targets. Following the termination of Oligo Exclusivity, if applicable, BicycleTx shall notify the Gatekeeper of any Target(s) that BicycleTx wishes to place on the Gatekeeper List pursuant to Section 4.8.3 or Section 4.8.6 (each, a "**BicycleTx Target**") to enable the Gatekeeper to determine whether such BicycleTx Targets are Collaboration Targets (and therefore not Available for BicycleTx). To screen a BicycleTx Target, BicycleTx shall provide the Gatekeeper with a confidential written description of the applicable Target including, to the extent available, [***] for such Target ("**BicycleTx Target Request**"). Within [***] following the Gatekeeper's receipt of the BicycleTx Target Request with respect to a BicycleTx Target, the Gatekeeper shall verify if such BicycleTx Target is Available and notify BicycleTx in writing.

4.10 Subcontracting. Each Party shall have the right to subcontract any of its Development activities to a Third Party; provided that (a) such Party remains responsible for the work allocated to, and payment to, such subcontractors to the same extent it would if it had done such work itself; (b) each subcontractor undertakes in writing obligations of confidentiality and non-use regarding Confidential Information that are substantially the same as those undertaken by the Parties pursuant to ARTICLE 8; and (c) each subcontractor agrees in writing to assign all intellectual property developed in the course of performing any such work to such Party in accordance with Section 7.1.3(a).

4.11 Regulatory Matters.

4.11.1 Regulatory Activities. As between the Parties, Ionis, at its sole expense, shall have the sole right to prepare, obtain, and maintain the Drug Approval Applications (including the setting of the overall regulatory strategy therefor), Regulatory Approvals, and other Regulatory Documentation, and to conduct communications with Regulatory Authorities, for Compounds and Licensed Products in the Territory, provided that following the termination of Oligo Exclusivity (if applicable), Ionis' right to conduct the foregoing regulatory activities shall apply only to Licensed Products directed to Collaboration Targets (and for clarity, such right with respect to Collaboration Targets shall be a sole right). Upon Ionis' request [***], BicycleTx shall provide Ionis with reasonable assistance in obtaining Regulatory Approvals for the Licensed Products, including providing necessary documents or other materials required by Applicable Law to obtain such Regulatory Approvals, provided that such assistance shall be limited to assistance that relates directly to the work BicycleTx conducted pursuant to the Research Plan, and provided further that nothing in this Section 4.11.1 shall obligate BicycleTx to generate any additional data or other Know-How.

4.11.2 Recalls. Ionis shall notify BicycleTx promptly following its determination that any event, incident, or circumstance has occurred that may result in the need for a recall, market suspension, or market withdrawal of a Licensed Product in the Territory, and shall include in such notice the reasoning behind such determination and any supporting facts. Ionis (or its Sublicensee) shall have the right to make the final determination whether to voluntarily implement any such recall, market suspension, or market withdrawal in the Territory. If a recall, market suspension, or market withdrawal is mandated by a Regulatory Authority in the Territory, Ionis (or its Sublicensee) shall initiate such a recall, market suspension, or market withdrawal in compliance with Applicable Law. For all recalls, market suspensions, or market withdrawals undertaken pursuant to this Section 4.11.2, Ionis (or its Affiliate or Sublicensee) shall be solely responsible for the execution thereof, and BicycleTx shall reasonably cooperate in all such recall efforts, [***].

4.12 Records. Each of BicycleTx and Ionis shall, and shall ensure that its contractors, maintain records in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes, and in compliance with Applicable Law, which shall be complete and accurate and shall properly reflect all work done and results achieved in the performance of its Research Activities and Development activities hereunder, which shall record only such activities and shall not include or be commingled with records of activities outside the scope of this Agreement. Such records shall be retained by BicycleTx or Ionis, as the case may be, for at least [***] after the termination of this Agreement, or for such longer period as may be required by Applicable Law.

ARTICLE 5
COMMERCIALIZATION

5.1 In General. Ionis (itself or through its Affiliates or Sublicensees) shall have the sole right and responsibility to Commercialize Licensed Products in the Field in the Territory, at its own expense, provided that following the termination of Oligo Exclusivity (if applicable), Ionis' right to conduct the foregoing Commercialization activities shall apply only to Licensed Products directed to Collaboration Targets (and for clarity, such right with respect to Collaboration Targets shall be a sole right).

5.2 Commercialization Diligence. For each Target for which Ionis has paid (or, for up to four Targets, as applicable, applied a credit toward) the IND Acceptance Fee (including, for clarity, any Collaboration Target), Ionis shall use Commercially Reasonable Efforts to Commercialize at least [***] following receipt of Regulatory Approval therefor in such Major Market. With respect to any such Target, if Ionis decides to discontinue the Development or Commercialization of a Compound and Licensed Product in favor of another Compound and Licensed Product directed to such Target, its obligations under this Section 5.2 shall cease with respect to such initial Compound and Licensed Product in favor of such other Compound and Licensed Product directed to such Target.

5.3 Commercial Updates. Ionis shall update BicycleTx on [***] basis regarding its significant Commercialization activities with respect to Licensed Products corresponding to each Target for which Ionis has paid (or, for [***], as applicable, applied a credit toward) the IND Acceptance Fee in the Territory. Each such update shall summarize Ionis and its Affiliates' and Sublicensees' significant Commercialization activities with respect to each such Licensed Product and Target in the Territory and shall contain information at a level of detail reasonably required by BicycleTx to determine Ionis' compliance with its diligence obligations set forth herein, provided however that such updates and reports need not be specifically generated in compliance with this section and Ionis may rely on existing reports and internal communications to its Research Management Committee or other executive management, as long as such reports appropriately encompass the information required under this Section 5.3.

5.4 Commercial Supply of Compounds and Licensed Products As between the Parties, Ionis shall have the sole right and responsibility, at its expense, to Manufacture (or have Manufactured) and supply Compounds and Licensed Products for commercial sale in the Territory by Ionis and its Affiliates and Sublicensees. If BicycleTx terminates Oligo Exclusivity in accordance with Section 4.5.4, such rights and responsibilities shall be limited to Compounds and Licensed Products directed to the Collaboration Targets.

ARTICLE 6
PAYMENTS AND RECORDS

6.1 Upfront Payment. Within [***] after the Effective Date, Ionis shall pay to BicycleTx a one-time, non-refundable, non-creditable (except as set forth in Section 6.3) payment in the amount of Thirty-One Million Dollars ($31,000,000). The Parties acknowledge and agree that the Three Million Dollar ($3,000,000) Option Fee (as defined in the Option Agreement) paid to BicycleTx by Ionis pursuant to Section 4.1 of the Option Agreement has been fully credited against the total agreed upfront payment under this Agreement of Thirty-Four Million Dollars ($34,000,000).

6.2 Equity Consideration. In partial consideration for the rights granted by BicycleTx under this Agreement, Bicycle Therapeutics plc and Ionis will enter into a Stock Purchase Agreement in the form set forth as Exhibit 6.2, pursuant to which Bicycle Therapeutics plc will issue to Ionis a number of Ordinary Shares equal to Eleven Million Dollars ($11,000,000) divided by the Share Value in accordance with the terms set forth therein (as the terms Ordinary Shares and Share Value are defined in the Stock Purchase Agreement).

6.3 IND Acceptance Fee. On a Target-by-Target basis, within [***] after IND Acceptance for the first Licensed Product directed to such Target being Developed by Ionis, its Affiliates or Sublicensees, Ionis shall pay to BicycleTx a one-time, non-refundable, non-creditable payment in the amount of [***] (the "**IND Acceptance Fee**"); provided, however, that Ionis will have a credit up to [***] (the "**IND Acceptance Credit**"), which shall be deemed included in (and pre-paid pursuant to) the upfront payment paid to BicycleTx under Section 6.1, and may be applied against the IND Acceptance Fee for the first Licensed Product directed to each of up to [***] Targets. For clarity, Ionis shall not be required to apply the IND Acceptance Credit against the first four Targets (and associated Licensed Products), and shall have sole discretion in determining, on a Licensed Product-by-Licensed Product basis, whether it wishes to pay the IND Acceptance Fee in cash, or apply a portion of the remaining IND Acceptance Credit against such Licensed Product, until the full amount of the IND Acceptance Credit has been exhausted. If Oligo Exclusivity expires, and Ionis has, at such time, not exhausted the IND Acceptance Credit, Ionis may apply any remaining amount against any prepayment of the IND Acceptance Fee for Targets that Ionis designates to be Collaboration Targets pursuant to Section 4.8.2. For clarity, if this Agreement is terminated prior to the exhaustion of the IND Acceptance Credit, BicycleTx will not be required to refund any unused portion of the IND Acceptance Credit to Ionis.

6.4 Development and Regulatory Milestones

6.4.1 Development and Regulatory Milestone Payments. In partial consideration of the rights granted by BicycleTx to Ionis under this Agreement and subject to the terms and conditions set forth in the remainder of this Section 6.4, on a Target-by-Target basis, Ionis shall pay to BicycleTx the non-refundable, non-creditable milestone payment set forth in the table below upon the first achievement of the corresponding milestone event by a Licensed Product directed to such Target by or on behalf of Ionis or its Affiliates or Sublicensees:

	Milestone Event (payable for the first Licensed Product directed to a given Target)	Milestone Payment Amount
1.	[***]	[***]
2.	[***]	[***]
3.	[***]	[***]
4.	[***]	[***]

6.4.2 One-Time Payment per Target; Deemed Achievement. For clarity, the foregoing milestone payments shall be payable one-time only with respect to each Target, regardless of the number of Licensed Products directed to such Target to achieve such milestone event. For further clarity, milestone #1 shall be deemed achieved and payable, if not already achieved, upon achievement of any of milestones #2, #3, or #4 by a Licensed Product directed to the same Target.

6.4.3 Ultra-Rare Disease Product Delay in Payment. Notwithstanding the foregoing, with respect to the achievement of any of the foregoing milestone events by an Ultra-Rare Disease Product, Ionis' payment to BicycleTx of the corresponding milestone payments will be deferred until the first to occur of [***].

6.4.4 Notice and Payment. Ionis shall notify BicycleTx within [***] after achieving any milestone event set forth in the table above. Except as otherwise provided in Section 6.4.3 with respect to an Ultra-Rare Disease Product, Ionis shall pay to BicycleTx the applicable milestone payment within [***] after receipt of an invoice for the achievement of the applicable milestone event.

6.5 Collaboration Milestones.

6.5.1 Collaboration Milestone Payments. In partial consideration of the rights granted by BicycleTx to Ionis hereunder and subject to the terms and conditions set forth in the remainder of this Section 6.5, Ionis shall pay to BicycleTx the following one-time, non-refundable, non-creditable milestone payments set forth in the table below following the end of the Calendar Quarter in which the first achievement by or on behalf of Ionis, its Affiliates or Sublicensees of the corresponding milestone event occurred:

[***]		Milestone Payment Amount
1.	[***]	[***]
2.	[***]	[***]

6.5.2 Notice and Payment. Ionis shall notify BicycleTx within [***] following the end of the Calendar Quarter in which such milestone event in the table above was achieved. Ionis shall pay to BicycleTx the applicable milestone payment within [***] after receipt of an invoice for the achievement of the applicable milestone event.

6.6 Royalties.

6.6.1 Royalty Rates. As further consideration for the rights granted to Ionis under this Agreement, subject to the remainder of this Section 6.6, during the Royalty Term, Ionis shall make quarterly, non-refundable (except as the result of an overpayment under Section 6.11), non-creditable royalty payments to BicycleTx on the annual Net Sales of each Licensed Product sold by or on behalf of Ionis, its Affiliates or Sublicensees in the Territory at the applicable rate set forth below:

Annual Net Sales in the Territory of a given Licensed Product in a Calendar Year	Royalty Rate
[***]	[***]
[***]	[***]

6.6.2 Royalty Term. Royalties shall be paid on a Licensed Product-by-Licensed Product and country-by-country basis in the Territory from the First Commercial Sale of such Licensed Product in a country by or on behalf of Ionis, its Affiliates, or Sublicensees, until the expiration of the Royalty Term for such Licensed Product in such country.

6.6.3 Permitted Reductions.

(a) On a Licensed Product-by-Licensed Product basis, if [***] to the extent necessary such that [***] for such Licensed Product in such Calendar Quarter, after giving effect to [***]; provided that during the [***] following the First Commercial Sale of such Licensed Product in [***] (each such period, a "Royalty Floor Period") in no event will the foregoing operate to reduce the royalty paid to BicycleTx on the Net Sales of such Licensed Product in any [***] of the amount that BicycleTx otherwise would have received on the Net Sales of such Licensed Product in [***] had no such reduction occurred.

(b) If following the Royalty Floor Period the amount of royalties paid to BicycleTx by Ionis is reduced as described in Section 6.6.3(a), Ionis will also pay to BicycleTx [***] sale of the applicable Licensed Product following the Royalty Floor Period until [***] of the amount that BicycleTx [***] after the Royalty Floor Period *minus* (ii) the royalty payments received by BicycleTx for such Net Sales in such countries. [***]. For instance, [***]. At the end of the quarter, [***].

Notwithstanding the foregoing, Ionis will use commercially reasonable efforts to obtain a minimum of a [***] royalty from its Sublicensees so that no reduction to the royalty payable to BicycleTx pursuant to Section 6.6.3(a) is implemented.

(c) Except as set forth in the foregoing Section 6.6.3(a), the royalties payable by Ionis to BicycleTx pursuant to Section 6.6.1 shall [***].

6.7 Royalty Payments and Reports. Ionis shall calculate all amounts payable to BicycleTx pursuant to Section 6.6 at the end of each Calendar Quarter, which amounts shall be converted to Dollars, in accordance with Section 6.8. Ionis shall pay to BicycleTx the royalty amounts due with respect to a given Calendar Quarter within [***] after the end of each Calendar Quarter. Each payment of royalties due to BicycleTx shall be accompanied by a report setting forth the Net Sales of the Licensed Products by Ionis and its Affiliates and Sublicensees in the Territory in sufficient detail to permit confirmation of the accuracy of the royalty payment made, including [***].

6.8 Mode of Payment. All payments to BicycleTx under this Agreement shall be made by deposit of Dollars in the requisite amount to such bank account as BicycleTx may from time to time designate by written notice to Ionis. For the purpose of calculating any sums due under, or otherwise reimbursable pursuant to, this Agreement (including the calculation of Net Sales expressed in currencies other than Dollars), a Party shall convert any amount expressed in a foreign currency into Dollar equivalents using its, its Affiliate's, or Sublicensee's standard conversion methodology consistent with Accounting Standards.

6.9 Taxes.

6.9.1 Taxes on Income. Except as provided herein, each Party shall be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

6.9.2 Withholding Amounts. If any sum due to be paid to BicycleTx under this Agreement is subject to any withholding or similar tax, the Parties shall use their commercially reasonable efforts to do all such acts and to sign all such documents as will enable them to take advantage of any applicable double taxation agreement or treaty. If there is no applicable double taxation agreement or treaty, or if an applicable double taxation agreement or treaty reduces but does not eliminate such withholding or similar tax, Ionis shall remit such withholding or similar tax to the appropriate government authority and any tax paid or required to be withheld by Ionis for the benefit of BicycleTx on account of any payments to BicycleTx under this Agreement will be deducted from the amount of royalties or other payments otherwise due. Ionis will secure and send to BicycleTx the best available proof of any such taxes so withheld and paid by Ionis for the benefit of BicycleTx. If withholding or similar taxes are paid to a government authority, each Party will provide the other such assistance as is reasonably required to obtain a refund of the withheld or similar taxes, or to obtain a credit with respect to such taxes paid.

6.9.3 Withholding Actions. Notwithstanding the foregoing, the Parties acknowledge and agree that if Ionis (or its assignee pursuant to Section 12.9) is required by Applicable Law to withhold taxes in respect of any amount payable under this Agreement, and if such withholding obligation arises as a result any action by Ionis, including any assignment of this Agreement by Ionis as permitted under Section 12.9, a change in tax residency of Ionis, or payments arise or are deemed to arise through a branch of Ionis and such withholding taxes exceed the amount of withholding taxes that would have been applicable if such action had not occurred (each, an "**Ionis Withholding Tax Action**"), then, notwithstanding anything to the contrary herein, any such amount payable to BicycleTx under this Agreement shall be increased to take into account such increased withholding taxes as may be necessary so that, after making all required withholdings, BicycleTx (or its assignee pursuant to Section 12.9) receives an amount equal to the sum it would have received had no such Ionis Withholding Tax Action occurred. BicycleTx shall (a) use its commercially reasonable efforts to obtain an exemption of such withheld amounts to the extent practicable under Applicable Law and (b) cooperate with Ionis, at Ionis' reasonable expense, to obtain a reduction or refund of such withheld amounts. Notwithstanding the foregoing, the Parties acknowledge and agree that as of the date of this Agreement and under Applicable Laws, no withholding tax will be applicable to payments made to BicycleTx pursuant to this Agreement provided BicycleTx provides Ionis with a completed IRS form W-8BEN-E claiming the benefits of the United States – United Kingdom Income Tax Convention. The failure by BicycleTx to provide the tax forms described herein shall not relieve Ionis (or its assignee pursuant to Section 12.9) of its obligations pursuant to this Section 6.9.3 unless Ionis has requested the applicable tax forms in writing sufficiently in advance of a payment so as to allow the BicycleTx a reasonable amount of time to obtain and provide the required forms. Notwithstanding the foregoing, if the increase in the withholding tax is directly a result of the transfer or assignment by BicycleTx of any intellectual property or a portion of the rights under this license Ionis will only be obligated to pay BicycleTx such gross up to the extent such transfer or assignment by BicycleTx did not cause such increase in the withholding tax.

6.9.4 Tax Credits. During the Term, to the extent of, and if directly as a result of, an additional payment paid to BicycleTx pursuant to Section 6.9.3, BicycleTx is able to utilize a foreign tax credit or claim a deduction in the year of any such payment or any later year to actually reduce otherwise payable cash taxes, BicycleTx will refund to Ionis an amount equal to the actual cash tax savings obtained by BicycleTx directly related to the increased payment BicycleTx received pursuant to Section 6.9.3 as reasonably determined in good faith by BicycleTx and supported by BicycleTx's tax records. Except in the case of a dispute between the Parties under this Section 6.9.4, BicycleTx will not be required to provide Ionis with any tax returns or other confidential tax, accounting, or financial information.

6.10 Interest on Late Payments. If any undisputed payment due to either Party under this Agreement is not paid when due, then such paying Party shall pay interest thereon (before and after any judgment, but excluding the period during which termination is tolled pursuant to Section 11.3.1) at [***] until [***]. For the purposes of this Agreement, [***].

6.11 Audit. Ionis shall keep, and shall require its Affiliates and Sublicensees to keep, complete and accurate records pertaining to the sale or other disposition of Licensed Products in sufficient detail to permit BicycleTx to confirm the accuracy of any milestone payment due under Section 6.5 and royalty payment due under Section 6.6. Ionis will keep such books and records for [***] following the Calendar Year to which they pertain, or such longer period of time as may be required by Applicable Law. Upon reasonable prior notice and during regular business hours at such place or places where such records are customarily kept, such records may be inspected on BicycleTx's behalf by an independent certified public accountant (the "**Auditor**") selected by BicycleTx and reasonably acceptable to Ionis for the sole purpose of verifying for BicycleTx the accuracy of any payments made, or required to be made, to BicycleTx pursuant to this Agreement. Before beginning its audit, the Auditor shall execute an undertaking reasonably acceptable to each Party by which the Auditor agrees to keep confidential all information reviewed during the audit. Such audits shall be limited to [***] each Calendar Year and [***]. Such auditor shall not disclose Ionis' Confidential Information to BicycleTx except to the extent necessary to confirm the accuracy of the financial reports and payments furnished by Ionis under this Agreement and the amount of any discrepancies. If the final result of the inspection reveals an undisputed underpayment, the underpaid amount shall be paid within [***] after the Auditor's report. If the final result of the inspection reveals an undisputed overpayment, the overpaid amount shall be applied as a credit against future royalty payments by Ionis. BicycleTx shall bear the full cost of such audit unless such audit reveals an underpayment owed by Ionis of more than [***] from the reported amounts, in which case Ionis shall bear the cost of such audit.

ARTICLE 7
INTELLECTUAL PROPERTY

7.1 Ownership of Intellectual Property.

7.1.1 United States Law. The determination of whether an Invention is discovered, made, conceived, or reduced to practice by a Party for the purpose of allocating proprietary rights (including Patent, copyright, or other intellectual property rights) therein, shall, for purposes of this Agreement, be made in accordance with Applicable Law in the United States.

7.1.2 Inventions.

(a) **Sole Ownership**. As between the Parties, (i) BicycleTx, or an Affiliate designated by BicycleTx, shall own all right, title, and interest in and to any and all TfR1 BicycleTx Inventions and (ii) with respect to all other Inventions, each Party shall solely own any Inventions made solely by its and its Affiliates' employees, agents, or independent contractors.

(b) **Joint Ownership**. Subject to Section 7.1.2(a)(i), the Parties shall jointly own any Inventions that are made jointly by employees, agents, or independent contractors of one Party and its Affiliates together with employees, agents, or independent contractors of the other Party and its Affiliates ("**Joint Inventions**"). Subject to the licenses granted under Section 2.1 and Section 2.3, and BicycleTx's Exclusivity Obligations hereunder, each Party shall have the right to Exploit the Joint Patents and Joint Inventions without a duty of seeking consent from or accounting to the other Party.

7.1.3 Assignment Obligation.

(a) Each Party shall cause all Persons who perform activities for such Party under this Agreement to be under an obligation to assign (or, if such Party is unable to cause such Person to agree to such assignment obligation despite such Party's using commercially reasonable efforts to negotiate such assignment obligation, provide a license under) their rights in any Inventions resulting therefrom to such Party, except where Applicable Law requires otherwise and except in the case of governmental, not-for-profit, and public institutions which have standard policies against such an assignment (in which case a suitable license, or right to obtain such a license, shall be obtained).

(b) Ionis will promptly disclose to BicycleTx in writing any TfR1 BicycleTx Inventions made (either solely or jointly) by Persons (other than BicycleTx) who perform activities for Ionis under this Agreement. Ionis, for itself and on behalf of its Affiliates, hereby assigns (and to the extent a present assignment of future rights is prohibited by Applicable Law, hereby agrees to and shall assign) to BicycleTx all of its right, title, and interest in and to any and all TfR1 BicycleTx Inventions (and any BicycleTx Patents relating thereto). Ionis will execute and record assignments and other necessary documents consistent with such ownership promptly upon BicycleTx's request.

(c) Each Party will promptly disclose to the other Party, in writing, the conception, discovery, development, generation, making or creation of any Joint Inventions made by Persons who perform activities for it under this Agreement. Each Party will execute and record assignments and other necessary documents consistent with such ownership promptly upon such other Party's request.

7.2 Patent Prosecution and Maintenance.

7.2.1 BicycleTx Patents other than BicycleTx Product Patents.

(a) BicycleTx shall have the sole right, but not the obligation, through the use of internal or outside counsel of its choice, to prepare, file, prosecute, and maintain (a) the BicycleTx Platform Patents, and (b) the BicycleTx Patents that do not Cover any Compound or Licensed Product worldwide, at BicycleTx's expense.

(b) BicycleTx shall have the first right, but not the obligation, through the use of internal or outside counsel of its choice, to prepare, file, prosecute, and maintain any BicycleTx Patent that Cover any Compound or Licensed Product, but which Patent is not a BicycleTx Product Patent (each, a "**BicycleTx Relevant Patent**") worldwide, at BicycleTx's expense. With respect to any BicycleTx Relevant Patents that [***], BicycleTx shall keep Ionis reasonably informed of all material steps with regard to the preparation, filing, prosecution, and maintenance of any such claims of such BicycleTx Relevant Patents, including by providing Ionis with a copy of material communications to and from any patent authority in the Territory regarding such claims of such BicycleTx Relevant Patents, and by providing Ionis drafts of any material filings to be made to such patent authorities in the Territory sufficiently in advance of submitting such filings so as to allow for a reasonable opportunity for Ionis to review and comment on such claims. Upon Ionis' request during the Term, BicycleTx shall use reasonable efforts, to the extent reasonably practicable under applicable patent law, to separate [***] from any BicycleTx Relevant Patent, and to file one or more divisional or continuation patent applications that [***] shall be deemed BicycleTx Product Patents hereunder as of the date of filing, and shall thereafter be subject to Section 7.2.3. For clarity, all Patents that issue from such [***], shall be included as BicycleTx Product Patents under this Agreement.

(c) If, in the reasonable opinion of BicycleTx's patent counsel, [***], BicycleTx shall consider in good faith the requests and suggestions of Ionis with respect to such BicycleTx drafts and with respect to strategies for filing and prosecuting such Patents in the Territory. If BicycleTx decides not to prosecute, or maintain any BicycleTx Relevant Patents that [***] in a country or other jurisdiction in the Territory, BicycleTx shall provide reasonable prior written notice to Ionis of such intention (which notice shall, in any event, be given no later than [***] prior to the next deadline for any action that may be taken with respect to such BicycleTx Relevant Patents that [***] in such country or other jurisdiction), and BicycleTx shall reasonably consider a request by Ionis to assume the control and direction of the preparation, filing, prosecution, and maintenance of such Patent at its sole cost and expense in such country or other jurisdiction. For clarity, BicycleTx shall [***]. If BicycleTx grants its consent to Ionis' assumption of such activities, Ionis shall assume the responsibility and control for the preparation, filing, prosecution, and maintenance of such BicycleTx Relevant Patent. In such event, Bicycle shall reasonably cooperate with Ionis with respect to such Patent in such country or other jurisdiction as provided under Section 7.2.4.

7.2.2 Ionis Patents. Ionis shall have the sole right, but not the obligation, through the use of internal or outside counsel, to prepare, file, prosecute, and maintain the Ionis Patents, BicycleTx Product Patents, and Joint Product Patents worldwide, at Ionis' expense.

7.2.3 BicycleTx Product Patents and Joint Patents. Ionis shall have the first right, but not the obligation, through the use of internal counsel, or outside counsel reasonably acceptable to BicycleTx, to prepare, file, prosecute, and maintain the BicycleTx Product Patents and the Joint Patents worldwide, at Ionis' expense. Ionis shall keep BicycleTx reasonably informed of all material steps with regard to the preparation, filing, prosecution, and maintenance of the BicycleTx Product Patents and Joint Patents, including by providing BicycleTx with a copy of material communications to and from any patent authority in the Territory regarding such Patents, and by providing BicycleTx drafts of any material filings to be made to such patent authorities in the Territory sufficiently in advance of submitting such filings so as to allow for a reasonable opportunity for BicycleTx to review and comment thereon. Ionis shall consider in good faith the requests and suggestions of BicycleTx with respect to such Ionis drafts and with respect to strategies for filing and prosecuting such Patents in the Territory. If Ionis decides not to prepare, file, prosecute, or maintain any BicycleTx Product Patent or Joint Patent in a country or other jurisdiction in the Territory, Ionis shall provide reasonable prior written notice to BicycleTx of such intention (which notice shall, in any event, be given no later than [***] prior to the next deadline for any action that may be taken with respect to such BicycleTx Product Patent or Joint Patent in such country or other jurisdiction), and BicycleTx shall thereupon have the option, in its sole discretion, to assume the control and direction of the preparation, filing, prosecution, and maintenance of such Patent at its sole cost and expense in such country or other jurisdiction. Upon BicycleTx's written acceptance of such option, BicycleTx shall assume the responsibility and control for the preparation, filing, prosecution, and maintenance of such BicycleTx Product Patent or Joint Patent, as applicable. In such event, Ionis shall reasonably cooperate with BicycleTx with respect to such Patent in such country or other jurisdiction as provided under Section 7.2.4. Notwithstanding the foregoing, following the termination of Oligo Exclusivity, BicycleTx shall assume sole responsibility for the prosecution and maintenance of BicycleTx Product Patents that solely Cover Licensed Products and Compounds directed to any Target that is not a Collaboration Target, and Ionis will reasonably cooperate with BicycleTx to transfer responsibility for such prosecution and maintenance activities to BicycleTx for any such BicycleTx Product Patents promptly following the loss of Oligo Exclusivity.

7.2.4 Cooperation. The Parties agree to cooperate fully in the preparation, filing, prosecution, and maintenance of the Product Patents and Joint Patents in the Territory under this Agreement. Cooperation shall include:

(a) without limiting any other rights and obligations of the Parties under this Agreement, cooperating with respect to the timing, scope, and filing of such Patents to preserve and enhance the patent protection for Compounds and Licensed Products, including the manufacture and use thereof;

(b) executing all papers and instruments, or requiring its employees or contractors to execute such papers and instruments, so as to (i) effectuate the ownership of intellectual property set forth in Section 7.1.2; (ii) enable the other Party to apply for and to prosecute Patent applications in the Territory; and (iii) obtain and maintain any Patent extensions, supplementary protection certificates, and the like with respect to the Product Patents and Joint Patents in the Territory, in each case ((i), (ii), and (iii)) to the extent provided for in this Agreement;

(c) consistent with this Agreement, assisting in any license registration processes with applicable governmental authorities that may be available in the Territory for the protection of a Party's interests in this Agreement; and

(d) promptly informing the other Party of any matters coming to such Party's attention that may materially affect the preparation, filing, prosecution, or maintenance of any such Patents in the Territory.

7.2.5 CREATE Act. It is the intention of the Parties that this Agreement is a "joint research agreement" as that phrase is defined in 35 USC § 102(c) (AIA) or 35 USC § 103(c) (pre-AIA). In the event that either Party to this Agreement intends to overcome a rejection of a claimed invention within the Joint Patents or Product Patents under this Agreement pursuant to the provisions of 35 USC § 102(c) or 35 USC § 103(c), such Party shall first obtain the prior written consent of the other Party. Following receipt of such written consent, such Party shall limit any amendment to the specification or statement to the patent office with respect to this Agreement to that which is strictly required by 35 USC § 102(c) or 35 USC § 103(c) and the rules and regulations promulgated thereunder and which is consistent with the terms and conditions of this Agreement. If the Parties agree that, in order to overcome a rejection of a claimed invention within the Joint Patents or Product Patents pursuant to the provisions of the CREATE Act, the filing of a terminal disclaimer is required or advisable, the Parties shall first agree on terms and conditions under which the patent application subject to such terminal disclaimer and the patent or application over which such application is disclaimed shall be jointly enforced, if and to the extent that the Parties have not previously agreed to such terms and conditions. If Ionis enters into an agreement with a Third Party with respect to the further Research, Development, or Commercialization of a Compound or Licensed Product, BicycleTx shall, upon Ionis' request, similarly enter into such agreement with such Third Party for the purposes of furthering the Parties' objectives under this Agreement, provided that such agreement is consistent with the rights of BicycleTx under this Section 7.2.5 and does not place any material obligation on BicycleTx.

7.2.6 Patent Term Extension and Supplementary Protection Certificate. Ionis shall have authority and sole discretion for making decisions regarding patent term extensions, including supplementary protection certificates and any other extensions that are now or become available in the future, wherever applicable, for Ionis Patents, Product Patents, and Joint Patents in any country or other jurisdiction and for applying for any extension or supplementary protection certificate with respect to such Patents in the Territory. BicycleTx shall provide prompt and reasonable assistance, as requested by Ionis, including by taking such action as patent holder as is required under any Applicable Law to obtain such patent extension or supplementary protection certificate. If Ionis desires that a patent term extension should be applied for a BicycleTx Patent other than a BicycleTx Product Patent, BicycleTx and Ionis shall discuss in good faith such patent term extension, provided that such decision shall be at BicycleTx's sole discretion. Ionis shall pay all expenses (including any expenses incurred by BicycleTx) with respect to obtaining any extension or supplementary protection certificate in the Territory requested by Ionis.

7.2.7 Patent Listings. Ionis will have the sole right to make all filings with Regulatory Authorities in the Territory with respect to Ionis Patents, Product Patents, and Joint Patents, including as required or allowed under Applicable Law, provided that with respect to Joint Patents and BicycleTx Product Patents, such right shall be solely with respect to Licensed Products. Ionis shall notify BicycleTx in writing of any BicycleTx Patents other than BicycleTx Product Patents that it intends to list with Regulatory Authorities related to the Licensed Products and, prior to filing any such listing, consult with and consider in good faith the requests and suggestions of BicycleTx regarding the same.

7.3 Patent Enforcement.

7.3.1 BicycleTx Patents other than BicycleTx Product Patents. Each Party shall promptly notify the other Party in writing of any alleged or threatened infringement of a BicycleTx Patent other than a BicycleTx Product Patent by a Third Party in the Territory of which such Party becomes aware based on the development or commercialization of, or an application to market a product containing, a Compound or a Licensed Product in the Territory. BicycleTx shall have the sole right, but not the obligation, to prosecute any such infringement involving any claims of BicycleTx Patents (other than BicycleTx Product Patents) for which it is responsible for prosecution and maintenance activities pursuant to Section 7.2.1, at its sole expense and BicycleTx shall retain control of prosecution of each such claim, suit, or proceeding. For clarity, Ionis shall have the first right, but not the obligation to prosecute any such infringement of BicycleTx Patents for which Ionis has assumed responsibility for prosecution and maintenance pursuant to Section 7.2.1.

7.3.2 Ionis Patents, Product Patents, and Joint Patents.

(a) Each Party shall promptly notify the other Party in writing of any alleged or threatened infringement of an Ionis Patent, a Product Patent, or a Joint Patent by a Third Party in the Territory of which such Party becomes aware (including alleged or threatened infringement based on the development or commercialization of, or an application to market a product containing, a Compound or Licensed Product in the Territory).

(b) Ionis shall have the sole right, but not the obligation, to prosecute any such infringement of Ionis Patents in the Territory at its sole expense, and Ionis shall retain control of the prosecution of such claim, suit, or proceeding.

(c) Ionis shall have the first right, but not the obligation, to prosecute any such infringement of BicycleTx Product Patents and Joint Patents, in each case for which it is responsible for prosecution and maintenance activities under Section 7.2.3, in each case in the Territory at its sole expense, and Ionis shall retain control of the prosecution of such claim, suit, or proceeding. If Ionis prosecutes any such infringement, BicycleTx shall have the right to join as a party to such claim, suit, or proceeding in the Territory and participate with its own counsel at its own expense; provided that Ionis shall retain control of the prosecution of such claim, suit, or proceeding. If Ionis does not take commercially reasonable steps to prosecute the alleged or threatened infringement in the Territory with respect to any such BicycleTx Product Patent or Joint Patent (i) within [***] following the first notice provided above with respect to such alleged infringement, or (ii) [***] before the time limit, if any, set forth in appropriate laws and regulations for filing of such actions, whichever comes first, then BicycleTx may prosecute the alleged or threatened infringement in the Territory at its own expense. For clarity, BicycleTx shall have the first right, but not the obligation to prosecute any such infringement of Joint Patents and BicycleTx Product Patents for which BicycleTx has assumed responsibility for prosecution and maintenance, including any such BicycleTx Product Patents following termination of Oligo Exclusivity.

7.3.3 Cooperation. The Parties agree to cooperate fully in any infringement action pursuant to this Section 7.3. To the extent necessary for a Party to bring such an action, the other Party shall, where necessary, furnish a power of attorney solely for such purpose or shall join in, or be named as a necessary party to, such action. Unless otherwise set forth herein, the Party entitled to bring any patent infringement litigation in accordance with this Section 7.3 shall have the right to settle such claim; provided that neither Party shall have the right to settle any patent infringement litigation under this Section 7.3 in a manner that materially diminishes or has a material adverse effect on the rights or interest of the other Party, or in a manner that imposes any costs or liability on, or involves any admission by, the other Party, without the express written consent of such other Party. The Party commencing the litigation shall provide the other Party with copies of all pleadings and other documents filed with the court and shall consider reasonable input from the other Party during the course of the proceedings.

7.3.4 Recovery. Any recovery realized as a result of such litigation described in Section 7.3.1 or Section 7.3.2 (whether by way of settlement or otherwise) shall be first allocated to reimburse the Parties for their costs and expenses in making such recovery (which amounts shall be allocated pro rata if insufficient to cover the totality of such expenses). Any remainder after [***].

7.4 Infringement Claims by Third Parties If the manufacture, sale, or use of a Licensed Product in the Territory pursuant to this Agreement results in, or may result in, any claim, suit, or proceeding by a Third Party alleging patent infringement by Ionis (or its Affiliates or Sublicensees), Ionis shall promptly notify BicycleTx thereof in writing. Ionis shall have the first right, but not the obligation, to defend and control the defense of any such claim, suit, or proceeding at its own expense, using counsel of its own choice. BicycleTx may participate in any such claim, suit, or proceeding with counsel of its choice at its own expense. Without limitation of the foregoing, if Ionis finds it necessary or desirable to join BicycleTx as a party to any such action, BicycleTx shall, at Ionis' expense, execute all papers and perform such acts as reasonably required. If Ionis elects (in a written communication submitted to BicycleTx within a reasonable amount of time after notice of the alleged patent infringement) not to defend or control the defense of, or otherwise fails to initiate and maintain the defense of, any such claim, suit, or proceeding, within such time periods so that BicycleTx is not prejudiced by any delays, BicycleTx may conduct and control the defense of any such claim, suit, or proceeding at its own expense. Each Party shall keep the other Party reasonably informed of all material developments in connection with any such claim, suit, or proceeding. Any recoveries by Ionis of any sanctions awarded to Ionis and against a party asserting a claim being defended under this Section 7.4 shall be applied first to reimburse each Party for its reasonable out-of-pocket costs of defending or participating in such claim, suit, or proceedings, on a pro rata basis. The balance of any such recoveries shall [***].

7.5 Invalidity or Unenforceability Defenses or Actions.

7.5.1 Notice. Each Party shall promptly notify the other Party in writing of any alleged or threatened assertion of invalidity or unenforceability of any of the BicycleTx Patents that Cover a Compound or Licensed Product, Ionis Patents, or Joint Patents by a Third Party, in each case in the Territory and of which such Party becomes aware.

7.5.2 BicycleTx Patents other than BicycleTx Product Patents. BicycleTx shall have the sole right, but not the obligation, to defend and control the defense of the validity and enforceability of the BicycleTx Patents other than the BicycleTx Product Patents at its own expense in the Territory.

7.5.3 Ionis Patents. Ionis shall have the sole right, but not the obligation, to defend and control the defense of the validity and enforceability of the Ionis Patents at its own expense in the Territory.

7.5.4 BicycleTx Product Patents and Joint Patents. Ionis shall have the first right, but not the obligation, to defend and control the defense of the validity and enforceability of the BicycleTx Product Patents and Joint Patents at its own expense in the Territory, in each case for which it is responsible for prosecution and maintenance activities under Section 7.2.3. BicycleTx may participate in any such claim, suit, or proceeding in the Territory related to the BicycleTx Product Patents and Joint Patents with counsel of its choice at its own expense; provided that Ionis shall retain control of the defense in such claim, suit, or proceeding. If Ionis elects not to defend or control the defense of the BicycleTx Product Patents or Joint Patents in a suit brought in the Territory, or otherwise fails to initiate and maintain the defense of any such claim, suit, or proceeding, then BicycleTx may conduct and control the defense of any such claim, suit, or proceeding, at its own expense; provided, that BicycleTx shall obtain the written consent of Ionis prior to settling or compromising such defense, such consent not to be unreasonably withheld, conditioned, or delayed. For clarity, BicycleTx shall have the first right, but not the obligation to defend and control the defense of the validity and enforceability of BicycleTx Product Patents and Joint Patents for which BicycleTx has assumed responsibility for prosecution and maintenance, including any such BicycleTx Product Patents following termination of Oligo Exclusivity.

7.5.5 Cooperation. Each Party shall assist and cooperate with the other Party as such other Party may reasonably request from time to time in connection with its activities set forth in this Section 7.5, including by being joined as a party plaintiff in such action or proceeding, providing access to relevant documents and other evidence, and making its employees available at reasonable business hours. In connection with any such defense or claim or counterclaim, the controlling Party shall consider in good faith any comments from the other Party, shall keep the other Party reasonably informed of any steps taken, and shall provide copies of all documents filed, in connection with such defense, claim, or counterclaim. In connection with the activities set forth in this Section 7.5, each Party shall consult with the other as to the strategy for the defense of the BicycleTx Patents, Ionis Patents, and Joint Patents.

7.6 Inventor's Remuneration Each Party shall be solely responsible for any remuneration that may be due such Party's inventors under any applicable inventor remuneration laws.

7.7 Common Interest All information exchanged between the Parties regarding the prosecution, maintenance, enforcement and defense of Patents under this ARTICLE 7 will be deemed to be Confidential Information of the disclosing Party. In addition, the Parties acknowledge and agree [***]. The Parties agree and acknowledge [***]. Notwithstanding anything to the contrary 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 7 is protected by attorney-client privilege or any other applicable legal privilege or immunity, such Party shall not be required to disclose such information and the Parties shall in good faith cooperate to agree upon a procedure (including entering into a specific common interest agreement or 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 8
CONFIDENTIALITY AND NON-DISCLOSURE

8.1 Confidentiality Obligations. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing by the Parties, during the Term and for [***] thereafter, the receiving Party shall keep confidential and shall not publish or otherwise disclose, and shall not use for any purpose other than as expressly provided for in this Agreement, any Confidential Information furnished or otherwise made known to it, directly or indirectly, by the other Party, and each Party shall keep confidential and shall not publish or otherwise disclose the terms of this Agreement except as permitted herein. Each Party may use the other Party's Confidential Information only to the extent required to accomplish the purposes of this Agreement, including exercising its rights and performing its obligations under this Agreement. Each Party will use at least the same standard of care as it uses to protect its own proprietary or confidential information (but no less than reasonable care) to ensure that its employees, agents, consultants, contractors, and other representatives do not disclose or make any unauthorized use of the other Party's Confidential Information. Each Party will promptly notify the other upon discovery of any loss or unauthorized use or disclosure of the other Party's Confidential Information.

8.2 Exceptions. The obligations of confidentiality and non-use set forth in Section 8.1 above shall not apply to any information that the receiving Party can demonstrate by written evidence:

8.2.1 is already known to the receiving Party, other than under an obligation of confidentiality, at the time of disclosure by the disclosing Party;

8.2.2 is now, or hereafter becomes, generally available to the public or otherwise part of the public domain through no fault of the receiving Party;

8.2.3 is disclosed to the receiving Party by a Third Party who had no obligation to the disclosing Party not to disclose such information to others; or

8.2.4 was independently discovered or developed by the receiving Party without the use of Confidential Information belonging to the disclosing Party.

Specific aspects or details of Confidential Information shall not be deemed to be within the public domain or in the possession of the receiving Party merely because the Confidential Information is embraced by more general information in the public domain or in the possession of the receiving Party. Further, any combination of Confidential Information shall not be considered in the public domain or in the possession of the receiving Party merely because individual elements of such Confidential Information are in the public domain or in the possession of the receiving Party unless the combination and its principles are in the public domain or in the possession of the receiving Party.

8.3 Permitted Disclosures.

8.3.1 Pursuant to Applicable Law. Each Party may disclose Confidential Information to the extent that such disclosure is, in the reasonable opinion of the receiving Party's legal counsel, required to be disclosed pursuant to law, regulation, or a valid order of a court of competent jurisdiction or other supra-national, federal, national, regional, state, provincial, or local governmental body of competent jurisdiction, provided that the receiving Party shall first have given prompt written notice (and to the extent possible, at least [***] notice) to the disclosing Party and given the disclosing Party a reasonable opportunity to take whatever action it deems necessary to protect its Confidential Information. If no protective order or other remedy is obtained, or the disclosing Party waives compliance with the terms of this Agreement, the receiving Party shall furnish only that portion of Confidential Information which the receiving Party is advised by counsel is legally required to be disclosed; for clarity, disclosures required in the reasonable opinion of the receiving Party's legal counsel to the U.S. Securities and Exchange Commission (or equivalent foreign agency) shall be subject to the following Section 8.3.2.

8.3.2 Securities Exchange Filings. The Parties acknowledge that either or both Parties (or its Affiliates) may be obligated to make one or more filings (including to file a copy of this Agreement or Stock Purchase Agreement) with the U.S. Securities and Exchange Commission (or equivalent foreign agency) or a governmental authority. Each Party will be entitled to make such a required filing, provided that if such filing includes a copy of this Agreement it will (a) submit in connection with such filing a copy of this Agreement in a form mutually agreed by the Parties in advance or, if, despite the reasonable efforts of the filing Party a form mutually agreed by the Parties cannot be agreed in advance, redacted to the extent permitted by Applicable Law, based on advice of filing Party's counsel (the "**Redacted Agreement**"), (b) request, and use reasonable efforts consistent with Applicable Laws to obtain, confidential treatment of all terms redacted in the Redacted Agreement, for a period of at least [***], (c) unless otherwise agreed in writing by the other Party, request an appropriate extension of the term of the confidential treatment period if legally justifiable. For clarity, following a request from a governmental authority to change the redactions requested by a Party in the Redacted Agreement, a Party will not be in breach of this Section 8.3.2 for unredacting those redactions rejected by the applicable governmental authority, provided that such Party shall provide the other Party with a notice of the required change(s) and a copy of the revised redactions. Each Party will be responsible for its own legal and other external costs in connection with any such filing, registration, or notification.

8.3.3 Additional Permitted Disclosures. In addition to disclosures pursuant to Sections 8.3.1 and 8.3.2 and as otherwise expressly permitted by this Agreement, each Party may disclose Confidential Information belonging to the other Party if and to the extent such disclosure is reasonably necessary in the following instances:

(a) under appropriate conditions of confidentiality and on a need-to-know basis to its legal and financial advisors;

(b) under appropriate conditions of confidentiality in connection with an actual or potential (i) permitted license or sublicense of its rights hereunder, (ii) debt, lease, or equity financing of such Party, (iii) merger, acquisition, consolidation, share exchange, or other similar transaction involving such Party and a Third Party, and (iv) co-funding or financing arrangement, provided that in each case ((i) to (iv)) the receiving Party takes reasonable and lawful actions to minimize the degree of such disclosure;

(c) under appropriate conditions of confidentiality to any Third Party that is or may be engaged to perform services in connection with the Development, Manufacturing, or Commercialization of the Licensed Products as necessary to enable such Third Party to perform such services;

(d) to any government agency or authority in connection with seeking government funding, support, or grants;

(e) filing, prosecuting, and maintaining Patents, and prosecuting and defending litigation, in each case as permitted by this Agreement;

(f) obtaining and maintaining Regulatory Approvals for, and conducting preclinical studies or Clinical Trials of, Licensed Products that such Party has a license or right to Develop or Commercialize under this Agreement in a given country or jurisdiction; and

(g) in the case of Confidential Information pertaining to TfR1 Bicycles, BicycleTx may disclose such information to [***], and *provided* that BicycleTx does not [***].

8.4 Use of Name. Except as expressly provided herein, neither Party shall mention or otherwise use the name, logo, or trademark of the other Party or any of its Affiliates (or any abbreviation or adaptation thereof) in any publication, press release, marketing and promotional material, or other form of publicity without the prior written approval of such other Party in each instance. The restrictions imposed by this Section 8.4 shall not prohibit either Party from making any disclosure identifying the other Party that, in the opinion of the disclosing Party's counsel, is required by Applicable Law; provided that such Party shall submit the proposed disclosure identifying the other Party in writing to the other Party as far in advance as reasonably practicable (and in no event less than five Business Days prior to the anticipated date of disclosure) so as to provide a reasonable opportunity to comment thereon.

8.5 Press Releases. The Parties agree to issue separate, mutually approved press releases at or shortly after the Effective Date within the time-period as required by relevant securities laws. It is understood that each Party may desire or be required to issue subsequent press releases relating to this Agreement or activities hereunder. The Parties agree to consult with each other reasonably and in good faith with respect to the text and timing of such press releases prior to the issuance thereof. Notwithstanding the foregoing, neither Party may unreasonably withhold, condition, or delay consent to such releases by more than five Business Days, and either Party may issue such press releases or make such disclosures to the U.S. Securities and Exchange Commission (or equivalent foreign agency) as it determines, based on advice of counsel, is reasonably necessary to comply with Applicable Laws or for appropriate market disclosure. Each Party shall provide the other Party with advance notice of legally required disclosures to the extent practicable, and to the extent possible, at least [***] prior to such disclosure. Following the initial joint press release announcing this Agreement, either Party shall be free to disclose, without the other Party's prior written consent, the existence of this Agreement, the identity of the other Party, and those terms of the Agreement which have already been publicly disclosed in accordance with this Section 8.5.

8.6 Publications. During the Term, the disclosure by either Party relating to any Compound or Licensed Product in any publication or presentation shall be in accordance with the procedure set forth in this Section 8.6. A Party ("**Publishing Party**") shall provide the other Party with a copy of any proposed publication or presentation at least [***] prior to submission for publication so as to provide such other Party with an opportunity to recommend any changes to the Publishing Party that it reasonably believes are necessary to continue to maintain such Party's Confidential Information in accordance with the requirements of this Agreement. The incorporation of such recommended changes shall not be unreasonably refused; and if such other Party notifies ("**Publishing Notice**") the Publishing Party in writing, within [***] after receipt of the copy of the proposed publication or presentation, that such publication or presentation in its reasonable judgment (a) contains an Invention, solely or jointly conceived or reduced to practice by the other Party, for which the other Party reasonably desires to obtain patent protection or (b) could be expected to have a material adverse effect on the commercial value of any Confidential Information disclosed by the other Party to the Publishing Party, the Publishing Party shall prevent such publication or delay such publication for a mutually agreed period of time. In the case of Inventions, a delay shall be for a period reasonably sufficient to permit the timely preparation and filing of a patent application(s) on such Invention, and in no event less than [***] from the date of the Publishing Notice.

8.7 Destruction or Return of Confidential Information. Upon the effective date of the termination of this Agreement for any reason, each Party shall, as soon as reasonably practicable, with respect to Confidential Information to which such Party does not retain rights under the surviving provisions of this Agreement, either return to the disclosing Party or destroy (at the receiving Party's election) all copies of such Confidential Information in the possession of the receiving Party, and confirm such destruction or complete return in writing to the disclosing Party, provided that the receiving Party shall be permitted to retain one copy of such Confidential Information for the sole purpose of performing any continuing obligations hereunder, as required by Applicable Law, or for archival purposes. Notwithstanding the foregoing, the receiving Party also shall be permitted to retain such additional copies of or any computer records or files containing such Confidential Information that have been created solely by such Party's automatic archiving and back-up procedures, to the extent created and retained in a manner consistent with such Party's standard archiving and back-up procedures, but not for any other use or purpose. If the termination this Agreement is with respect to one or more Terminated Targets but not in its entirety, the obligations under this Section 8.7 shall apply solely to the extent the applicable Confidential Information of the disclosing Party relates to such Terminated Targets and Terminated Assets, as applicable, and to the extent that such Confidential Information cannot be separated from information that relates to Targets and Licensed Products and Compounds other than the Terminated Targets and Terminated Assets, the receiving Party shall have no rights to use or disclose such Confidential Information in connection with Terminated Assets or Terminated Targets following the effective date of termination.

ARTICLE 9
REPRESENTATIONS AND WARRANTIES

9.1 Mutual Representations and Warranties. BicycleTx and Ionis each represents and warrants to the other, as of the Effective Date, as follows:

9.1.1 Organization. It is a corporation duly incorporated, validly existing, and in good standing under the laws of the jurisdiction of its incorporation, and has all requisite corporate power and authority, to execute, deliver, and perform this Agreement.

9.1.2 Authorization. The execution and delivery of this Agreement and the performance by it of the transactions contemplated hereby have been duly authorized by all necessary corporate action and do not violate (a) such Party's charter documents, bylaws, or other organizational documents, (b) in any material respect, any agreement, instrument, or contractual obligation to which such Party is bound, (c) any requirement of any Applicable Law, or (d) any order, writ, judgment, injunction, decree, determination, or award of any court or governmental agency presently in effect applicable to such Party.

9.1.3 Binding Agreement. This Agreement is a legal, valid, and binding obligation of such Party enforceable against it in accordance with its terms and conditions, subject to the effects of bankruptcy, insolvency, or other laws of general application affecting the enforcement of creditor rights, judicial principles affecting the availability of specific performance, and general principles of equity (whether enforceability is considered a proceeding at law or equity).

9.1.4 No Inconsistent Obligation. It is not under any obligation, contractual or otherwise, to any Person that conflicts with or is inconsistent in any material respect with the terms of this Agreement or that would impede the diligent and complete fulfillment of its obligations hereunder.

9.2 Additional Representations, Warranties, and Covenants of Bicycle. BicycleTx further represents, warrants, and covenants to Ionis, as of the Effective Date, as follows:

9.2.1 All BicycleTx Patents that Cover a TfR1 Bicycle existing as of the Effective Date are listed on Schedule 9.2.1 (the "**Existing Patents**").

9.2.2 There are no judgments, or settlements against, or amounts with respect thereto, owed by BicycleTx or any of its Affiliates relating to the Existing Patents. No claim or litigation has been brought or threatened in writing or any other form by any Person alleging, and BicycleTx has no knowledge of any claim, whether or not asserted, that the Existing Patents are invalid or unenforceable.

9.2.3 To BicycleTx's knowledge, no Person is infringing or threatening to infringe or misappropriating or threatening to misappropriate the Existing Patents.

9.2.4 To BicycleTx's knowledge, [***].

9.2.5 The [***].

9.2.6 BicycleTx is [***].

9.2.7 [***].

9.2.8 BicycleTx is the sole and exclusive owner of the entire right, title, and interest in the Existing Patents, and BicycleTx is entitled to grant the license granted to Ionis herein.

9.2.9 [***].

9.2.10 With respect to the BicycleTx Patents, all applicable official fees, maintenance fees and annuities for the BicycleTx Patents have been paid as of the Effective Date.

9.2.11 All employees and contractors of BicycleTx performing activities under the Option Agreement or this Agreement on behalf of BicycleTx (including for any Affiliate) will be obligated (or were obligated as the case may be) to assign all rights, title and interests in and to any inventions developed by them, whether or not patentable, to BicycleTx or such Affiliate, respectively, as the sole owner thereof, prior to performing any such activities, or otherwise grant to BicycleTx or such Affiliate sufficient rights to such inventions to the extent necessary to effect the license and ownership provisions of the Option Agreement or this Agreement.

9.2.12 During the Term, BicycleTx covenants that it will not enter into or amend any agreement, whether written or oral, that would conflict with or otherwise diminish the rights granted to Ionis hereunder.

9.2.13 Neither BicycleTx nor any of its employees is debarred or disqualified under the U.S. Federal Food, Drug and Cosmetic Act, as may be amended, or comparable laws in any country or jurisdiction other than the U.S., and it does not, and will not during the Research Term, employ or use the services of any person who is debarred or disqualified in connection with activities relating to the TfR1 Bicycles. If BicycleTx becomes aware of the debarment or disqualification or threatened debarment or disqualification of any Person providing services to BicycleTx, including BicycleTx itself or its or its Affiliate's employees or agents, that directly or indirectly relate to activities contemplated by this Agreement, BicycleTx shall immediately notify Ionis in writing and BicycleTx shall cease employing, contracting with, or retaining any such Person to perform any such services.

9.3 Additional Representations, Warranties and Covenants of Ionis. Ionis represents, warrants, and covenants to BicycleTx, as of the Effective Date, as follows:

9.3.1 Ionis is entitled to grant BicycleTx the license as specified in Section 2.2 with regard to Ionis Intellectual Property Controlled by Ionis or any of its Affiliates on the Effective Date.

9.3.2 Neither Ionis nor any of its employees is debarred or disqualified under the U.S. Federal Food, Drug and Cosmetic Act, as may be amended, or comparable laws in any country or jurisdiction other than the U.S., and it does not, and will not during the Term, employ or use the services of any person who is debarred or disqualified in connection with activities relating to the Compounds and Licensed Products. If Ionis becomes aware of the debarment or disqualification or threatened debarment or disqualification of any Person providing services to Ionis, including Ionis itself or its or its Affiliate's employees or agents, that directly or indirectly relate to activities contemplated by this Agreement, Ionis shall immediately notify BicycleTx in writing and Ionis shall cease employing, contracting with, or retaining any such Person to perform any such services.

9.4 DISCLAIMER OF WARRANTIES. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH HEREIN, NEITHER PARTY MAKES ANY REPRESENTATIONS OR GRANTS ANY WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND EACH PARTY SPECIFICALLY DISCLAIMS ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 10
INDEMNIFICATION; INSURANCE

10.1 Indemnification of Bicycle. Ionis shall indemnify, defend, and hold harmless BicycleTx, its Affiliates, and its and their respective directors, officers, employees, and agents (the "**BicycleTx Indemnitees**") from and against any and all losses, damages, liabilities, penalties, settlements, costs, taxes (including penalties and interest) and expenses (including reasonable attorneys' fees and other expenses of litigation) (collectively, "Losses") in connection with any and all suits, investigations, claims, or demands of Third Parties (collectively, "Third Party Claims") incurred by or rendered against the BicycleTx Indemnitees to the extent arising from or occurring as a result of: (a) the breach by Ionis or its Affiliates of this Agreement; (b) the negligence, recklessness, or willful misconduct on the part of Ionis or its Affiliates or their respective directors, officers, employees, and agents in performing any of its or their obligations under this Agreement; or (c) the Research or Exploitation of any Compounds or Licensed Products by Ionis or its Affiliates or Sublicensees; except in each case ((a) – (c)) to the extent that BicycleTx has an obligation to indemnify Ionis pursuant to Section 10.2.

10.2 Indemnification of Ionis. BicycleTx shall indemnify, defend, and hold harmless Ionis, its Affiliates and its and their respective directors, officers, employees, and agents (the "**Ionis Indemnitees**") from and against any and all Losses in connection with any and all Third Party Claims incurred by or rendered against the Ionis Indemnitees to the extent arising from or occurring as a result of: (a) the breach by BicycleTx or its Affiliates of this Agreement; or (b) the negligence, recklessness, or willful misconduct on the part of BicycleTx or its Affiliates or its or their respective directors, officers, employees, and agents in performing its obligations under this Agreement; except in each case ((a) – (b)) to the extent that Ionis has an obligation to indemnify BicycleTx pursuant to Section 10.1.

10.3 Notice of Claim. All indemnification claims in respect of a Party, its Affiliates, or its or their respective directors, officers, employees and agents shall be made solely by such Party to this Agreement (the "**Indemnified Party**"). The Indemnified Party shall give the indemnifying Party (the "**Indemnifying Party**") prompt written notice (an "**Indemnification Claim Notice**") of any Losses or discovery of fact upon which such Indemnified Party intends to base a request for indemnification under this ARTICLE 10, but in no event shall the Indemnifying Party be liable for any Losses that result from any delay by the Indemnified Party in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party shall furnish promptly to the Indemnified Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

10.4 Control of Defense. The Indemnifying Party shall have the right, but not the obligation, to conduct and control, through counsel of its choosing, any action for which indemnification is sought, and if the Indemnifying Party elects to assume the defense thereof, the Indemnifying Party shall not be liable to the Indemnified Party for any legal expenses of other legal counsel or any other expenses subsequently incurred by such Indemnified Party in connection with the defense thereof. The Indemnifying Party may settle any action, claim, or suit for which the Indemnified Party is seeking indemnification; provided that the Indemnifying Party shall first give the Indemnified Party advance written notice of any proposed compromise or settlement and such Indemnified Party provides prior written approval, such approval not to be unreasonably conditioned, withheld or delayed. The Parties and their employees shall cooperate fully with each other and their legal representatives in the investigation, defense, prosecution, negotiation, or settlement of any such claim or suit. Each Party's indemnification obligations under this ARTICLE 10 shall not apply to amounts paid by an Indemnified Party in settlement of any action with respect to a Third Party claim, if such settlement is effected without the prior written consent of the Indemnifying Party, which consent shall not be unreasonably conditioned, withheld or delayed. In no event shall the Indemnifying Party settle or abate any Third Party Claim in a manner that would diminish the rights or interests of the Indemnified Party, admit any liability, fault, or guilt by the Indemnified Party, or obligate the Indemnified Party to make any payment, take any action, or refrain from taking any action, without the prior written approval of the Indemnified Party.

10.5 Limitation of Liability. EXCEPT FOR DAMAGES PAYABLE FOR A PARTY'S BREACH OF ITS OBLIGATIONS UNDER ARTICLE 8 (BASED ON REASONABLE WRITTEN EVIDENCE) OR REQUIRED TO BE PAID PURSUANT TO A PARTY'S INDEMNIFICATION OBLIGATIONS UNDER THIS ARTICLE 10, NEITHER PARTY NOR ANY OF ITS AFFILIATES SHALL BE LIABLE FOR INDIRECT, INCIDENTAL, SPECIAL, EXEMPLARY, PUNITIVE, OR CONSEQUENTIAL DAMAGES, INCLUDING LOSS OF PROFITS OR BUSINESS INTERRUPTION, HOWEVER CAUSED AND ON ANY THEORY OF LIABILITY, WHETHER IN CONTRACT, TORT, NEGLIGENCE, BREACH OF STATUTORY DUTY OR OTHERWISE IN CONNECTION WITH THIS AGREEMENT OR THE EXERCISE OF ANY LICENSE GRANTED HERUNDER, EVEN IF ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

10.6 Insurance. Each Party shall maintain, at its own expense, commercial general liability insurance and other appropriate insurance in an amount consistent with sound business practice and reasonable in light of its obligations under this Agreement. Each Party shall maintain such insurance for the period commencing promptly after the Effective Date until [***] the Term. Each Party shall provide a certificate of insurance evidencing such coverage to the other Party upon request. It is understood that such insurance shall not be construed to create any limit of either Party's obligations or liabilities with respect to its indemnification obligations under this Agreement. Without limiting the generality of the foregoing, Ionis shall maintain, at a minimum, [***].

ARTICLE 11
TERM AND TERMINATION

11.1 Term. This Agreement shall commence on the Effective Date and, unless earlier terminated in accordance herewith, shall continue in force and effect 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 (such period, the "**Term**"). Upon the expiration of the Term for a particular Licensed Product in a particular country, the license grant to Ionis in Section 2.1 shall become non-exclusive, fully-paid, royalty-free, and irrevocable with respect to such Licensed Product in such country.

11.2 Termination for Convenience. Ionis may terminate this Agreement in its entirety or on a Target-by-Target basis (i.e. with respect to all Compounds and Licensed Products directed to such Target), for any or no reason, upon:

11.2.1 [***] prior written notice to BicycleTx if termination occurs [***]; and

11.2.2 [***] prior written notice to BicycleTx if termination occurs [***].

For clarity, with regard to termination of the Agreement in its entirety pursuant to this Section 11.2, the required notice period shall be that period that is applicable to the Licensed Product that is furthest advanced at the time of such termination.

11.3 Termination for Uncured Material Breach.

11.3.1 Material Breach. If either Party (the "**Non-Breaching Party**") believes that the other Party (the "**Breaching Party**") has materially breached one or more of its material obligations under this Agreement (other than for failure to achieve a diligence milestone under Section 4.5.2 the remedy for which is set forth in Section 4.5.4), then the Non-Breaching Party may deliver notice of such material breach to the Breaching Party (a "**Breach Notice**"). If (a) the Breaching Party does not dispute that it has committed a material breach of one or more of its material obligations under this Agreement, and (b) either (i) the Breaching Party fails to cure such breach within [***] ([***] with respect to any payment breach) after receipt of the Breach Notice ("**Breach Cure Period**"), or (ii) a cure cannot be fully achieved within such Breach Cure Period and the Breaching Party has failed to commence to cure or has failed to use diligent efforts to achieve a full cure within the Breach Cure Period, then the Non-Breaching Party may terminate this Agreement in whole or in part upon written notice to the Breaching Party, effective upon receipt by the Breaching Party, provided that if the Breaching Party is Ionis and such material breach relates solely to a Licensed Product and/or its corresponding Target (but not to all Licensed Products or Targets), then BicycleTx will only have the right to terminate the License Agreement solely with respect to such Licensed Product (and the corresponding Target) to which such material breach relates. If the Breaching Party disputes in good faith that it has materially breached one or more of its material obligations under this Agreement or that it has failed to timely or diligently cure such material breach, the Dispute shall be resolved pursuant to Section 12.2 and the Breach Cure Period shall be tolled until such dispute is so resolved. Upon a determination of material breach or failure to cure, the Breaching Party may have the remainder of the Breach Cure Period to cure such material breach. If such material breach is not cured within the Breach Cure Period, then absent withdrawal of the Non-Breaching Party's request for termination, this Agreement shall terminate, effective as of the expiration of the Breach Cure Period.

11.3.2 Adverse Ruling. Furthermore, if as a result of the application Section 12.2, the Breaching Party is determined to be in material breach of one or more of its material obligations under this Agreement (other than for failure to achieve a diligence milestone under Section 4.5.2 the remedy for which is set forth in Section 4.5.4), such that the Non-Breaching Party has the right to terminate this Agreement in whole or with respect to a particular Licensed Product and/or its corresponding Target (an "**Adverse Ruling**") and the Breaching Party fails to complete the actions specified in such Adverse Ruling, or to cure such material breach within [***] ([***] with respect to any payment breach) after such Adverse Ruling, or such other period (which may be shorter) as the arbitrators may provide in such Adverse Ruling, then the Non-Breaching Party may terminate this Agreement in whole or in part upon written notice to the Breaching Party, provided that if the Breaching Party is Ionis and such Adverse Ruling relates solely to a Licensed Product and/or its corresponding Target (but not to all Licensed Products or Targets), then BicycleTx will only have the right to terminate the License Agreement solely with respect to the Licensed Product (and the corresponding Target) to which such Adverse Ruling relates.

11.4 Termination for Insolvency. If either Party (a) files for protection under bankruptcy or insolvency laws, (b) makes an assignment for the benefit of creditors, (c) appoints or suffers appointment of a receiver or trustee over substantially all of its property that is not discharged within [***] after such filing, (d) is a party to any dissolution or liquidation, (e) files a petition under any bankruptcy or insolvency act or has any such petition filed against it that is not discharged within [***] of the filing thereof, or (f) admits in writing its inability generally to meet its obligations as they fall due in the general course, then the other Party may terminate this Agreement in its entirety effective immediately upon written notice to such Party.

11.5 Rights in Bankruptcy.

11.5.1 Applicability of 11 U.S.C. § 365(n). All rights and licenses (collectively, the "**Intellectual Property**") granted under or pursuant to this Agreement, including all rights and licenses to use improvements or enhancements developed during the Term, are intended to be, and shall otherwise be deemed to be, for purposes of Section 365(n) of the United States Bankruptcy Code (the "**Bankruptcy Code**") or any analogous provisions in any other country or jurisdiction, licenses of rights to "intellectual property" as defined under Section 101(35A) of the Bankruptcy Code. The Parties agree that the licensee of such Intellectual Property under this Agreement shall retain and may fully exercise all of its rights and elections under the Bankruptcy Code, including Section 365(n) of the Bankruptcy Code, or any analogous provisions in any other country or jurisdiction. All of the rights granted to either Party under this Agreement shall be deemed to exist immediately before the occurrence of any bankruptcy case in which the other Party is the debtor.

11.5.2 Rights of non-Debtor Party in Bankruptcy. If a bankruptcy proceeding is commenced by or against either Party under the Bankruptcy Code or any analogous provisions in any other country or jurisdiction, the non-debtor Party shall be entitled to a complete duplicate of (or complete access to, as appropriate) any Intellectual Property and all embodiments of such Intellectual Property, which, if not already in the non-debtor Party's possession, shall be delivered to the non-debtor Party within five Business Days of such request; provided, that the debtor Party is excused from its obligation to deliver the Intellectual Property to the extent the debtor Party continues to perform all of its obligations under this Agreement and the Agreement has not been rejected pursuant to the Bankruptcy Code or any analogous provision in any other country or jurisdiction.

11.6 Effects of Termination. Upon any termination of this Agreement in its entirety by either Party, the following terms will apply. Upon any termination of this Agreement with respect to a particular Target (such terminated Target, a "**Terminated Target**"), the following terms will apply solely with respect to such Terminated Target and corresponding Terminated Assets. For clarity, during the pendency of any dispute regarding material breach and/or any Breach Cure Period, all of the terms and conditions of this Agreement shall remain in effect and the Parties shall continue to perform all of their respective obligations hereunder.

11.6.1 Licenses. All licenses granted by either Party will automatically terminate.

11.6.2 Sublicenses. Any Ionis Sublicensee will, from the effective date of such termination, automatically become a direct licensee of BicycleTx, provided that such Sublicensee is not then in default of its sublicense agreement and such sublicense was granted in accordance with Section 2.4, and provided further that: (a) such direct license shall not obligate (i) such Sublicensee to perform contractual obligations greater than those set forth in the applicable sublicense or (ii) BicycleTx to perform contractual obligations greater than those set forth herein, (b) the scope of such direct license shall be consistent with the scope of the license sublicensed to such Sublicensee, and (c) the amounts payable to BicycleTx by such Sublicensee under such direct license shall be equivalent to the amounts BicycleTx would have received from Ionis under this Agreement as a result of such Sublicensee's activities had this Agreement remained in effect and such Sublicensee performed such activity under the sublicense agreement with Ionis.

11.6.3 Confidential Information. Each Party shall return or cause to be returned to the other Party or destroy (and certify such destruction to such other Party) all Confidential Information and all substances or compositions of the other Party or its Affiliates delivered or provided by or on behalf of such other Party in accordance with Section 8.7.

11.7 Accrued Rights; Surviving Obligations. Termination or expiration of this Agreement (either in its entirety or with respect to one or more Terminated Targets and Terminated Asset) for any reason shall be without prejudice to any rights that shall have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration shall not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. Without limiting the foregoing, the following Articles and Sections of this Agreement shall survive the termination or expiration of this Agreement for any reason: Articles 1 (to the extent applicable to other surviving Sections or Articles), 8 (excluding Section 8.6), 10, and 12 (excluding Section 12.6), and Section 4.12, Sections 6.4.4, 6.5.2, and 6.7 (in each case solely with respect to amounts accrued or owing as of the effective date of termination), 6.8, 6.9, 6.10, 6.11, 7.1, 7.7, 9.4, 11.1(last sentence only), 11.5, 11.6, 11.7]

ARTICLE 12
MISCELLANEOUS

12.1 Governing Law and Service.

12.1.1 Governing Law. This Agreement and the performance, enforcement, breach, and termination hereof shall be interpreted, governed by, and construed in accordance with the laws of the State of New York, United States excluding any conflicts or choice of law rule or principle that might otherwise refer construction or interpretation of this Agreement to the substantive law of another jurisdiction; provided, that all questions concerning (a) inventorship of Patents under this Agreement shall be determined in accordance with Section 7.1.1 and (b) the construction or effect of Patents shall be determined in accordance with the laws of the country or other jurisdiction in which the particular Patent has been filed or granted, as the case may be. The Parties agree to exclude the application to this Agreement of the United Nations Convention on Contracts for the International Sale of Goods.

12.1.2 Service. Each Party further agrees that service of any process, summons, notice, or document by registered mail to its address set forth in Section 12.10 shall be effective service of process for any action, suit, or proceeding brought against it by the other Party under this Agreement in any such court.

12.2 Dispute Resolution. Except as provided in Section 3.3 and Section 12.2.2, any dispute arising out of or relating to this Agreement that has not been resolved at the JSC or otherwise under the terms of this Agreement, including the determination of the scope or applicability of this Section 12.2 and the agreement to arbitrate, or any document or instrument delivered in connection herewith (a "**Dispute**"), shall be resolved pursuant to this Section 12.2.

12.2.1 General. Any Dispute shall first be referred to the Alliance Managers who will seek to resolve the issue within [***]. If no resolution is obtained, the issue will be elevated to the Senior Officers of the Parties, who shall confer in good faith on the resolution of the issue. Without limiting Section 12.5, any final decision mutually agreed to by the Senior Officers shall be conclusive and binding on the Parties. If the Senior Officers are not able to agree on the resolution of any such issue within [***] (or such other period of time as mutually agreed by the Senior Officers) after such issue was first referred to them, then, except as otherwise set forth in Section 12.2.2, the Dispute shall be finally settled by arbitration as set forth in Section 12.2.3. Any dispute concerning the commencement of the arbitration shall be finally settled by the arbitrators.

12.2.2 Intellectual Property Disputes. If a Dispute arises with respect to the validity, scope, enforceability, inventorship, or ownership of any Patent, trademark, or other intellectual property right, and such Dispute cannot be resolved in accordance with Section 12.2.1, then, unless otherwise agreed by the Parties in writing, such Dispute shall not be submitted to an arbitration proceeding in accordance with Section 12.2.3 and instead either Party may initiate litigation in a court of competent jurisdiction, notwithstanding Section 12.1, in any country or other jurisdiction in which such rights apply; provided, however, that the Parties expressly waive any right to a jury trial in connection with disputes under this Section 12.2.2. In case of a Dispute between the Parties with respect to inventorship, the Parties shall jointly select an independent Third Party patent attorney registered before the United States Patent and Trademark Office who has appropriate professional credentials in the relevant subject matter and jurisdiction and submit such Dispute to the mutually-selected independent Third Party patent attorney for resolution by expert determination under United States patent law. The decision of such patent attorney with respect to inventorship shall be final, and the Parties agree to be bound by the decision and share equally the expenses of such patent attorney. If within [***] after the Senior Officers have failed to settle a Dispute regarding inventorship the Parties have not been able to mutually agree on the selection of an independent Third Party patent attorney for such expert determination, each Party shall appoint a patent counsel within [***] and both Party-appointed patent counsels shall, within [***] following the last appointment of a patent counsel by a Party, nominate the patent counsel who will conduct the expert determination under this Section 12.2.2.

12.2.3 Arbitration. Any arbitration shall take place in accordance with Schedule 12.2.3.

12.2.4 Adverse Ruling. Any determination pursuant to this Section 12.2 that a Party is in material breach of its material obligations hereunder shall specify a (nonexclusive) set of actions to be taken to cure such material breach, if feasible.

12.2.5 Interim Relief. Notwithstanding anything herein to the contrary in this Section 12.2, in the event that a Party reasonably requires relief on a more expedited basis than would be possible pursuant to the procedure set forth in this ARTICLE 12, such Party may seek interim or provisional relief, including a temporary restraining order, preliminary injunction, or other interim equitable relief concerning a Dispute, if necessary to protect the interests of such Party. This Section 12.2.5 shall be specifically enforceable.

12.2.6 Pending Dispute. During a pending Dispute, where this Agreement has not yet been terminated, each Party shall continue to perform in good faith its obligations under this Agreement.

12.3 Entire Agreement; Amendments. This Agreement and the Stock Purchase Agreement, including any schedules, constitute the entire, final, and complete agreement and understanding between the Parties with respect to its subject matter and replaces and supersedes all prior discussions and agreements between them with respect to the subject matter hereof. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth in this Agreement. No modification of any terms or conditions hereof shall be effective unless made in writing and signed by a duly authorized representative of each Party.

12.4 Severability. If any provision of this Agreement is, becomes, or is deemed invalid or unenforceable by any court or other competent authority having jurisdiction, the remainder of this Agreement shall remain unimpaired and the Parties shall promptly negotiate in good faith to amend such invalid or unenforceable provision to conform to applicable laws so as to be valid and enforceable and best accomplish the original intent of the Parties.

12.5 Waiver and Non-Exclusion of Remedies. Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver shall be effective unless it is in writing and signed by the Party waiving such term or condition. The waiver by either Party hereto of any right hereunder or of a breach by the other Party shall not be deemed a waiver of any other right hereunder or of any other breach by such other Party whether of a similar nature or otherwise. The rights and remedies provided herein are cumulative and do not exclude any other right or remedy provided by Applicable Law or otherwise available except as expressly set forth herein.

12.6 Force Majeure. Each Party shall be excused from liability for the failure or delay in performance of any obligation under this Agreement (other than a payment obligation) by reason of any event beyond such Party's reasonable control, including acts of God, fire, flood, explosion, earthquake, epidemic or pandemic (including quarantine, lock-down, movement restriction or similar orders imposed by any governmental authority as of or after the Effective Date in connection therewith), or other natural forces, war, civil unrest, acts of terrorism, accident, destruction, or other casualty, any lack or failure of transportation facilities, any lack or failure of supply of raw materials or supplies, or any other event similar to those enumerated above. Such excuse from liability shall be effective to the extent and duration of the event(s) causing the failure or delay in performance and provided that the Party has not caused such event(s) to occur. Notice of a Party's failure or delay in performance due to force majeure must be given to the other Party as soon as reasonably practicable after its occurrence.

12.7 Export Control. This Agreement is made subject to any restrictions concerning the export of products or technical information from the United States or other countries that may be imposed on the Parties from time to time. Each Party agrees that it will not export, directly or indirectly, any technical information acquired from the other Party under this Agreement or any products using such technical information to a location or in a manner that at the time of export requires an export license or other governmental approval, without first obtaining the written consent to do so from the appropriate agency or other governmental entity in accordance with Applicable Law.

12.8 Relationship of the Parties. The relationship of the Parties is that of independent contractors, and nothing in this Agreement shall be construed to create a partnership, joint venture, franchise, employment, or agency relationship between the Parties. Neither Party shall be considered the agent of the other Party for any purpose whatsoever and neither Party has any authority to enter into any contract or assume any obligation for the other Party or to make any warranty or representation on behalf of the other Party. All persons employed by a Party shall be employees of such Party and not of the other Party and all costs and obligations incurred by reason of any such employment shall be for the account and expense of such Party. The Parties (and any successor, assignee, transferee, or Affiliate of a Party) shall (a) use commercially reasonable efforts to structure the arrangement and activities contemplated by this Agreement to avoid the arrangement contemplated by this Agreement being treated as a partnership that is engaged in a "United States trade or business" for United States tax purposes and (b) not treat or report the relationship between the Parties arising under this Agreement as a partnership for United States tax purposes without the prior written consent of the other Party unless required by a final "determination" as defined in Section 1313 of the United States Internal Revenue Code of 1986, as amended.

12.9 Assignment. Neither Party shall sell, transfer, assign, delegate, pledge, or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or obligations hereunder without the prior written consent of the other Party, such consent not to be unreasonably withheld, conditioned, or delayed; provided, that either Party may make such a transfer or assignment without the other Party's consent (a) to its Affiliate, provided that if the entity to which this Agreement is assigned ceases to be an Affiliate of the assigning Party, this Agreement will be automatically assigned back to the assigning Party or its successor or (b) to a successor in interest by way of merger, consolidation, sale of stock, or sale of all or substantially all of its business to which this Agreement relates. Any purported assignment or delegation in violation of this Section 12.9 shall be null and void. All validly assigned and delegated rights and obligations of the Parties hereunder shall be binding upon and inure to the benefit of and be enforceable by and against the successors and permitted assigns of BicycleTx or Ionis, as the case may be. The permitted assignee or transferee shall assume all obligations of its assignor or transferor under this Agreement. Without limiting the generality of the foregoing, the grant of rights set forth in this Agreement shall be binding upon any successor or permitted assignee of BicycleTx, and the obligations of Ionis (including all payment obligations) shall run in favor of any such successor or permitted assignee of BicycleTx's benefits under this Agreement. Notwithstanding the foregoing, all rights to Know-How, Patents, materials, and other intellectual property Controlled by a Third Party permitted assignee of a Party (or any of such Third Party's affiliates immediately prior to the closing of such assignment) immediately prior to such assignment shall be automatically excluded from the rights licensed or granted to the other Party under this Agreement.

12.10 Notices. Any notice required or permitted pursuant to this Agreement shall be in writing and delivered by personal delivery, overnight express courier service, electronic mail, facsimile transmission, or by certified or registered mail, return receipt requested, and shall be deemed given upon personal delivery, upon acknowledgement of receipt fax or electronic transmission, on the next Business Day after deposit if sent by overnight express courier service, or five days after deposit in the mail. Notices will be sent to the following addresses or such other address as either Party may specify in writing pursuant to this Section 12.10. BicycleTx will promptly provide notice information for the Gatekeeper once available.

If to BicycleTx, to:

BicycleTx Limited
Building 900
Babraham Research Campus
Cambridge CB22 3AT, UK
Attention: Chief Operating Officer

with a copy (which shall not constitute notice) to:

BicycleTx Limited
Building 900
Babraham Research Campus
Cambridge CB22 3AT, UK
Attention: General Counsel

Email: [***]

If to Ionis, to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
U.S.A.
Attention: Executive Vice President, Research

With a copy (which shall not constitute notice) to:

Attention: General Counsel
Email: [***]

12.11 English Language. This Agreement shall be written and executed in, and all other communications under or in connection with this Agreement shall be in, the English language. Any translation into any other language shall not be an official version thereof, and in the event of any conflict in interpretation between the English version and such translation, the English version shall control.

12.12 Performance by Affiliates. Each Party may use one (1) or more of its Affiliates to perform its obligations and duties hereunder and such Affiliates are expressly granted certain rights herein to perform such obligations and duties; provided that each such Affiliate shall be bound by the corresponding obligations of such Party; and provided further that such Party, subject to an assignment to such Affiliate pursuant to Section 12.9, shall remain liable hereunder for the prompt payment and performance of its obligations hereunder.

12.13 Construction. The terms of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each Party hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement. Except as otherwise explicitly specified to the contrary, (a) references to a Section, exhibit, appendix, or schedule means a Section of, or exhibit, appendix, or schedule to this Agreement, unless another agreement is specified, (b) the word "including" (in its various forms) means "including without limitation," (c) the words "will" and "shall" have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to a particular person include such person's successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, "$" is in reference to United States dollars, (h) the headings contained in this Agreement, in any exhibit, appendix, or schedule to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement, (i) the word "or" means "and/or" unless the context dictates otherwise because the subjects of the conjunction are mutually exclusive, (j) the words "herein", "hereof", and "hereunder" and other words of similar import refer to this Agreement as a whole and not to any particular Section or other subdivision, and (k) all references to days mean calendar days, unless otherwise specified.

12.14 Schedules. In the event of any inconsistencies between this Agreement and any schedules or other attachments hereto, the terms of this Agreement shall control.

12.15 Further Assurance. Each Party agrees to execute, acknowledge, and deliver such further instruments, and to do all such other acts, as may be necessary or appropriate in order to carry out the purposes and intent of this Agreement.

12.16 No Benefit to Third Parties. Except as provided in ARTICLE 10, covenants and agreements set forth in this Agreement are for the sole benefit of the Parties hereto and their successors and permitted assigns, and they shall not be construed as conferring any rights on any other Persons.

12.17 Counterparts. This Agreement may be executed in one or more counterparts in original, facsimile, PDF, or other electronic format, each of which shall be an original, and all of which together shall constitute one instrument.

[*SIGNATURE PAGE FOLLOWS***]**

THIS COLLABORATION AND LICENSE AGREEMENT is executed by the authorized representatives of the Parties as of the Effective Date.

BICYCLETX LIMITED	**IONIS PHARMACEUTICALS, INC.**
By: /s/Kevin Lee	By: /s/Brett Monia
Name: Kevin Lee	Name: Brett Monia
Title: CEO	Title: CEO

Schedule 1.22

[***]

Schedule 9.2.1

[***]

Schedule 12.2.3

[***]

Exhibit 6.2

SHARE PURCHASE AGREEMENT

THIS SHARE PURCHASE AGREEMENT ("***Agreement***") is entered into as of _____, 2021 (the "***Execution Date***"), by and between **Bicycle Therapeutics plc**, a company incorporated under the laws of England and Wales having an office at Building 900, Babraham Research Campus, Cambridge, United Kingdom CB22 3AT (the "***Company***"), and **Ionis Pharmaceuticals, Inc.** a Delaware corporation with a principal place of business at 2855 Gazelle Court, Carlsbad, California 92010, USA (the "***Purchaser***"). The capitalized terms used herein and not otherwise defined have the meanings given to them in Appendix 1.

RECITALS

BicycleTx Limited ("***BicycleTx***"), an affiliate of the Company, and Purchaser entered into that certain Evaluation and Option Agreement dated as of December 31, 2020 (the "***Option Agreement***") pursuant to which BicycleTx granted to the Purchaser an exclusive option to obtain an exclusive license under BicycleTx's technology to research, develop, manufacture, and commercialize products incorporating TfR1 Bicycles (as defined in the Collaboration Agreement (as defined below)) and Purchaser has exercised such option in accordance with the terms of the Option Agreement. Pursuant to the exercise of such option and contemporaneously with execution of this Agreement, BicycleTx and Purchaser are entering into that certain Collaboration and Licensing Agreement (the "***Collaboration Agreement***").

Pursuant to the Option Agreement, and as partial consideration for the Collaboration Agreement, the Company has agreed to sell, and the Purchaser has agreed to purchase, ordinary shares, nominal value £0.01 per share, of the Company (the "***Ordinary Shares***"), subject to and in accordance with the terms and provisions of this Agreement.

AGREEMENT

For good and valuable consideration, the Purchaser and the Company agree as follows:

1. Sale and Purchase of Ordinary Shares

1.1 Purchase of Ordinary Shares. Subject to the terms and conditions of this Agreement, at the Closing, the Company will issue and sell to the Purchaser, and the Purchaser will purchase from the Company, a number of Ordinary Shares equal to $11,000,000 divided by the Share Value, rounded down to the nearest whole share (such Ordinary Shares, the "***Shares***"). The aggregate purchase price shall equal the number of Shares multiplied by the Share Value, rounded to the nearest cent (the "***Purchase Price***"), *provided, however*, that if the number of Shares calculated in accordance with the preceding clause of this Section 1.1 exceeds the Share Cap, the Company will issue and sell to Purchaser, and the Purchaser will purchase from the Company, the number of Ordinary Shares equal to the Share Cap, at the Share Value, and shall pay to the Company in cash the difference between (i) $11,000,000 and (ii) the product of the Share Value multiplied by the Share Cap (any such amount, the "***Closing Cash***"**)**. In the event the Share Cap is applicable, the term "***Shares***" shall refer to the number of Ordinary Shares equal to the Share Cap, and the term "***Purchase Price***" shall refer to the product of the Share Value and the Share Cap.

1.2 Payment. At the Closing, Purchaser will pay the Purchase Price and the Closing Cash, if any, by wire transfer of immediately available funds in accordance with wire instructions, which instructions will have been provided by the Company to Purchaser at least three (3) Business Days prior to the Closing, and the Company will cause its registrar and transfer agent to issue such Shares in restricted book entry form registered in the name of the Purchaser.

1.3 Closing.

(a) Closing. The closing of the transaction contemplated by Section 1.1 (the "***Closing***") will be held at the offices of the Company or through the electronic exchange of documents and signatures, as promptly as practicable and upon the satisfaction of the closing conditions set forth in Section 6 hereof, and in no event more than ten (10) Business Days after the Execution Date.

(b) Closing Deliverables.

(i) At the Closing, the Company will deliver to Purchaser:

(1) a duly executed cross-receipt in form and substance reasonably satisfactory to each party (the "***Cross-Receipt***");

(2) a certificate in form and substance reasonably satisfactory to Purchaser and duly executed on behalf of the Company by an authorized officer of the Company, certifying that the conditions to the Closing set forth in Sections 6.2(a), (b), (c) and (d) of this Agreement have been fulfilled; and

(3) a certificate of the secretary of the Company dated as of the Closing Date certifying that attached thereto is a true and complete copy of all resolutions adopted by the Board authorizing the execution, delivery and performance of this Agreement and the transactions contemplated herein and that all such resolutions are in full force and effect and are all the resolutions adopted in connection with the transactions contemplated hereby as of the Closing Date.

(ii) At the Closing, Purchaser will deliver to the Company:

(1) a duly-executed Cross-Receipt; and

(2) a certificate in form and substance reasonably satisfactory to the Company and duly executed on behalf of Purchaser by an authorized officer of Purchaser, certifying that the conditions to the Closing set forth in Section 6.1(b) and (c) of this Agreement have been fulfilled.

2. Representations and Warranties of the Company

Except as otherwise specifically contemplated by this Agreement, the Company hereby represents and warrants to Purchaser that:

2.1 Private Placement. Neither the Company nor any Person acting on its behalf, has, directly or indirectly, made any offers or sales of any security or solicited any offers to buy any security, under any circumstances that would require registration of the Shares under the Securities Act. Subject to the accuracy of the representations made by Purchaser in Section 3, the Shares will be issued and sold to Purchaser in compliance with applicable exemptions from the registration and prospectus delivery requirements of the Securities Act and the registration and qualification requirements of all applicable securities Laws of the states of the United States. The Company has not engaged any brokers, finders or agents, or incurred, or will incur, directly or indirectly, any liability for brokerage or finder's fees or agents' commissions or any similar charges in connection with this Agreement and the transactions contemplated hereby.

2.2 Corporate Power and Qualification. The Company has full corporate power and authority to conduct its business as currently conducted. The Company is duly qualified to do business and is in good standing in every jurisdiction in which the nature of the business conducted by it or property owned by it makes such qualification necessary, except where the failure to be so qualified or in good standing, as the case may be, would not reasonably be expected to have a Material Adverse Effect on the Company.

2.3 Authorization; Enforcement. The Company has all requisite corporate power and authority to enter into and to perform its obligations under this Agreement, to consummate the transactions contemplated hereby and to issue the Shares in accordance with the terms and conditions hereof. The execution, delivery and performance of this Agreement by the Company and the consummation by it of the transactions contemplated hereby (including the issuance of the Shares at the Closing in accordance with the terms and conditions hereof) have been duly authorized by the Board and no further consent or authorization of the Company, the Board, or its shareholders is required. This Agreement has been duly executed by the Company and constitutes a legal, valid and binding obligation of the Company enforceable against the Company in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, or moratorium or similar Laws affecting creditors' and contracting parties' rights generally.

2.4 Issuance of Shares. The Shares, upon issuance in accordance with the terms of this Agreement, will be validly issued, fully paid and non-assessable and will not be subject to preemptive rights or other similar rights of shareholders of the Company.

2.5 SEC Documents, Financial Statements.

(a) The American Depositary Shares are registered pursuant to Section 12(b) or 12(g) of the Exchange Act. The Company has delivered or made available (by filing on the SEC's electronic data gathering and retrieval system (EDGAR)) to Purchaser complete copies of its most recent Annual Report on Form 10-K and each subsequent Quarterly Report on Form 10-Q, and any report on Form 8-K, in each case filed with the SEC prior to the Execution Date (the "***SEC Documents***"). As of its date, each SEC Document complied in all material respects with the requirements of the Exchange Act, and other Laws applicable to it, and, as of its date, such SEC Document did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading. No inquiries or any other investigation conducted by or on behalf of Purchaser or its representatives or counsel will modify, amend or affect Purchaser's right to rely on the truth, accuracy and completeness of the SEC Documents and the Company's representations and warranties contained in this Agreement.

(b) There are no outstanding or unresolved comments in comment letters received from the SEC or its staff.

(c) As of the Execution Date, other than the transactions that are the subject of this Agreement and the Collaboration Agreement, no material fact or circumstance exists that would be required to be disclosed in a current report on Form 8-K or in a registration statement filed under the Securities Act, were such a registration statement filed on the date hereof, that has not been disclosed in an SEC Document.

(d) The financial statements, together with the related notes, of the Company included in the SEC Documents comply as to form in all material respects with all applicable accounting requirements and the published rules and regulations of the SEC and all other applicable rules and regulations with respect thereto. Such financial statements, together with the related notes and schedules, have been prepared in accordance with GAAP applied on a consistent basis during the periods involved (except (i) as may be otherwise indicated in such financial statements or the notes thereto or (ii) in the case of unaudited interim statements, to the extent they may not include footnotes or may be condensed or summary statements), and fairly present in all material respects the financial condition of the Company and its consolidated subsidiaries as of the dates thereof and the results of operations and cash flows for the periods then ended (subject, in the case of unaudited statements, to normal year-end audit adjustments).

(e) The American Depositary Shares are listed on Nasdaq, and the Company has taken no action designed to, or that to its knowledge is likely to have the effect of, terminating the registration of the American Depositary Shares under the Exchange Act or delisting the American Depositary Shares from Nasdaq. As of the Execution Date, the Company has not received any notification that, and has no knowledge that, the SEC or Nasdaq is contemplating terminating such registration or listing.

2.6 Internal Controls; Disclosure Controls and Procedures. The Company maintains internal control over financial reporting as defined in Rule 13a-15(f) under the Exchange Act. The Company has implemented the "disclosure controls and procedures" (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) required in order for the principal executive officer and principal financial officer of the Company to engage in the review and evaluation process mandated by the Exchange Act, and is in compliance with such disclosure controls and procedures in all material respects. Each of the principal executive officer and the principal financial officer of the Company has made all certifications required by Sections 302 and 906 of the Sarbanes-Oxley Act of 2002 with respect to all reports, schedules, forms, statements and other documents required to be filed by the Company with the SEC.

2.7 Voting Rights.

(a) All of the Ordinary Shares are entitled to one (1) vote per share.

(b) Except as described or referred to in the SEC Documents, as of the Execution Date, there were not: (i) any outstanding equity securities, options, warrants, rights (including conversion or preemptive rights) or other agreements pursuant to which the Company is or may become obligated to issue, sell or repurchase any ordinary shares, ADSs or any other securities of the Company other than equity securities that may have been granted pursuant to its equity incentive plans, which plans are described in the SEC Documents; or (ii) any restrictions on the transfer of share capital of the Company other than pursuant to applicable U.K. or U.S. federal or state securities Laws or as set forth in this Agreement.

(c) The Company is not a party to or subject to any agreement or understanding relating to the voting of shares of or other securities of the Company or the giving of written consents by a shareholder or director of the Company.

2.8 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by the Company and the consummation by the Company of the transactions contemplated hereby (including the issuance of the Shares) will not (i) conflict with or result in a violation of any provision of the Company's Articles of Association, as in effect on the date hereof, (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which the Company is a party, or (iii) subject to Section 2.8(b), result in a violation of any Law (including United States federal, state and U.K. securities Laws and regulations and regulations of any self-regulatory organizations) applicable to the Company, except in the case of clauses (ii) and (iii) only, for such conflicts, breaches, defaults, and violations as would not reasonably be expected to have, a Material Adverse Effect on the Company or result in a liability for Purchaser.

(b) The Company is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory agency or self-regulatory organization in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms and conditions hereof, or to issue and sell the Shares in accordance with the terms and conditions hereof other than such as have been made or obtained, and except for any post-closing filings required to be made under federal, national or state securities Laws.

2.9 Litigation. Other than as set forth in the SEC Documents filed prior to the Execution Date, there is no action, suit, proceeding or investigation pending (of which the Company has received notice or otherwise has knowledge) or, to the Company's knowledge, threatened, against the Company or that the Company intends to initiate, except where such action, suit, proceeding or investigation, as the case may be, and would not reasonably be expected to have a Material Adverse Effect.

2.10 Licenses and Other Rights; Compliance with Laws. The Company has all franchises, permits, licenses and other rights and privileges ("***Permits***") necessary to permit it to own its properties and to conduct its business as presently conducted and is in compliance thereunder, except where the failure to be in compliance would not reasonably be expected to have a Material Adverse Effect. The Company has not taken any action that would interfere with its ability to renew all such Permit(s), except where the failure to renew such Permit(s) would not reasonably be expected to have, a Material Adverse Effect. The Company is and has been in compliance with all Laws applicable to its business, properties and assets, except where the failure to be in compliance has not had and would not reasonably be expected to have a Material Adverse Effect.

2.11 Intellectual Property.

(a) Other than as set forth in the SEC Documents filed prior to the Execution Date, the Intellectual Property that is owned by the Company or its subsidiaries is owned free from any Liens. All of the Company's material Intellectual Property Licenses are in full force and effect in accordance with their terms, are free of any Liens, and, to the Company's knowledge, neither the Company, nor any other party thereto, is in material breach of any such material Intellectual Property License. To the Company's knowledge, no event has occurred that with notice or lapse of time or both (i) would constitute a breach or default of any such material Intellectual Property License, (ii) would result in the termination thereof, or (iii) would cause or permit the acceleration or other change of any right or obligation or the loss of any benefit thereunder by the Company or its subsidiaries, except, in the case of each of clauses (i) through (iii), as would not reasonably be expected to have a Material Adverse Effect.

(b) Except as set forth in the SEC Documents, there is no legal claim or demand of any Person or any proceeding that is pending or threatened in writing, (i) challenging the right of the Company in respect of any Intellectual Property of the Company, or (ii) claiming that any default exists under any Intellectual Property License, except, in the case of clauses (i) and (ii) above, where any such claim, demand or proceeding has not had, and would notreasonably be expected to have, a Material Adverse Effect.

(c) Except as set forth in the SEC Documents: (i) the Company or one of its subsidiaries owns, free and clear of any Lien, or, to the Company's knowledge, has a valid license, or an enforceable right to use, as it is used or held for use, all U.S. and non-U.S. patents, trade secrets, know-how, trademarks, service marks, copyrights, and other proprietary and Intellectual Property rights, and all grants and applications with respect to the foregoing (collectively, the "***Proprietary Rights***") necessary for the conduct of the Company's business, except where the failure to own or have any of the foregoing would not reasonably be expected to have a Material Adverse Effect (such Proprietary Rights owned by or licensed to the Company collectively, the "***Company Rights***"); and (ii) the Company and its subsidiaries have taken reasonable measures to protect the Company Rights, consistent with prudent commercial practices in the biotechnology industry, except where failure to take such measures has not had, and would not reasonably be expected to have, a Material Adverse Effect.

2.12 Health Care Matters. The Company: (i) has operated and currently operates its business in compliance in all material respects with applicable provisions of the Health Care Laws (as defined below) of the Food and Drug Administration ("***FDA***"), the Department of Health and Human Services and any comparable state, foreign or other regulatory authority to which they are subject (collectively, the "***Applicable Regulatory Authorities***") applicable to the ownership, testing, development, manufacture, packaging, processing, use, sale, promotion, distribution, storage, import, export or disposal of any of the Company's product candidates or any product manufactured or distributed by the Company; (ii) has not received any FDA Form 483, written notice of adverse finding, warning letter, untitled letter or other correspondence or written notice from any court or arbitrator or the Applicable Regulatory Authorities alleging or asserting non-compliance with any licenses, certificates, approvals, clearances, exemptions, authorizations, permits and supplements or amendments thereto required by any such Health Care Laws ("***Regulatory Authorizations***"); (iii) possesses all Regulatory Authorizations required to conduct its business as currently conducted and such Regulatory Authorizations are valid and in full force and effect and the Company is not in violation, in any material respect, of any term of any such Regulatory Authorizations; (iv) has not received notice of any claim, action, suit, proceeding, hearing, enforcement, investigation, arbitration or other action from any court or arbitrator or the Applicable Regulatory Authorities or any other third party alleging that any product operation or activity is in material violation of any Health Care Laws and has no knowledge that the Applicable Regulatory Authorities or any other third party is considering any such claim, litigation, arbitration, action, suit, investigation or proceeding; (v) has not received notice that any of the Applicable Regulatory Authorities has taken, is taking or intends to take action to limit, suspend, modify or revoke any material Regulatory Authorizations and has no knowledge that any of the Applicable Regulatory Authorities is considering such action; (vi) has filed, obtained, maintained or submitted all material reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments as required by any Health Care Laws or Regulatory Authorizations and that all such reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments were materially complete and correct on the date filed (or were materially corrected or supplemented by a subsequent submission); (vii) is not a party to and does not have any ongoing reporting obligations pursuant to any corporate integrity agreements, deferred prosecution agreements, monitoring agreements, consent decrees, settlement orders, plans of correction or similar agreements with or imposed by any Applicable Regulatory Authority; and (viii) along with its employees, officers and directors, has not been excluded, disqualified, suspended or debarred from participation in any government health care program or human clinical research or, to the Company's knowledge, subject to a governmental inquiry, investigation, proceeding, or other similar action that could reasonably be expected to result in debarment, suspension, disqualification or exclusion.

2.13 Clinical Trials. None of the Company's product candidates has received marketing approval from any Applicable Regulatory Authority. All clinical and pre-clinical studies and trials conducted by or on behalf of or sponsored by the Company, or in which the Company has participated, with respect to the Company's product candidates, including any such studies and trials that are described in the SEC Documents, or the results of which are referred to in the SEC Documents, as applicable (collectively, "***Company Trials***"), were, and if still pending are, to the Company's knowledge, being conducted in all material respects in accordance with all applicable Health Care Laws of the Applicable Regulatory Authorities, including the FDA's current Good Clinical Practices and Good Laboratory Practices, standard medical and scientific research procedures and any applicable rules, regulations and policies of the jurisdiction in which such trials and studies are being conducted. The descriptions in the SEC Documents of the results of any Company Trials are accurate and complete descriptions in all material respects and fairly present the data derived therefrom as of the date of such SEC Documents. The Company has no knowledge of any other studies or trials not described in the SEC Documents, the results of which are inconsistent with or call into question the results described or referred to in the SEC Documents. The Company has not received any written notices, correspondence or other communications from the Applicable Regulatory Authorities or any other governmental entity or any institutional review board ("***IRB***") or independent ethics committee ("***IEC***") requiring or threatening the termination, material modification or suspension of Company Trials, other than ordinary course communications with respect to modifications in connection with the design and implementation of such studies or trials, and, to the Company's knowledge, there are no reasonable grounds for the same. No investigational new drug application or comparable submission filed by or on behalf of the Company with the FDA has been terminated or suspended by the FDA or any other Applicable Regulatory Authority. The Company has obtained (or caused to be obtained) informed consent by or on behalf of each human subject who participated in a Company Trial, and the Company has obtained (or caused to be obtained) applicable IRB or IEC approvals for each Company Trial. To the Company's knowledge, none of the Company Trials involved any investigator who has been disqualified as a clinical investigator or has been found by the FDA to have engaged in scientific misconduct.

2.14 Absence of Certain Changes.

(a) Except as disclosed in the SEC Documents filed prior to the Execution Date, since March 31, 2021, no change or event has occurred, except where such change or event has not had, and would not reasonably be expected to have, a Material Adverse Effect on the Company.

(b) Except as set forth in the SEC Documents filed prior to the Execution Date or as contemplated by this Agreement or the Collaboration Agreement, since December 31, 2020, the Company has not (i) declared or paid any dividends, or authorized or made any distribution upon or with respect to any class or series of its share capital, or (ii) sold, exchanged or otherwise disposed of any of its material assets or rights.

(c) Since March 31, 2021, the Company has not admitted in writing its inability to pay its debts generally as they become due, filed or consented to the filing against it of a petition in bankruptcy or a petition to take advantage of any insolvency act, made an assignment for the benefit of creditors, consented to the appointment of a receiver for itself or for the whole or any substantial part of its property, or had a petition in bankruptcy filed against it, been adjudicated a bankrupt, or filed a petition or answer seeking reorganization or arrangement under the federal bankruptcy Laws or any other Laws of the United States or any other jurisdiction.

2.15 Not an Investment Company. The Company is not, and after receipt of the Purchase Price, will not be, an "investment company" as defined in the Investment Company Act of 1940, as amended.

2.16 Critical Technology. The Company does not produce, design, test, manufacture, fabricate, or develop one or more "critical technologies" within the meaning of the Defense Production Act of 1950, as amended, including all implementing regulations thereof.

2.17 No Integration. The Company has not, directly or through any agent, sold, offered for sale, solicited offers to buy or otherwise negotiated in respect of, any security (as defined in the Securities Act) that is or will be integrated with the Shares sold pursuant to this Agreement in a manner that would require the registration of the Shares under the Securities Act.

Except as otherwise specifically contemplated by this Agreement, Purchaser hereby represents and warrants to the Company that:

3.1 Authorization; Enforcement. Purchaser has the requisite corporate or other similar power and authority to enter into this Agreement and to consummate the transactions contemplated hereby. Purchaser has taken all necessary corporate or other similar action to authorize the execution, delivery and performance of this Agreement. Upon the execution and delivery of this Agreement, this Agreement will constitute a valid and binding obligation of Purchaser enforceable against Purchaser in accordance with its terms and conditions, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar Laws affecting creditors' and contracting parties' rights generally.

3.2 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by Purchaser and the consummation by Purchaser of the transactions contemplated hereby (including the purchase of the Shares) will not (i) conflict with or result in a violation of any provision of Purchaser's memorandum and articles of association or equivalent organizational documents, (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which Purchaser is a party, or (iii) result in a violation of any Law (including U.S. federal and state securities Laws and regulations and regulations of any self-regulatory organizations) applicable to Purchaser, except in the case of clauses (ii) and (iii) only, for such conflicts, breaches, defaults, and violations as have not had, and would not reasonably be expected to have, a Material Adverse Effect on Purchaser or result in a liability for the Company.

(b) Purchaser is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory agency or self-regulatory organization in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms and conditions hereof, or to purchase the Shares in accordance with the terms and conditions hereof, other than such as have been made or obtained, except if and to the extent applicable for compliance with any requirements of the HSR Act and any other antitrust Law.

3.3 Investment Purpose. Purchaser is purchasing the Shares for its own account and not with a present view toward the public distribution thereof and has no arrangement or understanding with any other Persons regarding the distribution of such Shares except as would not result in a violation of the Securities Act. Without limiting Section 5.1 and Section 5.2, Purchaser will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) any of the Shares except in accordance with the Securities Act.

3.4 Reliance on Exemptions. Purchaser understands that the Company intends for the Shares to be offered and sold to it in reliance upon specific exemptions from the registration requirements of United States federal and state securities Laws and that the Company is relying upon the truth and accuracy of, and Purchaser's compliance with, the representations, warranties, agreements, acknowledgments and understandings of Purchaser set forth herein in order to determine the availability of such exemptions and the eligibility of Purchaser to acquire the Shares.

3.5 Accredited Investor; Access to Information. Purchaser is an "accredited investor" as defined in Regulation D under the Securities Act and is knowledgeable, sophisticated and experienced in making, and is qualified to make, decisions with respect to investments in shares presenting an investment decision like that involved in the purchase of the Shares. Purchaser has been furnished with materials relating to the offer and sale of the Shares that have been requested by Purchaser, including the SEC Documents, and Purchaser has had the opportunity to review the SEC Documents. Purchaser has been afforded the opportunity to ask questions of the Company. Neither such inquiries nor any other investigation conducted by or on behalf of Purchaser or its representatives or counsel will modify, amend or affect Purchaser's right to rely on the truth, accuracy and completeness of the SEC Documents and the Company's representations and warranties contained in this Agreement.

3.6 Restricted Securities. Purchaser understands that the Shares will be characterized as "restricted securities" under the U.S. federal securities Laws inasmuch as they are being acquired from the Company in a private placement under Section 4(a)(2) of the Securities Act and that under such Laws and applicable regulations such Shares may be resold without registration under the Securities Act only in certain limited circumstances.

3.7 Governmental Review. Purchaser understands that no U.S. federal or state or U.K. agency or any other Governmental Authority has passed upon or made any recommendation or endorsement of the Shares or an investment therein.

4. Standstill Agreement

4.1 During the period commencing on the date of this Agreement (the "***Standstill Commencement Date***") and ending on the 18-month anniversary of the Standstill Commencement Date (the "Standstill Period"), neither Purchaser, any of Purchaser's controlled Affiliates nor any of Purchaser's representatives acting on behalf of or in concert with Purchaser will, in any manner, directly or indirectly:

(a) make, effect, initiate, cause or participate in (i) any acquisition of beneficial ownership of any securities of the Company or any securities (including derivatives thereof) of any subsidiary or other controlled Affiliate of the Company, (ii) any acquisition of all or a material portion of the assets of the Company and its subsidiaries on a consolidated basis or (iii) any tender offer, exchange offer, merger, business combination, recapitalization, restructuring, liquidation, dissolution or extraordinary transaction involving the Company or any subsidiary or other controlled Affiliate of the Company or involving any securities or assets of the Company or any securities or assets of any subsidiary, division or other affiliate of the Company (provided that the Purchaser may tender its shares in any tender or exchange offer made by any third party provided that Ionis is not in breach of or won't be in breach of this Section 4.1 of this Agreement), or (iv) any "solicitation" of "proxies" (as those terms are used in the proxy rules of the SEC) or consents with respect to any securities of the Company;

(b) form, join or in any way participate in a "*group*" (as defined under the Exchange Act) with respect to the beneficial ownership of any securities of the Company or any subsidiary or division of the Company;

(c) otherwise act, alone or in concert with others, to seek to control or influence the management, Board or policies of the Company (other than such policies as may be within the scope of the Collaboration Agreement (including any amendments thereto));

(d) take any action that would reasonably be expected to require the Company to make a public announcement regarding any of the types of matters set forth in clause (a) above; or

(e) agree or offer to take, or knowingly encourage or propose (publicly or otherwise) the taking of, any action referred to in clauses (a), (b), (c), or (d) above;

(f) assist, induce or encourage any other Person to take any action of the type referred to in clauses (a), (b), (c), (d) or (e) above (provided that the Purchaser shall not be deemed to be in violation of this clause (f) unless the Person providing such assistance, inducement or encouragement knew or reasonably should have known at the time he or she did so that doing so violated this clause (f), or knew or reasonably should have known after such time and did not attempt to halt such actions); or

(g) enter into any discussions, negotiations, arrangement or agreement with any other Person with the intent to effect any of the foregoing (provided that the Purchaser shall not be deemed to be in violation of this clause (g) with respect to discussions or negotiations unless the Person entering into such discussions or negotiations knew or reasonably should have known at the time he or she did so that doing so violated this clause (g) or knew or reasonably should have known after such time and did not attempt to halt such actions.

4.2 Purchaser also agrees during the Standstill Period not to request the Company (or its representatives), directly or indirectly, amend or waive any provision of this Section 4 other than by means of a confidential communication to the Company's Chairman of the Board or the Company's Chief Executive Officer.

4.3 Purchaser represents and warrants that, as of the Execution Date, neither Purchaser nor any of its Affiliates owns, of record or beneficially, any voting securities of the Company, or any securities convertible into or exercisable for any voting securities of the Company.

4.4 Notwithstanding the provisions set forth in Sections 4.1 and 4.2 (the "***Standstill Provisions***"), Purchaser shall immediately, and without any other action by the Company, be released from its obligations under the Standstill Provisions if: (a) the Company enters into a definitive written agreement with any Person other than the Purchaser (or any of its Affiliates) to consummate a merger, consolidation or similar transaction pursuant to which (i) any Person other than the Purchaser (or any of its Affiliates) will acquire 50% or more of the outstanding voting shares of the Company or (ii) the Company and its subsidiaries will sell to any Person other than the Purchaser (or any of its Affiliates) all or substantially all of the consolidated assets of the Company and its consolidated subsidiaries ((i) or (ii), a "***Company Sale***"), (ii) a Third Party makes a tender or exchange offer for securities of the Company and the Board either accepts such offer or fails to recommend that its shareholders reject such offer within 10 Business Days from the date of commencement of such offer, or (iii) the Company publicly announces that its Board is engaging in a formal process that is intended to result in a transaction that if consummated would constitute a Company Sale.

4.5 Notwithstanding any other provision of this Agreement to the contrary, nothing in this Agreement will be deemed to prohibit a party from confidentially communicating to the other party's board of directors or senior management or external financial advisors any non-public proposals regarding a possible transaction of any kind in such a manner as would not reasonably be expected to require public disclosure thereof under applicable Law or listing standards of any securities exchange, including Nasdaq.

5. Transfer, Resale, Legends, Deposit for American Depositary Shares

5.1 **Transfer or Resale.** Purchaser understands that:

(a) the Shares have not been and are not being registered under the Securities Act or any applicable state securities Laws and, consequently, Purchaser may have to bear the risk of owning the Shares for an indefinite period of time because the Shares may not be transferred unless (i) the resale of the Shares is registered pursuant to an effective registration statement under the Securities Act; (ii) Purchaser has delivered to the Company an opinion of counsel (in form, substance and scope customary for opinions of counsel in comparable transactions) to the effect that the Shares to be sold or transferred may be sold or transferred pursuant to an exemption from such registration; or (iii) the Shares are sold or transferred pursuant to Rule 144 under the Securities Act ("***Rule 144***"); and

(b) any sale of the Shares made in reliance on Rule 144 may be made only in accordance with the terms of Rule 144 and, if Rule 144 is not applicable, any resale of the Shares under circumstances in which the seller (or the Person through whom the sale is made) may be deemed to be an underwriter (as that term is defined in the Securities Act) may require compliance with some other exemption under the Securities Act or the rules and regulations of the SEC thereunder.

5.2 Lock-Up. Purchaser agrees that it will hold and will not sell any of the Shares (or otherwise make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale of the Shares) until the earlier of (i) the one-year anniversary of the Closing Date, and (ii) the termination of the Collaboration Agreement, provided that in the event the termination occurs less than six months after the Closing Date, the Purchaser shall hold and will not sell or otherwise enter into a transaction regarding the Shares until at least the date that is six months after the Closing Date. Notwithstanding the foregoing, this Section 5.2 will not preclude (i) distributions of Shares to general or limited partners, members, shareholders, Affiliates or wholly-owned subsidiaries of Purchaser or any investment fund or other entity controlled or managed by Purchaser; *provided*, in each case, that following any such transfer such Shares will remain subject to the provisions of this Section 5.2; or (ii) transfers pursuant to a *bona fide* third party tender offer for all outstanding Ordinary Shares, merger, consolidation or other similar transaction made to all holders of the Company's securities involving a change of control of the Company (including the entering into any lock-up, voting or similar agreement pursuant to which Purchaser may agree to transfer, sell, tender or otherwise dispose of Shares or other such securities in connection with such transaction, or vote any Shares or other such securities in favor of any such transaction); *provided*, that in the event that such tender offer, merger, consolidation or other such transaction is not completed, the Shares shall remain subject to the provisions of this Section 5.2.

5.3 Legends. Purchaser understands the Shares will bear restrictive legends in substantially the following form (and a stop-transfer order may be placed against transfer of the Shares):

THE SHARES HAVE NOT BEEN REGISTERED UNDER THE U.S. SECURITIES ACT OF 1933, AS AMENDED, OR ANY APPLICABLE STATE SECURITIES LAWS. THEY MAY NOT BE SOLD, OFFERED FOR SALE, PLEDGED OR HYPOTHECATED UNLESS (I) THE SHARES ARE REGISTERED PURSUANT TO AN EFFECTIVE REGISTRATION STATEMENT UNDER THE SECURITIES ACT; (II) AN OPINION OF COUNSEL HAS BEEN DELIVERED (IN FORM, SUBSTANCE AND SCOPE CUSTOMARY FOR OPINIONS OF COUNSEL IN COMPARABLE TRANSACTIONS) TO THE EFFECT THAT THE SHARES TO BE SOLD OR TRANSFERRED MAY BE SOLD OR TRANSFERRED PURSUANT TO AN EXEMPTION FROM SUCH REGISTRATION; OR (III) THE SHARES ARE SOLD OR TRANSFERRED PURSUANT TO RULE 144 UNDER THE SECURITIES ACT.

THE SALE, PLEDGE, HYPOTHECATION OR TRANSFER OF THESE SECURITIES IS SUBJECT TO THE TERMS AND CONDITIONS OF A SHARE PURCHASE AGREEMENT DATED JULY 9, 2021 BETWEEN BICYCLE THERAPEUTICS PLC AND IONIS PHARMACEUTICALS, INC.

If such Shares may be transferred pursuant to Section 5.2 (excluding transfers pursuant to Section 5.2(i)), Purchaser may request that the Company remove, and the Company agrees to authorize and instruct (including by causing any required legal opinion to be provided) the removal of any legend from the Shares, if permitted by applicable securities Law, within two (2) Business Days of any such request; *provided, however*, that each party will be responsible for any fees it incurs in connection with such request and removal.

5.4 Deposit of Shares and Issuance of American Depositary Shares. Upon the written request of the Purchaser to the Company, and in accordance with the other limitations of this Agreement, the Company will deposit or cause to be deposited such number of Shares with the Depositary as is requested by the Purchaser, and issue or cause to be issued to the Purchaser the corresponding American Depositary Shares, with any and all costs associated with such deposit and issuance paid for by the Purchaser. The Company shall (a) use its reasonable best efforts to (i) register or qualify its American Depositary Shares under the securities or blue sky Laws of such jurisdictions in the United States as the Purchaser reasonably requests and do any and all other acts and things which may be reasonably necessary or advisable to enable the Purchaser to consummate the disposition in such jurisdictions of the American Depositary Shares owned by the Purchaser in accordance with Rule 144 or some other exemption under the Securities Act or the rules and regulations of the SEC thereunder, provided that the Company shall not be required to register the Shares or any American Depositary Shares held by the Purchaser on a Registration Statement on Form S-1 or Registration Statement on Form S-3 and (ii) cause all such American Depositary Shares to be eligible and remain eligible for registration of the American Depositary Shares pursuant to Form F-6, and (b) cooperate with the Purchaser and the Depositary to facilitate the timely delivery of American Depositary Shares (in book entry or certificated form), which American Depositary Shares shall be free of all restrictive legends unless the Company reasonably determines on advice from legal counsel that such legends are required by applicable law (it being understood that the American Depositary Shares may be restricted American Depositary Shares subject to restrictions imposed by the Depositary if and for so long as the Purchaser is an Affiliate of the Company).

5.5 Rule 144 Reporting. With a view to making available to Purchaser the benefits of certain rules and regulations of the SEC that may permit the sale of registrable securities to the public without registration, the Company agrees to use its best efforts to:

(a) Make and keep public information available, as those terms are understood and defined in Rule 144 or any similar or analogous rule promulgated under the Securities Act, at all times after the effective date of the first registration filed by the Company for an offering of its securities to the general public;

(b) File with the SEC, in a timely manner, all reports and other documents required of the Company under the Exchange Act; and

(c) So long as Purchaser owns Shares, furnish to Purchaser upon request: a written statement by the Company as to its compliance with the reporting requirements of said Rule 144 of the Securities Act, and of the Exchange Act; a copy of the most recent annual or quarterly report of the Company filed with the Commission; and such other reports and documents as Purchaser may reasonably request in connection with availing itself of any rule or regulation of the SEC allowing it to sell any such securities without registration.

6. Conditions to Closing

6.1 Conditions to Obligations of the Company. The Company's obligation to complete the purchase and sale of the Shares and deliver the Shares to Purchaser is subject to the fulfillment or waiver of the following conditions at or prior to the Closing:

(a) Receipt of Funds. The Company will have received immediately available funds in the full amount of the Purchase Price for the Shares being purchased hereunder.

(b) Representations and Warranties. The representations and warranties made by Purchaser in Section 3 will be true and correct in all material respects as of the Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct in all material respects as of such other date.

(c) Covenants. All covenants and agreements contained in this Agreement to be performed or complied with by Purchaser on or prior to the Closing Date shall have been performed or complied with in all material respects.

(d) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, will have been instituted or be pending before any Governmental Authority.

(e) No Governmental Prohibition. The sale of the Shares by the Company and the purchase of the Shares by Purchaser will not be prohibited by any applicable Law at the time of the Closing.

(f) Collaboration Agreement. Purchaser and the Company shall have duly executed and delivered the Collaboration Agreement, such agreement shall be in full force and effect, each of the conditions contained therein shall have been satisfied or waived (if legally permissible) and the provisions of such agreement shall have become effective.

(g) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(ii) shall have been delivered by Purchaser to the Company.

6.2 Conditions to Purchaser's Obligations at the Closing. Purchaser's obligation to complete the purchase and sale of the Shares is subject to the fulfillment or waiver of the following conditions at or prior to the Closing:

(a) Representations and Warranties. The representations and warranties made by the Company in Section 2 will be true and correct in all material respects as of the Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct in all material respects as of such other date.

(b) Covenants. All covenants and agreements contained in this Agreement to be performed or complied with by the Company on or prior to the Closing Date shall have been performed or complied with in all material respects.

(c) Transfer Agent Instructions. The Company will have delivered to its transfer agent and registrar irrevocable written instructions to issue the Shares to Purchaser in a form and substance acceptable to such transfer agent.

(d) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, will have been instituted or be pending before any Governmental Authority.

(e) Collaboration Agreement. Purchaser and the Company shall have duly executed and delivered the Collaboration Agreement, such agreement shall be in full force and effect, each of the conditions contained therein shall have been satisfied or waived (if legally permissible) and the provisions of such agreement shall have become effective.

(f) No Governmental Prohibition. The sale of the Shares by the Company, and the purchase of the Shares by Purchaser will not be prohibited by any applicable Law at the time of the Closing.

(g) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(i) shall have been delivered by the Company to Purchaser.

7. Indemnification

7.1 Indemnification by the Company. The Company shall indemnify and hold harmless Purchaser and its Affiliates, and the directors, officers, employees and other agents and representatives of Purchaser and its Affiliates, from and against any and all liabilities, judgments, claims, settlements, losses, damages, fees, Liens, Taxes, penalties, obligations and expenses (including reasonable attorney's fees and expenses and costs and expenses of investigation) (collectively, "***Losses***") incurred or suffered, directly or indirectly, by any such Person arising from, by reason of or in connection with: (a) any breach or inaccuracy of any representation or warranty of the Company contained in this Agreement or any certificate delivered by the Company or on its behalf hereunder; and (b) the non-fulfillment or breach by the Company of any agreements or obligations under this Agreement.

7.2 Indemnification by Purchaser. Purchaser shall indemnify and hold harmless the Company and its Affiliates, and the directors, officers, employees and other agents and representatives of the Company and its Affiliates, from and against any and all Losses incurred or suffered, directly or indirectly, by any such Person arising from, by reason of or in connection with: (a) any breach or inaccuracy of any representation or warranty of Purchaser contained in this Agreement or any certificate delivered by the Purchaser or on its behalf hereunder; and (b) the non-fulfillment or breach by Purchaser of any agreements or obligations under this Agreement.

7.3 Calculation of Losses. Any indemnity payment hereunder shall be treated as an adjustment to the Purchase Price to the extent permitted by applicable Law. Where the receipt of any such payment is treated for Tax purposes in a manner other than as an adjustment to the Purchase Price, the amount of the payment shall be adjusted to take account of any net Tax cost actually incurred, or benefit actually enjoyed, by the Indemnified Party in respect thereof.

7.4 Certain Procedures for Indemnification.

(a) If any Person entitled to indemnification under this Agreement (an "***Indemnified Party***") asserts a claim for indemnification, or receives notice of the assertion of any claim or of the commencement of any action by any Person not a party to this Agreement against such Indemnified Party, for which a party to this Agreement is required to provide indemnification under this Section 7 (an "***Indemnifying Party***"), the Indemnified Party shall promptly notify the Indemnifying Party in writing of the claim or the commencement of that action; *provided, however*, that the failure to so notify the Indemnifying Party shall not relieve the Indemnifying Party from any liability which it may have to the Indemnified Party, except to the extent that such failure materially prejudices the Indemnifying Party's ability to defend such action.

(b) With respect to third party claims for which indemnification is claimed hereunder, (i) the Indemnifying Party shall be entitled to participate in the defense of any such claim, and (ii) if, in the reasonable judgment of the Indemnified Party, such claim can properly be resolved by money damages alone and the Indemnifying Party has the financial resources to pay such damages, and the Indemnifying Party admits that this indemnity fully covers the claim or litigation, then the Indemnifying Party shall be entitled (y) to direct the defense of any claim at its sole cost and expense, but such defense shall be conducted by legal counsel reasonably satisfactory to the Indemnified Party, and (z) to settle and compromise any such claim or action for money damages alone; *provided, however*, that if the Indemnified Party has elected to be represented by separate counsel pursuant to the proviso below, or if such settlement or compromise does not include an unconditional release of the Indemnified Party for any liability arising out of such claim or action, such settlement or compromise shall be effected only with the written consent of the Indemnified Party. After notice from the Indemnifying Party to the Indemnified Party of its election to assume the defense of such claim or action, the Indemnifying Party shall not be liable to the Indemnified Party under this Section 7.4 for any legal or other expenses subsequently incurred by the Indemnified Party in connection with the defense thereof other than reasonable costs of investigation or of assistance as contemplated by this Section 7.4; *provided, however*, that if, in the opinion of the Indemnified Party, it is advisable for the Indemnified Party to be represented by separate counsel due to actual or potential conflicts of interest, the Indemnified Party shall have the right to employ counsel to represent it and in that event the fees and expenses of such separate counsel shall be paid by the Indemnifying Party; *provided further*, that in no event shall the Indemnifying Party be responsible for the fees of more than one counsel to the Indemnified Party. The Indemnified Party and the Indemnifying Party shall each render to each other such assistance as may reasonably be requested in order to ensure the proper and adequate defense of any such claim or proceeding.

7.5 Survival; Expiration.

(a) Notwithstanding any investigation made by or on behalf of the Company or Purchaser prior to, on or after the Closing Date, the representations and warranties contained in this Agreement (including the exhibits and schedules hereto) and any certificate delivered hereunder shall survive the Closing and shall terminate on the second anniversary of the Closing Date.

(b) The covenants of the parties hereto shall survive until fully performed and discharged, unless otherwise expressly provided herein.

(c) Any right of indemnification or reimbursement pursuant to this Section 7 with respect to a claimed breach, inaccuracy or non-fulfillment of any representation, warranty, agreement or obligation shall expire on the applicable date of termination of the representation, warranty or covenant claimed to be breached (the "***Expiration Date***"), unless on or prior to the applicable Expiration Date, the Indemnifying Party has received written notice from the Indemnified Party of such breach, inaccuracy or non-fulfillment from the Indemnified Party or is based on fraud or intentional or willful breach of the Indemnifying Party, in which case the Indemnified Party may continue to pursue its right of indemnification or reimbursement hereunder beyond the Expiration Date of the applicable representation, warranty, agreement or obligation. For the avoidance of doubt, no claims based on fraud or intentional or willful breach will be subject to any of the limitations set forth in this Section 7.5.

8. Dispute Resolution

8.1 **(a)**If the parties cannot amicably resolve any dispute (a "***Dispute***") arising under this Agreement, then a party seeking further resolution of such Dispute shall submit such Dispute to final and binding arbitration conducted in accordance with the terms of this Section 8.1. The party initiating arbitration will give written notice to that effect to the other party. The legal seat of arbitration will be New York City, New York, U.S., and the arbitration will be administered by JAMS according to the JAMS International Arbitration Rules applicable at the time of commencement of the arbitration except as otherwise provided herein and applying the substantive law specified in Section 10.1. The arbitration will be conducted by a single arbitrator appointed in accordance with the Rules, provided that such arbitrator must have significant business or legal experience in the pharmaceutical industry and the applicable law concerning the subject matter of the dispute. In any case, the arbitrator will not be an Affiliate, employee, consultant, officer, director, shareholder or stockholder of either party, or otherwise have any current or previous relationship with either party or their respective Affiliates. After conducting any hearing and taking any evidence deemed appropriate for consideration, the arbitrator will render a written opinion within 30 days after the final arbitration hearing. The arbitrator's decision will include findings of fact and conclusions of law. The determination of the arbitrator as to the resolution of any Dispute will be binding and conclusive on the parties. Judgment on the award so rendered may be entered in any court of competent jurisdiction, and the parties undertake to carry out any award without delay. Nothing contained herein will be construed to permit the arbitrator to award punitive, exemplary, or any similar damages and any arbitral award that purports to award such damages is expressly prohibited and void *ab initio*. Each party will bear its own attorneys' fees, costs and disbursements arising out of the arbitration and will pay an equal share of the fees and costs of the arbitrator. Except to the extent necessary to confirm, enforce, or challenge an award of the arbitration, to protect or pursue a legal right, or as otherwise required by applicable law or regulation, no party nor the arbitrator may disclose the existence, content, or results of an arbitration under this Section 8.1 without the express, prior written consent of each of the parties. In no event shall any party initiate arbitration after the date when commencement of a legal or equitable proceeding based on the Dispute, controversy, or claim would be barred by the applicable New York statute of limitations. Any Disputes concerning the propriety of the commencement of the arbitration, or the validity or application of this Section 8.1, shall be finally settled by the arbitrator. Nothing in this Section 8.1 shall preclude either party from (a) seeking interim or provisional relief, including a temporary restraining order, preliminary injunction, or other interim equitable relief concerning a dispute in any court of competent jurisdiction, before or after the initiation of an arbitration as set forth in this Section 8.1, if necessary to protect the interests of such party, or (b) bringing an action in any court of competent jurisdiction to resolve a dispute regarding the intellectual property rights hereunder, and this sentence shall be specifically enforceable.

(b) For the avoidance of doubt, any disputes with respect to the terms of the Collaboration Agreement shall be resolved in accordance with the dispute resolution provisions therein, and shall not be subject to the provisions of this Section 8.

9. Termination

9.1 **Ability to Terminate**. This Agreement may be terminated prior to the Closing:

(a) at any time by mutual written consent of the Company and Purchaser;

(b) by the Company, upon three (3) days' written notice to Purchaser, so long as the Company is not then in breach of its representations, warranties, covenants or agreements under this Agreement such that any of the conditions set forth in Section 6.1, as applicable, could not be satisfied by the Termination Date, (i) upon a breach of any covenant or agreement on the part of Purchaser set forth in this Agreement that has not been cured within such 3-day notice period, or (ii) if any representation or warranty of Purchaser shall have been or become untrue, in each case such that any of the conditions set forth in Section 6.1 could not be satisfied by the Termination Date;

(c) by Purchaser, upon three (3) days' written notice to the Company, so long as Purchaser is not then in breach of its representations, warranties, covenants or agreements under this Agreement such that any of the conditions set forth in Section 6.2 of this Agreement, as applicable, could not be satisfied by the Termination Date, (i) upon a breach of any covenant or agreement on the part of the Company set forth in this Agreement that has not been cured within such 3-day notice period, or (ii) if any representation or warranty of the Company shall have been or become untrue, in each case such that any of the conditions set forth in Section 6.2 of this Agreement could not be satisfied by the Termination Date;

(d) by either the Company or Purchaser, upon written notice to the other, if the Closing has not occurred on or before _____, 2021 (the "***Termination Date***").

9.2 Effect of Termination. In the event of the termination of this Agreement pursuant to Section 9, (a) this Agreement (except for this Section 9.2, and Section 7, Section 8, Section 10.1 and Sections 10.3 through 10.14 and any definitions set forth in this Agreement and used in such Sections) shall forthwith become void and have no effect, without any liability on the part of any party hereto or its Affiliates, and (b) any and all filings, applications and other submissions made pursuant to this Agreement, to the extent practicable, shall be withdrawn from the agency or other Person to which they were made or appropriately amended to reflect the termination of the transactions contemplated hereby; *provided*, *however*, that nothing contained in this Section 10.2 shall relieve any party from liability for fraud or any intentional or willful breach of this Agreement.

10. Governing Law; Miscellaneous

10.1 Governing Law. This Agreement will be governed by and interpreted in accordance with the laws of the State of New York without regard to the principles of conflict of laws that would require the application of the substantive Laws of another jurisdiction.

10.2 Market Listing. From the Execution Date through the Closing, the Company shall use commercially reasonable efforts to maintain the listing and trading of the Company's American Depositary Shares on Nasdaq.

10.3 Counterparts; Electronic Signatures. This Agreement may be executed and delivered (including by facsimile transmission or PDF or any other electronically transmitted signatures) in two counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

10.4 Headings. The headings of this Agreement are for convenience of reference only, are not part of this Agreement and do not affect its interpretation.

10.5 Rules of Construction.

(a) For purposes of this Agreement, whenever the context requires: the singular number shall include the plural, and vice versa; the masculine gender shall include the feminine and neuter genders; the feminine gender shall include the masculine and neuter genders; and the neuter gender shall include the masculine and feminine genders.

(b) As used in this Agreement, (i) the words "include" and "including," and variations thereof, shall not be deemed to be terms of limitation, but rather shall be deemed to be followed by the words "without limitation", (ii) the words "hereby," "herein," "hereunder" and "hereto" shall be deemed to refer to this Agreement in its entirety and not to any specific section of this Agreement and (iii) "or" has the inclusive meaning represented by the phrase "and/or".

(c) Except as otherwise indicated, all references in this Agreement to "Sections" and "Appendices" are intended to refer to Sections of this Agreement, as appropriate, and Appendices to this Agreement.

(d) As used in this Agreement, the term "days" means calendar days unless otherwise specified. When calculating the period of time before which, within which or following which any act is to be done or step taken pursuant to this Agreement, the date that is the reference date in calculating such period shall be excluded. If the last day of such period is a non-Business Day, the period in question shall end on the next succeeding Business Day.

(e) Unless otherwise indicated, all monetary amounts herein are in United States dollars.

10.6 Severability. If any provision of this Agreement should be held invalid, illegal or unenforceable in any jurisdiction, the parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

10.7 Entire Agreement; Amendments. This Agreement, the Option Agreement, and the Collaboration Agreement (including any schedules, appendices and exhibits hereto or thereto and any certificates delivered hereunder) constitute the entire agreement between the parties hereto with respect to the subject matter hereof and thereof. There are no restrictions, promises, warranties or undertakings, other than those set forth or referred to herein or therein. This Agreement supersedes all prior agreements and understandings between the parties hereto with respect to the subject matter hereof. No provision of this Agreement may be waived or amended other than by an instrument in writing signed by the party to be charged with enforcement. Any amendment or waiver effected in accordance with this Section 10.7 shall be binding upon Purchaser and the Company.

10.8 Notices. All notices required or permitted hereunder will be in writing and will be deemed effectively given: (a) upon personal delivery to the party to be notified, (b) when sent by confirmed email if sent during normal business hours of the recipient, if not, then on the next Business Day, or (c) one Business Day after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. The addresses for such communications are:

If to the Company, to:

Bicycle Therapeutics plc
Building 900
Babraham Research Campus
Cambridge CB22 3AT, UK
Attention: General Counsel
Email: [***]

with a copy (which shall not constitute notice) to:

Cooley LLP
3175 Hanover Street
Palo Alto, CA 94304-1130
Attention: Laura Berezin
E-mail: lberezin@cooley.com

If to the Purchaser, to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Financial Officer
Email: [***]

With a copy (which shall not constitute notice) to:

Attention: General Counsel
Email: [***]

10.9 Successors and Assigns. This Agreement is binding upon and inures to the benefit of the parties and their successors and assigns. The Company will not assign this Agreement or any rights or obligations hereunder without the prior written consent of Purchaser, and Purchaser will not assign this Agreement or any rights or obligations hereunder without the prior written consent of the Company.

10.10 Third Party Beneficiaries. This Agreement is intended for the benefit of the parties hereto, their respective permitted successors and assigns, and is not for the benefit of, nor may any provision hereof be enforced by, any other Person.

10.11 Further Assurances. Each party will do and perform, or cause to be done and performed, all such further acts and things, and will execute and deliver all other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

10.12 No Strict Construction. The language used in this Agreement is deemed to be the language chosen by the parties to express their mutual intent, and no rules of strict construction will be applied against a party.

10.13 Equitable Relief. The Company recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at Law may prove to be inadequate relief to Purchaser. The Company therefore agrees that Purchaser is entitled to seek temporary and permanent injunctive relief or specific performance in any such case. Purchaser also recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at Law may prove to be inadequate relief to the Company. Purchaser therefore agrees that the Company is entitled to seek temporary and permanent injunctive relief or specific performance in any such case.

10.14 Expenses. The Company and Purchaser are each liable for, and will pay, their own expenses incurred in connection with the negotiation, preparation, execution and delivery of this Agreement, including attorneys' and consultants' fees and expenses.

10.15 Public Disclosure. On or shortly after the Effective Date, the Company and Purchaser shall issue a joint press release in a form mutually agreed to by the Company and Purchaser. In addition, the Company shall file a Current Report on Form 8-K with the SEC within the time period required by such form and including such disclosures as required by such form with respect to this Agreement and the transactions contemplated herein, such Current Report on Form 8-K to be in a form mutually agreed to by the Company and Purchaser. No other written release, public announcement, disclosure or filing concerning the purchase of the Shares, this Agreement or the transactions contemplated hereby or thereby shall be issued, filed or furnished, as the case may be, by any party without the prior written consent of the other party (which consent shall not be unreasonably withheld, conditioned or delayed) and, except as set forth in this Section 10.15, the parties agree to keep the terms of this Agreement confidential. Notwithstanding the foregoing, the parties acknowledge and agree that applicable Law or the requirements of a national securities exchange or another similar regulatory body may require either party to file or otherwise disclose a copy of this Agreement. The party required to make such filing or otherwise disclose shall notify the other party and shall, to the extent possible, provide the other party with at least five (5) Business Days to request redactions thereof prior to making such filing or disclosure. The disclosing party shall use commercially reasonable efforts to procure confidential treatment of such proposed redactions pursuant to the Securities Act and the Exchange Act, in each case as amended, and the rules, regulations and guidelines promulgated thereunder, or any other applicable Law or the rules, regulations or guidelines promulgated hereunder; *provided* that the foregoing shall not prevent the party from making such public disclosures as it must make to comply with applicable Law.

[Remainder of page intentionally left blank.]

In Witness Whereof, Purchaser and the Company have caused this Agreement to be duly executed as of the date first above written.

COMPANY:

Bicycle Therapeutics plc

By: _____

Name: _____

Title: _____

Purchaser:

Ionis Pharmaceuticals, Inc.

By: _____

Name: _____

Title: _____

[*Signature page to Share Purchase Agreement*]

APPENDIX 1

DEFINED TERMS

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity that directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with it. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities, capital stock or share capital (or such lesser percentage that is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***Agreement***" has the meaning set forth in the preamble.

"***American Depositary Shares***" shall mean shares issued by the Depositary pursuant to the Deposit Agreement, each representing one Ordinary Share.

"***Applicable Regulatory Authorities***" has the meaning set forth in Section 2.12.

"***BicycleTx***" has the meaning set forth in the recitals.

"***Board***" means the board of directors of the Company.

"***Business Day***" means a day Monday through Friday on which banks are generally open for business in the State of California, the State of New York and London, England.

"***Change of Control Transaction***" has the meaning set forth in Section 5.2.

"***Closing***" has the meaning set forth in Section 1.3(a).

"***Closing Cash***" has the meaning set forth in Section 1.1.

"***Closing Date***" means the date on which the Closing actually occurs.

"***Collaboration Agreement***" has the meaning set forth in the recitals.

"***Company Rights***" has the meaning set forth in Section 2.11(c).

"***Company Sale***" has the meaning set forth in Section 4.4.

"***Company Trials***" has the meaning set forth in Section 2.13.

"***Cross-Receipt***" has the meaning set forth in Section 1.3(b)(i)(A).

"***Deposit Agreement***" means the Deposit Agreement, dated as May 28, 2019, as amended from time to time, among the Company, the Depositary, and holders from time to time of the American Depositary Shares.

"***Depositary***" means mean Citibank, N.A.

"***Dispute***" has the meaning set forth in Section 8.1.

"***DOJ***" means the U.S. Department of Justice.

"***Exchange Act***" means the Securities Exchange Act of 1934, as amended, and the rules and regulations of the SEC thereunder.

"***Execution Date***" has the meaning set forth in the preamble.

"***Expiration Date***" has the meaning set forth in Section 7.5(c).

"***FDA***" has the meaning set forth in Section 2.12.

"***FTC***" means the U.S. Federal Trade Commission.

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

"Good Clinical Practices" means the legal, scientific and ethical standards for the performance of clinical research on medicinal products involving humans, including as reflected in the regulations of the FDA at 21 C.F.R. parts 50, 54, 56, and 312.

"Good Laboratory Practices" means the legal, scientific and ethical standards for the performance of nonclinical laboratory studies, including as set out in the regulations of the FDA at 21 C.F.R. part 58.

"***Governmental Authority***" means any federal, state, provincial, local, municipal, foreign or other governmental or quasi-governmental authority, including any arbitrator and applicable securities exchanges, or any department, minister, agency, commission, commissioner, board, subdivision, bureau, agency, instrumentality, court or other tribunal of any of the foregoing.

"***Health Care Laws***" means Title XVIII of the Social Security Act, 42 U.S.C. §§ 1395-1395lll (the Medicare statute); Title XIX of the Social Security Act, 42 U.S.C. §§ 1396-1396w-5 (the Medicaid statute); the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b); the civil False Claims Act, 31 U.S.C. §§ 3729 et seq.; the criminal False Claims Act 42 U.S.C. 1320a-7b(a); any other criminal laws relating to health care fraud and abuse, including but not limited to 18 U.S.C. Sections 286 and 287 and the health care fraud criminal provisions under the Health Insurance Portability and Accountability Act of 1996, 42 U.S.C. §§ 1320d et seq., ("***HIPAA***"); the Civil Monetary Penalties Law, 42 U.S.C. §§ 1320a-7a; the Physician Payments Sunshine Act, 42 U.S.C. § 1320a-7h; the Exclusion Laws, 42 U.S.C. § 1320a-7; HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, 42 U.S.C. §§ 17921 et seq.; the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 et seq.; the Public Health Service Act, 42 U.S.C. §§ 201 et seq.; the regulations promulgated pursuant to such laws; and any similar federal, state and local laws and regulations, each and all as may be amended from time to time.

"***HIPAA***" has the meaning set forth in the definition of "Health Care Laws."

"***IEC***" has the meaning set forth in Section 2.13.

"***Indemnified Party***" has the meaning set forth in Section 7.4(a).

"***Indemnifying Party***" has the meaning set forth in Section 7.4(a).

"***Intellectual Property***" shall mean trademarks, trade names, trade dress, service marks, copyrights, and similar rights (including registrations and applications to register or renew the registration of any of the foregoing), patents and patent applications, trade secrets, and any other similar intellectual property rights.

"***Intellectual Property License***" shall mean any license, permit, authorization, approval, contract or consent granted, issued by or with any Person relating to the use of Intellectual Property.

"***IRB***" has the meaning set forth in Section 2.13.

"***Law***" means any federal, state, local or foreign constitution, treaty, law, statute, ordinance, rule, regulation, interpretation, directive, policy, order, writ, decree, injunction, judgment, stay or restraining order of any Governmental Authority, the terms of any permit, and any other ruling or decision of, agreement with or by, or any other requirement of, any Governmental Authority.

"***Lien***" means any lien (statutory or otherwise), charge, security interest, pledge, mortgage, restriction on use or transfer, financing statement or similar encumbrance of any kind or nature whatsoever (including any conditional sale or other title retention agreement and any lease having substantially the same effect as any of the foregoing and any assignment or deposit arrangement in the nature of a security device).

"***Losses***" has the meaning set forth in Section 7.1.

"***Material Adverse Effect***" means any change, effect or circumstance, individually or in the aggregate, (a) that is reasonably likely to be materially adverse to the business, operations, assets or financial condition of the Company or Purchaser, as the case may be, taken as a whole, or (b) that materially impairs the ability of the Company or Purchaser to perform its obligations pursuant to the transactions contemplated by this Agreement or the Collaboration Agreement; *provided however*, that, none of the following (alone or when aggregated with any other effects), shall be deemed to be a Material Adverse Effect, and none of the following (alone or when aggregated with any other effects), shall be taken into account for purposes of clause (a) above: (A) (1) general market, economic or political conditions or (2) conditions (or any changes therein) in the industries in which the Company or Purchaser conducts business, in each case, including any acts of terrorism or war, weather conditions, global virus pandemics, epidemics or other force majeure events, in the case of each of clauses (1) and (2), solely to the extent that such effects do not have and are not reasonably likely to have a material disproportionate impact on the Company or Purchaser, as the case may be; (B) this Agreement, the Collaboration Agreement (including any amendments thereto), and the transactions contemplated hereby and thereby; or (C) changes in the trading price or volume of the American Depositary Shares or the Purchaser's ordinary shares, in and of themselves.

"***Nasdaq***" means The Nasdaq Global Select Market.

"***Option Agreement***" has the meaning set forth in the recitals.

"***Ordinary Shares***" has the meaning set forth in the recitals.

"***Purchaser***" has the meaning set forth in the preamble.

"***Permits***" has the meaning set forth in Section 2.10.

"***Person***" means a human being, labor organization, partnership, firm, enterprise, association, joint venture, corporation, limited liability company, cooperative, legal representative, foundation, society, political party, estate, trust, trustee, trustee in bankruptcy, receiver or any other organization or entity whatsoever, including any Governmental Authority.

"***Proprietary Rights***" has the meaning set forth in Section 2.11(c).

"***Purchase Price***" has the meaning set forth in Section 1.1.

"***Regulatory Authorizations***" has the meaning set forth in Section 2.12.

"***Rule 144***" has the meaning set forth in Section 5.1(a).

"***SEC***" means the United States Securities and Exchange Commission or any successor entity.

"***SEC Documents***" has the meaning set forth in Section 2.5(a).

"***Securities Act***" means the Securities Act of 1933, as amended, and the rules and regulations of the SEC thereunder.

"***Share Cap***" means a number of Ordinary Shares equal to 9.99% of the Ordinary Shares issued and outstanding on the Execution Date, rounded down to nearest number of Ordinary Shares.

"***Share Value***" means a price per Share (rounded to the nearest cent) equal to the product of (a) 1.3 and (b) the volume weighted average price per American Depositary Share as displayed under the heading "Bloomberg VWAP" on Bloomberg page "BCYC AQR" (or its equivalent successor if such page is not available) for a twenty (20) Trading Day period, starting with the scheduled opening of trading on the twentieth (20th) Trading Day prior to the date of the Purchaser's exercise of its option under the Option Agreement and ending with the scheduled close of trading of the primary trading session on the Trading Day prior to date of Purchaser's exercise of its option under the Option Agreement, as reported on Nasdaq.com, without regard to after-hours trading or any other trading outside of the regular trading session trading hours; *provided* that the Share Value shall in no event be lower than the Minimum Price (as defined in accordance with the rules and regulations of Nasdaq) on the Execution Date.

"***Shares***" has the meaning set forth in Section 1.1.

"***Standstill Period***" has the meaning set forth in Section 4.1.

"***Standstill Provisions***" has the meaning set forth in Section 4.4.

"***Tax***" means any federal, state, local, or foreign income, gross receipts, license, payroll, employment, excise, severance, stamp, occupation, premium, windfall profits, environmental (including taxes under Section 59A of the Internal Revenue Code of 1986, as amended), customs duties, capital stock, share capital, franchise, profits, withholding, social security (or similar), unemployment, disability, real property, personal property, sales, use, transfer, registration, value added, alternative or add-on minimum, estimated, or other tax of any kind whatsoever, including any interest, penalty, or addition thereto, whether disputed or not.

"***Termination Date***" has the meaning set forth in Section 9.1(d).

"Third Party" means any entity other than BicycleTx, the Company, the Purchaser or an Affiliate of BicycleTx, the Company, or the Purchaser.

"***Trading Day***" means a day on which Nasdaq is open for trading.

"***The Company***" has the meaning set forth in the preamble.]

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: November 3, 2021

/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: November 3, 2021

/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 September 30, 2021, 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: November 3, 2021

/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.