UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 2018

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 0-19125

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, CA	**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	Name of each exchange on which registered
Common Stock, $.001 Par Value	The Nasdaq Stock Market, LLC

Securities registered pursuant to Section 12(g) of the Act: **None**

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 and posted on its corporate Web site, if any, 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 and post 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. (Check one):

Large accelerated filer ☐	Accelerated filer ☒
Non-accelerated filer ☐ (Do not check if a smaller reporting company)	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 7(a)(2)(B) of the Securities 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 July 31, 2018 was 137,273,907.

IONIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

TRADEMARKS

"Ionis," the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this report are the property of Ionis Pharmaceuticals, Inc. "Akcea," the Akcea logo, and other trademarks or service marks appearing in this report, including TEGSEDI (inotersen) and WAYLIVRA (volanesorsen), are the property of Akcea Therapeutics, Inc. 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)

	June 30, 2018	December 31, 2017 (as revised*)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 805,490	$ 129,630
Short-term investments	1,174,960	893,085
Contracts receivable	16,761	62,955
Inventories	9,067	9,982
Other current assets	76,994	73,082
Total current assets	2,083,272	1,168,734
Property, plant and equipment, net	127,940	121,907
Patents, net	23,452	22,004
Deposits and other assets	12,651	10,129
Total assets	$ 2,247,315	$ 1,322,774
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 13,291	$ 24,886
Accrued compensation	15,089	25,151
Accrued liabilities	58,486	66,618
Current portion of long-term obligations	1,164	1,621
Current portion of deferred contract revenue	160,589	125,336
Total current liabilities	248,619	243,612
Long-term deferred contract revenue	556,586	108,026
1 percent convertible senior notes	550,328	533,111
Long-term obligations, less current portion	14,539	12,974
Long-term mortgage debt	59,807	59,771
Total liabilities	1,429,879	957,494
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 137,156,361 and 124,976,373 shares issued and outstanding at June 30, 2018 and December 31, 2017, respectively	137	125
Additional paid-in capital	2,011,561	1,553,681
Accumulated other comprehensive loss	(32,634)	(31,759)
Accumulated deficit	(1,282,809)	(1,241,034)
Total Ionis stockholders' equity	696,255	281,013
Noncontrolling interest in Akcea Therapeutics, Inc.	121,181	84,267
Total stockholders' equity	817,436	365,280
Total liabilities and stockholders' equity	$ 2,247,315	$ 1,322,774

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. 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 June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Revenue:		(as revised*)		(as revised*)
Commercial revenue:				
SPINRAZA royalties	$ 56,653	$ 22,366	$ 97,734	$ 27,577
Licensing and other royalty revenue	545	1,322	1,487	3,912
Total commercial revenue	57,198	23,688	99,221	31,489
Research and development revenue under collaborative agreements	60,549	88,585	162,944	196,584
Total revenue	117,747	112,273	262,165	228,073
Expenses:				
Research, development and patent	101,830	83,506	205,897	166,144
Selling, general and administrative	66,198	22,317	109,851	35,994
Total operating expenses	168,028	105,823	315,748	202,138
Income (loss) from operations	(50,281)	6,450	(53,583)	25,935
Other income (expense):				
Investment income	5,134	2,465	8,748	4,744
Interest expense	(11,113)	(11,778)	(22,051)	(23,141)
Other income (expenses)	45	—	(123)	(1,438)
Income (loss) before income tax expense	(56,215)	(2,863)	(67,009)	6,100
Income tax expense	(358)	(222)	(372)	(222)
Net income (loss)	(56,573)	(3,085)	(67,381)	5,878
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	16,215	—	25,606	—
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (40,358)	$ (3,085)	$ (41,775)	$ 5,878
Basic net income (loss) per share	$ (0.29)	$ (0.02)	$ (0.30)	$ 0.05
Shares used in computing basic net income (loss) per share	128,712	123,989	127,030	123,428
Diluted net income (loss) per share	$ (0.29)	$ (0.02)	$ (0.30)	$ 0.05
Shares used in computing diluted net income (loss) per share	128,712	123,989	127,030	125,511

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 2, *Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017 (as revised*)	2018	2017 (as revised*)
Net income (loss)	$ (56,573)	$ (3,085)	$ (67,381)	$ 5,878
Unrealized gains (losses) on debt securities, net of tax	563	130	(967)	396
Reclassification adjustment for realized gains included in net income (loss)	—	—	—	(374)
Currency translation adjustment	37	(42)	92	(36)
Comprehensive income (loss)	(55,973)	(2,997)	(68,256)	5,864
Comprehensive loss attributable to noncontrolling interests	16,237	—	25,659	—
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. stockholders	$ (39,736)	$ (2,997)	$ (42,597)	$ 5,864

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. 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)

	Six Months Ended June 30,	
	2018	**2017**
Operating activities:		**(as revised*)**
Net income (loss)	$ (67,381)	$ 5,878
Adjustments to reconcile net income (loss) to net cash provided by operating activities:		
Depreciation	4,858	3,990
Amortization of patents	895	802
Amortization of premium on investments, net	1,845	3,558
Amortization of debt issuance costs	853	797
Amortization of convertible senior notes discount	16,364	15,163
Amortization of long-term financing liability for leased facility	—	3,352
Stock-based compensation expense	62,327	42,170
Gain on investment in Regulus Therapeutics, Inc.	—	(374)
Non-cash losses related to patents, licensing and property, plant and equipment	415	129
Changes in operating assets and liabilities:		
Contracts receivable	46,193	57,428
Inventories	915	985
Other current and long-term assets	(5,177)	(39,371)
Accounts payable	(14,239)	(10,030)
Accrued compensation	(10,062)	(13,888)
Accrued liabilities and deferred rent	(8,218)	(1,149)
Deferred contract revenue	483,814	55,588
Net cash provided by operating activities	513,402	125,028
Investing activities:		
Purchases of short-term investments	(648,902)	(347,916)
Proceeds from the sale of short-term investments	364,048	202,475
Purchases of property, plant and equipment	(8,977)	(9,453)
Acquisition of licenses and other assets, net	(1,854)	(1,593)
Proceeds from the sale of Regulus Therapeutics stock	—	2,507
Net cash used in investing activities	(295,685)	(153,980)
Financing activities:		
Proceeds from equity awards	10,178	9,927
Proceeds from the issuance of common stock to Novartis	—	71,640
Proceeds from the issuance of common stock to Biogen	447,965	—
Stock issuance costs paid	—	(1,031)
Principal payments on debt and capital lease obligations	—	(3,278)
Net cash provided by financing activities	458,143	77,258
Net increase in cash and cash equivalents	675,860	48,306
Cash and cash equivalents at beginning of period	129,630	84,685
Cash and cash equivalents at end of period	$ 805,490	$ 132,991
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,753	$ 3,607
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 2,645	$ 1,705
Unpaid deferred offering costs	$ —	$ 473

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. 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 six months ended June 30, 2018 and 2017 on the same basis as the audited financial statements for the year ended December 31, 2017. 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. Results for the interim periods are not necessarily indicative of the results 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, 2017 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In the condensed consolidated financial statements, we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our majority owned affiliate, Akcea Therapeutics, Inc., which we formed in December 2014. Prior to Akcea's initial public offering, or IPO, in July 2017, we owned 100 percent of Akcea. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In April 2018, we received eight million shares of Akcea's stock when we licensed TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea and we purchased an additional 10.7 million shares of Akcea's stock for $200 million, increasing our ownership percentage to approximately 75 percent. We reflected this increase in our ownership percentage in these financial statements. In August 2018, we received an additional 1.6 million shares of Akcea's stock when TEGSEDI received marketing authorization in the European Union, or EU. Refer to the section titled "Noncontrolling Interest in Akcea" in Note 2, *Significant Accounting Policies*, for further information related to our accounting for our investment in Akcea.

Unless the context requires otherwise, "Ionis", "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals, Inc. and its majority owned affiliate, Akcea Therapeutics, Inc.

2. Significant Accounting Policies

Revenue Recognition

Adoption of New Revenue Recognition Accounting Standard (Topic 606)

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. This guidance supersedes the revenue recognition requirements we previously followed in Accounting Standards Codification, or ASC, Topic 605, *Revenue Recognition*, or Topic 605, and created a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. Under Topic 606, an entity will recognize revenue when it transfers control of promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. Further, an entity will recognize revenue upon satisfying the performance obligation(s) under the related contract. We adopted Topic 606 on January 1, 2018 under the full retrospective approach, which required us to revise our prior period revenue. Under Topic 606, we were required to review all of our ongoing collaboration agreements in which we recognized revenue after January 1, 2016. We were required to assess what our revenue would have been for the period from January 1, 2016 to December 31, 2017 under Topic 606. As a result of this analysis, we determined that the cumulative revenue we would have recognized under Topic 606 decreased by $53.6 million. We recorded this amount as a cumulative adjustment to our accumulated deficit as of December 31, 2017. We have labeled our prior period financial statements "as revised" to indicate the change required under the accounting rules.

The following tables summarize the adjustments we were required to make to amounts we originally reported in 2017 to adopt Topic 606 (in thousands, except per share amounts):

Condensed Consolidated Balance Sheet

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred revenue	$ 72,708	$ 35,318	$ 108,026
Accumulated deficit	$ (1,187,398)	$ (53,636)	$ (1,241,034)
Noncontrolling interest in Akcea Therapeutics, Inc.	$ 87,847	$ (3,580)	$ 84,267
Total stockholders' equity	$ 418,719	$ (53,439)	$ 365,280

Condensed Consolidated Statement of Operations

	Three Months Ended June 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 22,366	$ —	$ 22,366
Licensing and other royalty revenue	557	765	1,322
Total commercial revenue	22,923	765	23,688
Research and development revenue under collaborative agreements	81,229	7,356	88,585
Total revenue	$ 104,152	$ 8,121	$ 112,273
Income (loss) from operations	$ (1,671)	$ 8,121	$ 6,450
Net income (loss)	$ (11,206)	$ 8,121	$ (3,085)
Net income (loss) per share, basic and diluted	$ (0.09)	$ 0.07	$ (0.02)

	Six Months Ended June 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 27,577	$ —	$ 27,577
Licensing and other royalty revenue	4,103	(191)	3,912
Total commercial revenue	31,680	(191)	31,489
Research and development revenue under collaborative agreements	182,776	13,808	196,584
Total revenue	$ 214,456	$ 13,617	$ 228,073
Income from operations	$ 12,318	$ 13,617	$ 25,935
Net income (loss)	$ (7,739)	$ 13,617	$ 5,878
Net income (loss) per share, basic and diluted	$ (0.06)	$ 0.11	$ 0.05

Condensed Consolidated Statement of Cash Flows

	Six Months Ended June 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (7,739)	$ 13,617	$ 5,878
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Deferred contract revenue	$ 69,205	$ (13,617)	$ 55,588
Cash and cash equivalents at beginning of period	$ 84,685	$ —	$ 84,685
Cash and cash equivalents at end of period	$ 132,991	$ —	$ 132,991

During the three and six months ended June 30, 2017, our revenue increased $8.1 million and $13.6 million, respectively, under Topic 606, compared to Topic 605. The change in our revenue was primarily due to:

- A change in how we recognize milestone payments: Topic 606 requires us to amortize more of the milestone payments we achieve, rather than recognizing the milestone payments in full in the period in which we achieved the milestone event as we did under Topic 605. This change resulted in an increase of $17.1 million and $27.3 million for the three and six months ended June 30, 2018, respectively.

- A change in how we calculate revenue for payments we are recognizing into revenue over time: Under Topic 605, we amortized payments into revenue evenly over the period of our obligations. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. Each period, we will review our "inputs" such as our level of effort expended or costs incurred relative to the total expected inputs to satisfy the performance obligation. For certain collaborations, such as Novartis and Bayer, the input method resulted in a change to the revenue we had previously recognized using a straight-line amortization method. This change resulted in a decrease of $9.7 million and $13.5 million for the three and six months ended June 30, 2018, respectively.

Our updated revenue recognition policy reflecting Topic 606 is as follows:

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. As a result of the EU's approval of TEGSEDI, we expect to add product sales from TEGSEDI to our commercial revenue this year. We will further increase our commercial revenue if TEGSEDI is approved in additional markets and from WAYLIVRA, assuming it is approved. We will also recognize future sales milestone payments and royalties we earn under our partnerships as commercial revenue.

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.

Our collaboration agreements are detailed in Note 6, *Collaborative Arrangements and Licensing Agreements.* Under each collaboration note we discuss our specific revenue recognition conclusions, including our significant performance obligations under each collaboration.

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 is probable.

2. Identify the performance obligations

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

Often times when we enter into a collaboration agreement in which we provide our partner with an option to license a drug 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 drug in the future or to provide additional goods and services as requested by our partner are not material rights. These items are contingent upon future events that may not occur. When a partner exercises its option to license a drug 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 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. 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.

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 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 on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- 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 number of internal hours we estimate 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.

We do not reallocate the transaction price after the start of an agreement to reflect subsequent changes in stand-alone selling prices.

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 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 will recognize each period. The approach requires numerous estimates and 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 in the period in which the counterparty sells the related product, which in certain cases may require us to estimate our royalty revenue. We recognize royalties from SPINRAZA sales in the period Biogen records the sale of SPINRAZA. Our accounting for SPINRAZA royalties did not change as a result of adopting Topic 606.

Research and development revenue under collaboration agreements:

Upfront Payments

When we enter into a collaboration agreement with 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 new SMA collaboration with Biogen, we received a $25 million upfront payment in December 2017. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $25 million upfront payment using an input method over the estimated period of time we are providing R&D services. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion. Under Topic 605, we amortized upfront payments evenly over the period of our obligation.

Milestone Payments

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the third quarter of 2017, we initiated a Phase 1/2a clinical study of IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease. We earned a $10 million milestone payment from Biogen related to the initiation of this study. Under Topic 606, we allocated this payment to our R&D services performance obligation. We are recognizing revenue from this milestone payment over our estimated period of performance. Under Topic 605, this milestone payment was recognized in full in the third quarter of 2017, which was the period in which we achieved the milestone event.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event. For example, in the second quarter of 2017, we earned a $50 million milestone payment from Biogen for the EU approval of SPINRAZA. Our revenue recognition of milestone payments we earn based on our partners' activities did not change as a result of adopting Topic 606.

License Fees

We generally recognize as revenue the total amount we determine to be the 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. Our recognition of license fees did not change as a result of adopting Topic 606.

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 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 at their standalone 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 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 IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, 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*, for further discussion of our accounting treatment for our Bayer collaboration. Our allocation of the consideration we received for the Bayer amendment did not change as a result of adopting Topic 606. However, the method in which we are recognizing revenue related to our R&D services performance obligation did change. We are amortizing revenue related to our R&D services performance obligation using the input method under Topic 606.

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. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the 2018 strategic neurology collaboration with Biogen.

Contracts Receivable

Our contracts receivable balance represents the amounts we have billed our partners for goods we have delivered or services we have performed that are due to us unconditionally. When we bill our partners with payment terms based on the passage of time, we consider the contract receivable to be unconditional. We typically receive payment within one quarter of billing our partner. Our contracts receivable balance as of December 31, 2017 did not change when we adopted Topic 606.

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. Our unbilled SPINRAZA royalties as of December 31, 2017 did not change when we adopted Topic 606.

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 and six months ended June 30, 2018, we recognized $33.3 million and $62.0 million of revenue from amounts that were in our beginning deferred revenue balances for those periods, respectively. During the three and six months ended June 30, 2017, we recognized $35.5 million and $60.0 million of revenue from amounts that were in our beginning deferred revenue balances for those periods, respectively. Refer to our revenue recognition policy above detailing how we recognize revenue for further discussion.

The following table summarizes the adjustments we were required to make to our deferred revenue amounts to adopt Topic 606 (in thousands):

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred revenue	72,708	35,318	108,026
Total deferred revenue	$ 179,173	$ 54,189	$ 233,362

Our deferred revenue balance increased $54.2 million at December 31, 2017 under Topic 606, compared to Topic 605. The increase was primarily related to the change in the accounting for certain milestone payments and the way in which we amortize payments. Under Topic 605, we previously recognized the majority of the milestone payments we earned in the period we achieved the milestone event, which did not impact our deferred revenue balance. Under Topic 606 we are now amortizing more milestone payments over the period of our performance obligation, which adds to our deferred revenue balance. Additionally, under Topic 605 we amortized payments evenly over the period of our obligation. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. The increase in deferred revenue relates to agreements with the following partners:

- $24.2 million from Biogen;
- $15.9 million from AstraZeneca;
- $11.8 from Novartis; and
- $2.3 million from other partners.

Noncontrolling Interest in Akcea Therapeutics, Inc.

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In April 2018, we received eight million shares of Akcea's stock when we licensed TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea and we purchased an additional 10.7 million shares of Akcea's stock for $200 million, increasing our ownership percentage to approximately 75 percent. We reflected this increase in our ownership percentage in these financial statements as an adjustment to noncontrolling interest. In August 2018, we received an additional 1.6 million shares of Akcea's stock when TEGSEDI was approved in the EU. The shares third parties own represent an interest in Akcea's equity that is not controlled by us. However, as we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our condensed consolidated balance sheet. In addition, we record a noncontrolling interest adjustment to account for the stock options Akcea grants, which if exercised, will dilute our ownership in Akcea. This adjustment is a reclassification within stockholders' equity from additional paid-in capital to noncontrolling interest in Akcea equal to the amount of stock-based compensation expense Akcea had recognized.

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. We use the specific identification method to determine the cost of securities sold.

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At June 30, 2018, we held an equity investment in one publicly held company, Antisense Therapeutics Limited, or ATL. We also held equity investments in four privately-held companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science CO.

In January 2018, we adopted the amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires us to measure and record our equity investments at fair value. Additionally, the amended accounting guidance requires us to recognize the changes in fair value in our consolidated statement of operations, instead of through accumulated other comprehensive income. Prior to 2018, we accounted for our equity investments in privately held companies under the cost method of accounting. Under the amended guidance 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. Our adoption of this guidance did not have an impact on our results.

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs 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 drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we begin to manufacture API for a particular drug. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs. We did not record any inventory write-offs for the six months ended June 30, 2018 and 2017. Total inventory was $9.1 million and $10.0 million as of June 30, 2018 and December 31, 2017, respectively.

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 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 United States 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. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs acquired from third parties, 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

The preparation of condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States requires 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 those estimates.

Basic and diluted net income (loss) per share

Basic net income (loss per share)

We compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period.

The calculation of total net income (loss) attributable to our common stockholders for the three and six months ended June 30, 2018 considered our net income for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. For the three and six months ended June 30, 2017, we owned 100 percent of Akcea. As a result, we did not have to adjust our basic earnings (loss) per share calculation.

Our basic net loss per share for the three months ended June 30, 2018, was calculated as follows (in thousands, except per share amounts):

Three months ended June 30, 2018	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Income (Loss) Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	60,832	$ (0.72)	$ (43,814)
Akcea's net loss attributable to our ownership			$ (43,814)
Ionis' stand-alone net income			5,882
Net loss available to Ionis common stockholders			$ (37,932)
Weighted average shares outstanding			128,712
Basic net loss per share			$ (0.29)

Our basic net loss per share for the six months ended June 30, 2018, was calculated as follows (in thousands, except per share amounts):

Six months ended June 30, 2018	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Income (Loss) Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	53,183	$ (1.19)	$ (63,198)
Akcea's net loss attributable to our ownership			$ (63,198)
Ionis' stand-alone net income			24,668
Net income available to Ionis common stockholders			$ (38,530)
Weighted average shares outstanding			127,030
Basic net loss per share			$ (0.30)

Dilutive net income (loss per share)

For the three and six months ended June 30, 2018 and for the three months ended June 30, 2017, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 1 percent convertible senior notes;
- 2¾ percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

For the six months ended June 30, 2017, we had net income available to Ionis common stockholders. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during those periods. Diluted common equivalent shares for the six months ended June 30, 2017 consisted of the following (in thousands except per share amounts):

Six months ended June 30, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 5,878	123,428	$ 0.05
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,659	
Shares issuable upon restricted stock award issuance	—	401	
Shares issuable related to our ESPP	—	23	
Income available to Ionis common stockholders, plus assumed conversions	$ 5,878	125,511	$ 0.05

For the six months ended June 30, 2017, the calculation excluded the 1 percent and 2¾ percent notes because the effect on diluted earnings per share was anti-dilutive.

Accumulated other comprehensive loss

We include unrealized gains and losses on investments, net of taxes, in accumulated other comprehensive income (loss) along with adjustments we make to reclassify realized gains and losses on investments from other accumulated comprehensive income (loss) to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income (loss) for the three and six months ended June 30, 2018 and 2017 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Beginning balance accumulated other comprehensive loss	$ (33,234)	$ (30,460)	$ (31,759)	$ (30,358)
Unrealized gains (losses) on securities (1)	563	130	(967)	396
Amounts reclassified from accumulated other comprehensive loss	—	—	—	(374)
Currency translation adjustment	37	(42)	92	(36)
Net current period other comprehensive income (loss)	600	88	(875)	(14)
Ending balance accumulated other comprehensive loss	$ (32,634)	$ (30,372)	$ (32,634)	$ (30,372)

(1) There was no income tax expense or benefit related to elements of other comprehensive income (loss) for the three and six months ended June 30, 2018 and 2017.

Convertible debt

We account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component, and the associated non-cash interest expense.

We assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing our debt issuance costs and debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method.

Segment information

We have two operating segments, our Ionis Core segment and Akcea Therapeutics. Akcea is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with rare and serious diseases. We provide segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We allocate a portion of Ionis' development, R&D support expenses and general and administrative expenses to Akcea for work we perform on behalf of Akcea.

Stock-based compensation expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, 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. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. For the six months ended June 30, 2018 and 2017, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2018	**2017**
Risk-free interest rate	2.3%	1.8%
Dividend yield	0.0%	0.0%
Volatility	63.1%	66.1%
Expected life	4.6 years	4.5 years

ESPP:

	Six Months Ended June 30,	
	2018	**2017**
Risk-free interest rate	1.6%	0.7%
Dividend yield	0.0%	0.0%
Volatility	44.4%	66.5%
Expected life	6 months	6 months

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four-year period. The weighted-average grant date fair value of RSUs granted to employees for the six months ended June 30, 2018 was $52.83 per share.

We did not grant stock options or RSUs to our Board of Directors during the six months ended June 30, 2018 or 2017.

The following table summarizes stock-based compensation expense for the three and six months ended June 30, 2018 and 2017 (in thousands). Our consolidated non-cash stock-based compensation expense includes $12.1 million and $3.9 million of stock-based compensation expense for Akcea for the three months ended June 30, 2018 and 2017, respectively, and $18.5 million and $7.1 million for the six months ended June 30, 2018 and 2017, respectively.

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	**2017**	**2018**	**2017**
Research, development and patent	$ 19,236	$ 16,140	$ 38,918	$ 32,262
Selling, general and administrative	14,640	5,118	23,409	9,908
Total non-cash stock-based compensation expense	$ 33,876	$ 21,258	$ 62,327	$ 42,170

As of June 30, 2018, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $151.8 million and $33.6 million, respectively. We will adjust total unrecognized compensation cost for future forfeitures. We expect to recognize the cost of non-cash stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.4 years and 1.7 years, respectively.

Impact of recently issued accounting standards

In February 2016, the FASB issued amended accounting guidance related to lease accounting, which will require us to record all leases with a term longer than one year on our balance sheet. When we record leases on our balance sheet under the new guidance, we will record a liability with a value equal to the present value of payments we will make over the life of the lease and an asset representing the underlying leased asset. The new accounting guidance requires us to determine if our leases are operating or financing leases. We will record expense for operating leases on a straight-line basis as an operating expense. If we determine a lease is a financing lease, we will record both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease. The new lease standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted. We will adopt this guidance on January 1, 2019. We can choose from two methods of adoption. The first method requires us to reflect our leases on our balance sheet in the earliest comparative period presented in our financial statements. The second method requires us to reflect the impact of adoption on the date we adopt the new guidance and recognize a cumulative-effect adjustment to the opening balance of our accumulated deficit in that period. We are currently determining the method we will use to adopt the new guidance and assessing the effects the new guidance will have on our consolidated financial statements and disclosures.

In June 2016, the FASB issued guidance that changes the measurement of credit losses for most financial assets and certain other instruments. If we have credit losses, this updated guidance requires us to record allowances for these instruments under a new expected credit loss model. This model requires us to estimate the expected credit loss of an instrument over its lifetime, which represents the portion of the amortized cost basis we do not expect to collect. The new guidance requires us to remeasure our allowance in each reporting period we have credit losses. The new standard is effective for annual and interim periods beginning after December 15, 2019. Early adoption is permitted for periods beginning after December 15, 2018. When we adopt the new standard, we will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. We plan to adopt this guidance on January 1, 2020. We are currently assessing the effects it will have on our consolidated financial statements and disclosures.

In December 2017, the SEC staff issued guidance to address how companies should account for the Tax Act of 2017, or the Tax Act, when an entity does not have the necessary information to complete the accounting for the Tax Act and gives entities up to one year from the enactment of the Tax Act to finalize their amounts. We recognized provisional amounts in our 2017 financial statements and in these financial statements. The ultimate impact may differ materially from these provisional amounts due to, among other things, additional analysis, changes in our interpretations and assumptions, additional regulatory guidance that may be issued, and other actions we may take resulting from the Tax Act. We will assess and update our provisional amounts and disclosures, as necessary, throughout the remainder of 2018.

In February 2018, the FASB issued updated guidance for reclassification of tax effects from accumulated other comprehensive income (loss). The updated guidance gives entities an option to reclassify amounts included in accumulated other comprehensive income (loss) that under the Tax Act do not have a way to be relieved, and allows a one-time reclassification to retained earnings. The updated guidance is effective for all entities for fiscal years beginning after December 31, 2018, and interim periods within those fiscal years. Early adoption is permitted, and adoption is optional. We are currently assessing the effects this updated guidance could have on our consolidated financial statements and timing of potential adoption.

In June 2018, the FASB issued updated guidance to simplify the accounting for stock-based compensation expense for nonemployees. Specifically, we are now expensing grants to nonemployees in a similar manner as grants to employees. Previously, we had to re-value these grants at each reporting period to reflect the current fair value. Under the amended guidance, we value grants to nonemployees when we grant them and we will not adjust their value for future changes. We adopted this guidance in the second quarter of 2018. The updated guidance did not have a material impact to our financial results.

3. Investments

As of June 30, 2018, we had invested our excess cash primarily in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or S&P, or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of June 30, 2018:

One year or less	81%
After one year but within two years	16%
After two years but within three and a half years	3%
Total	100%

As illustrated above, at June 30, 2018, 97 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.

At June 30, 2018, we had an ownership interest of less than 20 percent in four private companies and one public company with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science CO. The publicly-traded company is Antisense Therapeutics Limited.

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

		Gross Unrealized		
June 30, 2018	**Cost** (1)	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities:				
Corporate debt securities (2)	$ 747,172	$ 2	$ (1,210)	$ 745,964
Debt securities issued by U.S. government agencies	137,915	5	(233)	137,687
Debt securities issued by the U.S. Treasury (2)	138,778	7	(34)	138,751
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	29,414	—	(190)	29,224
Total securities with a maturity of one year or less	1,053,279	14	(1,667)	1,051,626
Corporate debt securities	199,673	28	(1,607)	198,094
Debt securities issued by U.S. government agencies	3,986	—	(72)	3,914
Debt securities issued by states of the U.S. and political subdivisions of the states	48,766	—	(749)	48,017
Total securities with a maturity of more than one year	252,425	28	(2,428)	250,025
Total available-for-sale securities	$ 1,305,704	$ 42	$ (4,095)	$ 1,301,651

		Gross Unrealized		
December 31, 2017	**Cost** (1)	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities:				
Corporate debt securities	$ 500,599	$ 2	$ (752)	$ 499,849
Debt securities issued by U.S. government agencies	83,926	—	(212)	83,714
Debt securities issued by the U.S. Treasury	29,428	—	(17)	29,411
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	29,240	4	(122)	29,122
Total securities with a maturity of one year or less	643,193	6	(1,103)	642,096
Corporate debt securities	148,663	8	(1,059)	147,612
Debt securities issued by U.S. government agencies	52,779	—	(168)	52,611
Debt securities issued by the U.S. Treasury	1,409	—	(2)	1,407
Debt securities issued by states of the U.S. and political subdivisions of the states	65,550	—	(740)	64,810
Total securities with a maturity of more than one year	268,401	8	(1,969)	266,440
Total available-for-sale securities	$ 911,594	$ 14	$ (3,072)	$ 908,536

(1) Our available-for-sale securities are held at amortized cost.

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

Investments we consider to be temporarily impaired at June 30, 2018 were as follows (in thousands):

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	**Estimated Fair Value**	**Unrealized Losses**	**Estimated Fair Value**	**Unrealized Losses**	**Estimated Fair Value**	**Unrealized Losses**
Corporate debt securities	543	$ 841,374	$ (2,060)	$ 61,915	$ (757)	$ 903,289	$ (2,817)
Debt securities issued by U.S. government agencies	44	106,489	(296)	19,141	(9)	125,630	(305)
Debt securities issued by the U.S. Treasury	8	63,634	(34)	—	—	63,634	(34)
Debt securities issued by states of the U.S. and political subdivisions of the states	50	42,933	(514)	33,968	(425)	76,901	(939)
Total temporarily impaired securities	645	$ 1,054,430	$ (2,904)	$ 115,024	$ (1,191)	$ 1,169,454	$ (4,095)

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.

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 the majority 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. During the six months ended June 30, 2018, there were no transfers between our Level 1 and Level 2 investments. When we recognize transfers between levels of the fair value hierarchy, we recognize the transfer on the date the event or change in circumstances that caused the transfer occurs.

The following tables present the major security types we held at June 30, 2018 and December 31, 2017 that are regularly measured and carried at fair value. At June 30, 2018 and December 31, 2017, we did not have any financial instruments that we valued using Level 3 inputs. The tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At June 30, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 635,795	$ 635,795	$ —
Corporate debt securities (2)	944,058	—	944,058
Debt securities issued by U.S. government agencies (3)	141,601	—	141,601
Debt securities issued by the U.S. Treasury (3)	138,751	138,751	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	77,241	—	77,241
Total	$ 1,937,446	$ 774,546	$ 1,162,900

	At December 31, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 86,262	$ 86,262	$ —
Corporate debt securities (3)	647,461	—	647,461
Debt securities issued by U.S. government agencies (3)	136,325	—	136,325
Debt securities issued by the U.S. Treasury (3)	30,818	30,818	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	93,932	—	93,932
Total	$ 994,798	$ 117,080	$ 877,718

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

(2) At June 30, 2018, $95.4 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(3) Included in short-term investments on our condensed consolidated balance sheet.

(4) At December 31, 2017, $3.5 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

Other Fair Value Disclosures

Novartis Future Stock Purchase

In January 2017, we and Akcea entered into a SPA with Novartis. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or our common stock at a premium if an IPO did not occur by April 2018. Therefore, at the inception of the SPA, we recorded a $5.0 million asset representing the fair value of the potential future premium we could have received if Novartis purchased our common stock. We determined the fair value of the future premium by calculating the value based on the stated premium in the SPA and estimating the probability of an Akcea IPO. We also included a lack of marketability discount when we determined the fair value of the premium because we would have issued unregistered shares to Novartis if they had purchased our common stock. We measured this asset using Level 3 inputs and recorded it in other assets on our consolidated balance sheet. Because Akcea completed its IPO before April 2018, Novartis did not purchase additional shares of Ionis stock. Therefore, we wrote-off the remaining balance to other expenses in the third quarter of 2017 because this asset no longer had any value.

The following is a reconciliation of the potential premium we would have received if Akcea had not completed its IPO, measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the six months ended June 30, 2017 (in thousands):

Beginning balance of Level 3 instruments at January 1, 2017	$ —
Value of the potential premium we would have received from Novartis at inception of the SPA (January 2017)	5,035
Recurring fair value adjustment during the six months ended June 30, 2017	(1,438)
Ending balance of Level 3 instruments at June 30, 2017	$ 3,597

Convertible Notes

Our 1 percent notes had a fair value of $671.7 million at June 30, 2018. 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. Long-Term Obligations

Line of Credit Arrangement

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, we can borrow up to a maximum of $30 million of revolving credit for general working capital purposes. Under the credit agreement interest is payable monthly in arrears on the outstanding principal at a borrowing rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of June 30, 2018 we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which we used to fund our capital equipment needs consistent with our historical practice to finance these costs.

The credit agreement includes customary affirmative and negative covenants and restrictions. We are in compliance with all covenants of the credit agreement.

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million. We also purchased our manufacturing facility in July 2017 for $14.0 million. We financed the purchase of our primary R&D facility and our manufacturing facility, with mortgage debt of $51.3 million and $9.1 million, respectively. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility 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.

6. Collaborative Arrangements and Licensing Agreements

Below, we have included all of our significant collaborations because we adopted Topic 606 on January 1, 2018. We have included new disclosures for each of our collaborations as required under Topic 606.

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 drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved drug to treat people with spinal muscular atrophy, or SMA. In December 2017, we entered into a collaboration with Biogen to identify new antisense drugs for the treatment of SMA. Additionally, we and Biogen are currently developing six other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$ for ALS, IONIS-MAPT$_{Rx}$ for Alzheimer's disease, IONIS-C9$_{Rx}$ for ALS, and IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. Most recently, in April 2018, we entered into a new strategic collaboration for the treatment of neurological diseases with Biogen. From inception through June 2018, we have received over $1.8 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 when we entered into the 2018 strategic neurology collaboration.

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. In December 2016, the FDA approved SPINRAZA for the treatment of SMA in pediatric and adult patients.

From inception through June 2018, we earned $647 million in total revenue under our SPINRAZA collaboration, including $211 million in revenue from SPINRAZA royalties and $436 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on any sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on sales of SPINRAZA. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

Over the course of our SPINRAZA collaboration, we identified two performance obligations, which were to perform R&D services and to deliver the SPINRAZA license to Biogen. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance through December 2016. We recognized the $75 million license fee for SPINRAZA as revenue when we delivered the license to Biogen in July 2016 because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen.

We also earned additional milestone payments that we recognized in full in the period each milestone payment became probable because we did not have a performance obligation related to each milestone payment. For example, we received $90 million of milestone payments for the approval of SPINRAZA in the EU and Japan in 2017 and recognized the full amounts into revenue in the period Biogen achieved the milestone events.

Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurodegenerative diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-MAPT$_{Rx}$ for Alzheimer's disease under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities and costs for that drug.

Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. The $210 million per program consists of up to $10 million in development milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales of any drugs resulting from each of the three programs. From inception through June 2018, we have received $58 million in milestone payments and upfront fees under this collaboration. We will achieve the next payment of $7.5 million if we continue to advance IONIS-MAPT$_{Rx}$.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $30 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in December 2020. From inception through June 2018, we have included $40 million in total payments in the transaction price for our R&D services performance obligation.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs Biogen is pursuing under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs after Phase 2 proof of concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities and costs for that drug. We are currently advancing five drugs, IONIS-SOD1$_{Rx}$, IONIS-C9$_{Rx}$, IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ under this collaboration. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and milestone payments per program. The $260 million per program consists of approximately $60 million in development milestones, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any antisense drugs developed under this collaboration. If Biogen chooses to advance drugs using other modalities, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in milestone payments per program. The $90 million per program consists of up to $35 million in development milestone payments and up to $55 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered single-digit royalties on sales from any drugs using non-antisense modalities developed under this collaboration. From inception through June 2018, we have received over $170 million in upfront fees, milestone payments and other payments under this collaboration, including $15 million in milestone payments we received in 2017 for validating two undisclosed neurological disease targets. We will achieve the next payment of up to $10 million if we advance a program under this collaboration.

At the commencement of our strategic neurology collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $100 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in September 2019. From inception through June 2018, we have included $145 million in total payments in the transaction price for our R&D services performance obligation.

New antisense drugs for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense drugs for the treatment of SMA. Biogen will have the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for all further global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in December 2017. We will receive development and regulatory milestone payments from Biogen if new drugs advance towards marketing approval. In total over the term of our collaboration, we are eligible to receive up to $1.2 billion in license fees, milestone payments and other payments, including up to $80 million for the achievement of development milestones, up to $180 million for the achievement of commercialization milestones and up to $800 million for the achievement of sales milestones. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales. We will achieve the next payment of up to $60 millionfor the license of a drug under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined the transaction price to be the $25 million upfront payment we received when we entered into the collaboration. We allocated the transaction price to our single performance obligation. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in December 2020.

2018 Strategic Neurology Collaboration

In April 2018, we and Biogen entered into a new strategic collaboration to develop novel antisense drugs for a broad range of neurological diseases and entered into a SPA. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for these diseases for 10 years. We are responsible for the identification of antisense drug candidates based on selected targets, while Biogen will have the option to license therapies arising out of this collaboration and will be responsible for and pay for non-clinical studies, clinical development, manufacturing, and commercialization.

In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at a 25 percent cash premium and $375 million in an upfront payment. We are eligible to receive up to $270 million for each drug that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales. We will achieve the next payment of $7.5 million if Biogen designates a target under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined our transaction price to be $552 million, comprised of $375 million from the upfront payment and $177 million for the premium paid by Biogen for its purchase of our common stock. We determined the fair value of the premium we received by using the stated premium in the SPA and applying a lack of marketability discount. We included a lack of marketability discount in our valuation of the premium because Biogen received restricted shares. We allocated the transaction price to our single performance obligation. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in June 2028.

During the three and six months ended June 30, 2018 and 2017, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
SPINRAZA royalties (commercial revenue)	$ 56.7	$ 22.4	$ 97.7	$ 27.6
R&D revenue	21.3	58.8	32.2	82.2
Total revenue from our relationship with Biogen	78.0	81.2	129.9	109.8
Percentage of total revenue	66%	72%	50%	48%

Our condensed consolidated balance sheet at June 30, 2018 and December 31, 2017 included deferred revenue of $618.3 million and $93.6 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

AstraZeneca

Cardiac, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiac, renal and metabolic diseases. Under our collaboration AstraZeneca has licensed three drugs from us. As part of the agreement, we granted AstraZeneca an exclusive license to IONIS-AZ4-2.5-L_{Rx}, a drug we designed to treat cardiovascular disease and our first drug that combines our Generation 2.5 and LIgand-Conjugated Antisense, or LICA, technology. We also granted AstraZeneca the option to license a drug for each additional target advanced under this research collaboration. In February 2018, AstraZeneca licensed a second drug under our collaboration, IONIS-AZ5-2.5$_{Rx}$, a drug we designed to treat a genetically associated form of kidney disease. In March 2018, AstraZeneca licensed a third drug under our collaboration, IONIS-AZ6-2.5-L_{Rx}, a drug we designed to inhibit an undisclosed target to treat patients with nonalcoholic steatohepatitis, or NASH. AstraZeneca is responsible for all further global development, regulatory and commercialization activities and costs for IONIS-AZ4-2.5-L_{Rx}, IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L_{Rx} and any other future drugs AstraZeneca licenses.

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $4 billion as drugs under this collaboration advance, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through June 2018, we have received over $155 million in upfront fees, license fees, milestone payments, and other payments under this collaboration. We will achieve the next payment of $10 million under this collaboration if we advance a drug under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for AstraZeneca. We determined the transaction price to be the $65 million upfront payment we received and we allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy this performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy this performance obligation in August 2021. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. From inception through June 2018, we have included $90 million in payments in the transaction price for our R&D services performance obligation.

We identified separate performance obligations upon AstraZeneca's license of IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L_{Rx} in the first quarter of 2018 because the licenses are distinct from our other performance obligation and each other. We recognized each $30 million license fee in the first quarter of 2018 because AstraZeneca had full use of the licenses without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the licenses after we delivered them to AstraZeneca.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs to treat cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize danvatirsen (formerly IONIS-STAT3-2.5$_{Rx}$) for the treatment of cancer. AstraZeneca is now responsible for all global development, regulatory and commercialization activities for danvatirsen. We and AstraZeneca have evaluated danvatirsen in people with head and neck cancer, advanced lymphoma and advanced metastatic hepatocellular carcinoma. AstraZeneca is evaluating danvatirsen in combination with Imfinzi (durvalumab), AstraZeneca's programmed death ligand, or PD-L1, blocking drug, in people with head and neck cancer, advanced lymphoma, metastatic bladder cancer and metastatic non-small cell lung cancer. In addition, we and AstraZeneca established an oncology research program. AstraZeneca has the option to license drugs resulting from the program, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities and costs for such drug. The first drug identified under the anti-cancer research program was IONIS-KRAS-2.5$_{Rx}$, which AstraZeneca licensed from us in December 2016. IONIS-KRAS-2.5$_{Rx}$ is a Generation 2.5 antisense drug we designed to directly target KRAS, one of the most frequently mutated genes in cancer.

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. If AstraZeneca successfully develops danvatirsen, IONIS-KRAS-2.5$_{Rx}$ and another drug under the research program, we could receive license fees and milestone payments of up to more than $750 million, including up to $226 million for the achievement of development milestones and up to $485 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low to mid-teens on sales from any drugs resulting from these programs. From inception through June 2018, we have received $97.8 million in upfront fees, milestone payments, and other payments under this oncology collaboration. We will achieve the next payment of up to $17.5 million if we advance a drug under our cancer research program with AstraZeneca.

At the commencement of this collaboration, we identified four performance obligations. We determined the transaction price to be the $31 million in upfront payments we received. We allocated the transaction price based on the estimated stand-alone selling price of each of our performance obligations and recognized the associated revenue over the period of our performance. We recognized revenue for three of our obligations over our period of performance, concluding in March 2014. Our remaining performance obligation was to perform R&D services. We allocated $7.6 million to this performance obligation and recognized the associated revenue over the period of our performance, which ended in February 2018. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation.

We identified a new performance obligation upon AstraZeneca's license of IONIS-KRAS-2.5$_{Rx}$ in December 2016 because the license we granted AstraZeneca was distinct from our other performance obligations. We recognized the $13 million license fee for IONIS-KRAS-2.5$_{Rx}$ in December 2016 because AstraZeneca had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to AstraZeneca.

During the three and six months ended June 30, 2018 and 2017, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
R&D revenue	$ 3.9	$ 5.0	$ 72.3	$ 9.9
Percentage of total revenue	3%	4%	28%	4%

Our condensed consolidated balance sheet at June 30, 2018 and December 31, 2017 included deferred revenue of $48.1 million and $57.7 million, respectively, related to our relationship with AstraZeneca.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. We were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis. Under the terms of the agreement, we received a $100 million upfront payment in the second quarter of 2015. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. In conjunction with the decision to advance these programs, we received a $75 million payment from Bayer. We are conducting a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to develop IONIS-FXI-L$_{Rx}$ through Phase 1. Following these studies and Bayer's decision to further advance these programs, Bayer will be responsible for all global development, regulatory and commercialization activities and costs for both drugs.

We are eligible to receive additional milestone payments as each drug advances toward the market. In total over the term of this collaboration, we are eligible to receive up to $385 million in license fees, milestone payments and other payments, including up to $125 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both drugs combined. From inception through June 2018, we have received over $175 million from our Bayer collaboration. We will achieve the next payment of $10 million if a program advances under this collaboration.

At the commencement of this collaboration, we identified three performance obligations. We determined the transaction price to be the $100 million in upfront payment we received. We allocated the transaction price based on the relative stand-alone selling prices of each of our performance obligations and recognized the associated revenue as follows:

- We recognized $91.2 million for the exclusive license of IONIS-FXI$_{Rx}$ in May 2015 because Bayer had full use of the license without any continuing involvement from us.
- We recognized $4.3 million for the R&D services for IONIS-FXI$_{Rx}$ over the period of our performance, which ended in November 2016.
- We allocated $4.5 million for API, which we are recognizing into revenue as we deliver the API.

In February 2017, when we amended our collaboration with Bayer, we identified two new performance obligations, one for the license of IONIS-FXI-L$_{Rx}$ and one for R&D services. We determined the transaction price to be the $75 million payment. We allocated $64.9 million to the license of IONIS-FXI-L$_{Rx}$ based on its estimated stand-alone selling price and recognized the associated revenue upon our delivery of the license in the first quarter of 2017. We allocated $10.1 million to our R&D services performance obligation based on an estimated stand-alone selling price. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our R&D services performance obligation in May 2019.

During the three and six months ended June 30, 2018 and 2017, we earned the following revenue from our relationship with Bayer (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
R&D revenue	$ 0.8	$ 0.4	$ 1.5	$ 65.6
Percentage of total revenue	1%	0%	1%	29%

Our condensed consolidated balance sheet at June 30, 2018 and December 31, 2017 included deferred revenue of $7.8 million and $9.3 million, respectively, related to our relationship with Bayer.

Janssen Biotech, Inc.

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the gastrointestinal tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under the terms of the agreement, we received $35 million in upfront payments. We are eligible to receive up to more than $800 million in license fees and milestone payments for these programs, including up to $175 million for the achievement of development milestones, up to $440 million for the achievement of regulatory milestones and up to $180 million for the achievement of commercialization milestones. From inception through June 2018, we have received $72 million, including $15 million in license fees when Janssen licensed IONIS-JBI1-2.5$_{Rx}$ and IONIS-JBI2-2.5$_{Rx}$ from us in 2016 and 2017, respectively. We also received $5 million in January 2018 for the initiation of a Phase 1 study of IONIS-JBI1-2.5$_{Rx}$ in late 2017. In addition, we are eligible to receive tiered royalties up to the near teens on sales from any drugs resulting from this collaboration. We will achieve the next payment of $5 million if Janssen continues to advance a target under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Janssen. We determined the transaction price to be the $35 million upfront payments we received. We allocated the $35 million to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, through November 2017.

We identified separate performance obligations each time Janssen licensed one of our drugs under our collaboration because the licenses we granted to Janssen were distinct from our other performance obligations. We recognized the $10 million license fee for IONIS-JBI1-2.5$_{Rx}$ in July 2016 and $5 million for the license of IONIS-JBI2-2.5$_{Rx}$ in November 2017, because Janssen had full use of the licenses without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the licenses after we delivered them to Janssen.

During the three and six months ended June 30, 2018 and 2017, we earned the following revenue from our relationship with Janssen (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
R&D revenue	$ 5.5	$ 12.2	$ 5.7	$ 14.7
Percentage of total revenue	5%	11%	2%	6%

We did not have any deferred revenue from our relationship with Janssen at June 30, 2018 or December 31, 2017.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease, or HD, based on our antisense technology. Roche had the option to license the drugs from us through the completion of the first Phase 1 trial. Under the agreement, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We evaluated a drug targeting HTT, IONIS-HTT$_{Rx}$, in a Phase 1/2a clinical study in people with early stage HD.

In December 2017, upon completion of the Phase 1/2a study, Roche exercised its option to license IONIS-HTT$_{Rx}$ and is now responsible for the global development, regulatory and commercialization activities for IONIS-HTT$_{Rx}$. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013. In December 2016, we updated development activities for IONIS-HTT$_{Rx}$ and as a result we were eligible for an additional $3 million payment, which we achieved in 2017. We are eligible to receive up to $365 million in a license fee and milestone payments including up to $70 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on any sales of any product resulting from this alliance. From inception through June 2018, we have received over $107 million in upfront fees, milestone payments and license fees for advancing IONIS-HTT$_{Rx}$, including the $45 million license fee we received in January 2018 for IONIS-HTT$_{Rx}$. We will achieve the next payment of $10 million if Roche initiates a Phase 2 trial for IONIS-HTT$_{Rx}$.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the $30 million upfront payment we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, through September 2017.

We identified a second performance obligation upon Roche's license of IONIS-HTT_{Rx} in the fourth quarter of 2017 because the license we granted to Roche is distinct from our other performance obligation. We recognized the $45 million license fee for IONIS-HTT_{Rx} as revenue at that time because Roche had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Roche.

We do not have any remaining performance obligations under our collaboration with Roche, however we can still earn additional payments and royalties as Roche advances IONIS-HTT_{Rx}.

During the three and six months ended June 30, 2018 and 2017, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
R&D revenue	$ 1.7	$ 2.9	$ 3.6	$ 1.4
Percentage of total revenue	1%	3%	1%	1%

During the first quarter of 2017, we recorded a reversal of revenue of $1.6 million, related to our updated estimate of our performance period for our R&D services. We did not have any deferred revenue from our relationship with Roche at June 30, 2018 or December 31, 2017.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Under the terms of the agreement, we received upfront payments of $35 million.

GSK is advancing two drugs targeting hepatitis B virus, or HBV, under our collaboration: IONIS-HBV_{Rx} and IONIS-HBV-L_{Rx}. GSK is currently conducting Phase 2 studies for both of these drugs, which we designed to reduce the production of viral proteins associated with HBV infection. In March 2016, we and GSK amended the development plan for IONIS-HBV_{Rx} to allow GSK to conduct all further development activities for this program. GSK has the exclusive option to license the drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee.

Under our agreement, if GSK successfully develops these drugs and achieves pre-agreed sales targets, we could receive license fees and milestone payments of $262 million, including up to $47.5 million for the achievement of development milestones, up to $120 million for the achievement of regulatory milestones and up to $70 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance. From inception through June 2018, we have received more than $162 million in payments under this alliance with GSK. We will achieve the next payment of $15 million if GSK initiates a Phase 3 study for the HBV program.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for GSK. We determined the transaction price to be the $35 million upfront payment we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, through March 2015. We do not have any remaining performance obligations under our collaboration with GSK, however we can still earn additional payments and royalties as GSK advances these drugs.

During the three and six months ended June 30, 2018 and 2017, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
R&D revenue	$ 1.3	$ 3.0	$ 1.4	$ 9.8
Percentage of total revenue	1%	3%	1%	4%

We did not have any deferred revenue from our relationship with GSK at June 30, 2018 or December 31, 2017.

Akcea Collaborations

The following collaboration agreements relate to Akcea, our majority owned affiliate. Our consolidated results include all the revenue earned and cash received under these collaboration agreements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our condensed consolidated balance sheet.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Novartis has an exclusive option to further develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and providing initial quantities of API for each drug. If Novartis exercises an option for one of these drugs, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such drug.

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it retained $60 million and paid us $15 million as a sublicense fee. If Novartis exercises its option for a drug, Novartis will pay Akcea a license fee equal to $150 million for each drug it licenses. In addition, for AKCEA-APO(a)-L_{Rx}, Akcea is eligible to receive up to $600 million in milestone payments, including $25 million for the achievement of a development milestone, up to $290 million for the achievement of regulatory milestones and up to $285 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx}, Akcea is eligible to receive up to $530 million in milestone payments, including $25 million for the achievement of a development milestone, up to $240 million for the achievement of regulatory milestones and up to $265 million for the achievement of commercialization milestones. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee. Akcea plans to co-commercialize any licensed drug commercialized by Novartis in selected markets under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize WAYLIVRA (volanesorsen).

In conjunction with this collaboration, we and Akcea entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for $100 million in the first quarter of 2017. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or our common stock at a premium if an IPO did not occur by April 2018.

At the commencement of this collaboration, we identified four separate performance obligations:

- R&D services for AKCEA-APO(a)-L_{Rx};
- R&D services for AKCEA-APOCIII-L_{Rx};
- API for AKCEA-APO(a)-L_{Rx}; and
- API for AKCEA-APOCIII-L_{Rx}.

We determined that the R&D services for each drug and the API for each drug were distinct from our other performance obligations.

We determined our transaction price to be $108.4 million, comprised of the following:

- $75 million from the upfront payment;
- $28.4 million for the premium paid by Novartis for its purchase of our common stock at a premium in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future.

We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $64.0 million for the R&D services for AKCEA-APO(a)-L_{Rx};
- $40.1 million for the R&D services for AKCEA-APOCIII-L_{Rx};
- $1.5 million for the delivery of AKCEA-APO(a)-L_{Rx} API; and
- $2.8 million for the delivery of AKCEA-APOCIII-L_{Rx} API.

We are recognizing revenue related to the R&D services for the AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} performance obligations based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy the significant portion of our performance obligation for AKCEA-APO(a)-L_{Rx} by December 2018 with the remainder by the end of March 2019. We currently estimate we will satisfy the significant portion of our performance obligation for AKCEA-APOCIII-L_{Rx} by June 2019 with the remainder by the end of December 2019. We recognized the amount attributed to the API supply for AKCEA-APO(a)-L_{Rx} when we delivered it to Novartis in 2017. We recognized the amount attributed to the API supply for AKCEA-APOCIII-L_{Rx} when we delivered it to Novartis in May 2018.

Akcea is responsible for the development activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations, and we recognize all of Akcea's revenue in our consolidated results. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue on our stand-alone Ionis results and Akcea recognizes the fees as R&D expense. Any cash Akcea receives is included in our consolidated balance sheet. In our consolidated results, we eliminate this sublicense revenue and expense.

During the three and six months ended June 30, 2018 and 2017, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
R&D revenue	$ 18.3	$ 5.7	$ 35.4	$ 11.8
Percentage of total revenue	16%	5%	14%	5%

Our condensed consolidated balance sheet at June 30, 2018 and December 31, 2017 included deferred revenue of $41.6 million and $70.7 million, respectively, related to our relationship with Novartis.

PTC Therapeutics

In August 2018, Akcea entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Under the license agreement, Akcea will receive an $18 million upfront payment, $12 million which is due in the third quarter of 2018 and $6 million which will be paid on the earlier of FDA or EMA approval of WAYLIVRA. Akcea has the potential to earn $8 million of additional regulatory milestone payments for the approval of each drug. Akcea will receive royalties from PTC in the mid-20 percent range on net sales in Latin America for each drug. PTC's obligation to pay Akcea royalties begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC recognizes revenue of at least $10 million in Latin America. Consistent with the agreements between Ionis and Akcea, the companies will share all payments, including royalties.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics. Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In April 2018, we received eight million shares of Akcea's stock when we licensed TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea and we purchased an additional 10.7 million shares of Akcea's stock for $200 million, increasing our ownership percentage to approximately 75 percent. In August 2018, we received an additional 1.6 million shares of Akcea's stock when TEGSEDI was approved in the EU. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting our antisense technology to generate a broad pipeline of first-in-class and/or best-in-class drugs for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with rare and serious diseases.

The following tables show our segment revenue and income (loss) from operations for the three and six months ended June 30, 2018 and 2017 (in thousands), respectively.

Three Months Ended June 30, 2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 56,653	$ —	$ —	$ 56,653
Licensing and other royalty revenue	545	—	—	545
Total commercial revenue	57,198	—	—	57,198
R&D revenue under collaborative agreements	42,228	18,321	—	60,549
Total segment revenue	$ 99,426	$ 18,321	$ —	$ 117,747
Total operating expenses	$ 85,875	$ 81,744	$ 409	$ 168,028
Income (loss) from operations	$ 13,551	$ (63,423)	$ (409)	$ (50,281)

Three Months Ended June 30, 2017 (as revised)	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 22,366	$ —	$ —	$ 22,366
Licensing and other royalty revenue	1,322	—	—	1,322
Total commercial revenue	23,688	—	—	23,688
R&D revenue under collaborative agreements	85,802	5,713	(2,930)	88,585
Total segment revenue	$ 109,490	$ 5,713	$ (2,930)	$ 112,273
Total operating expenses	$ 83,381	$ 25,402	$ (2,960)	$ 105,823
Income (loss) from operations	$ 26,109	$ (19,689)	$ 30	$ 6,450

Six Months Ended June 30, 2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 97,734	$ —	$ —	$ 97,734
Licensing and other royalty revenue	1,487	—	—	1,487
Total commercial revenue	99,221	—	—	99,221
R&D revenue under collaborative agreements	132,744	35,429	(5,229)	162,944
Total segment revenue	$ 231,965	$ 35,429	$ (5,229)	$ 262,165
Total operating expenses	$ 191,419	$ 129,179	$ (4,850)	$ 315,748
Income (loss) from operations	$ 40,546	$ (93,750)	$ (379)	$ (53,583)

Six Months Ended June 30, 2017 (as revised)	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 27,577	$ —	$ —	$ 27,577
Licensing and other royalty revenue	3,912	—	—	3,912
Total commercial revenue	31,489	—	—	31,489
R&D revenue under collaborative agreements	239,184	11,807	(54,407)	196,584
Total segment revenue	$ 270,673	$ 11,807	$ (54,407)	$ 228,073
Total operating expenses	$ 161,733	$ 94,872	$ (54,467)	$ 202,138
Income (loss) from operations	$ 108,940	$ (83,065)	$ 60	$ 25,935

The following table shows our total assets by segment at June 30, 2018 and December 31, 2017 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
June 30, 2018	$ 2,351,098	$ 395,005	$ (498,788)	$ 2,247,315
December 31, 2017 (as revised)	$ 1,342,578	$ 268,804	$ (288,608)	$ 1,322,774

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as ten percent or more of our total revenue, was as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017 (as revised)	2018	2017 (as revised)
Partner A	66 %	72 %	50 %	48 %
Partner B	16 %	5 %	14 %	5 %
Partner C	3 %	4 %	28 %	4 %
Partner D	5 %	11 %	2 %	6 %
Partner E	1%	0%	1%	29%

Contracts receivables from four significant partners comprised approximately 92 percent of our contracts receivables at June 30, 2018. Contracts receivables from two significant partners comprised approximately 84 percent of our contracts receivables at December 31, 2017.

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 majority owned affiliate, Akcea Therapeutics, Inc.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA, TEGSEDI, WAYLIVRA and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority owned affiliate. 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, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. 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. 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. These and other risks concerning our programs are described in additional detail in our annual report on Form 10-K for the year ended December 31, 2017, 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.

Overview

We are leaders in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics. Using this platform, we have developed a large, diverse and advanced pipeline of potentially first-in-class and/or best-in-class drugs that we believe can provide high value for patients with significant unmet medical needs. In this way, we believe we are fundamentally changing medicine with the goal to transform the lives of those suffering from severe, often life-threatening, diseases.

We made significant progress toward this goal with the commercial launch of SPINRAZA for the treatment of SMA in pediatric and adult patients. SMA is a leading genetic cause of death in infants marked by progressive, debilitating muscle weakness. SPINRAZA became the first and only approved drug to treat people with SMA and is now the standard of care for this debilitating disease. Our partner, Biogen, is responsible for global commercial activities. Since regulatory approval in December 2016, we have earned $211 million in commercial revenue from SPINRAZA royalties.

In July 2018, TEGSEDI (inotersen) received marking authorization approval from the European Commission, or EC, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR, making it the first RNA-targeted therapeutic approved for patients with hATTR. TEGSEDI is currently under regulatory review for marketing authorization in the U.S. and Canada. The Food and Drug Administration, or FDA, set a PDUFA date of October 6, 2018 for TEGSEDI. Launch activities are underway in Europe. Akcea expects to launch first in Germany after the summer holidays. We believe TEGSEDI has the potential to become the preferred treatment option for many people with hATTR. Our goal is to free these people from the burden of their disease. hATTR is a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body. We licensed TEGSEDI to Akcea, our majority owned affiliate, focused on developing and commercializing drugs to treat patients with rare and serious diseases. By licensing TEGSEDI to Akcea, we believe we will maximize the commercial potential of TEGSEDI, while optimizing our commercial participation. We estimate that there are approximately 50,000 patients globally with hATTR, the majority of which have symptoms of polyneuropathy. Additionally, we and Akcea are continuing to build our TTR franchise by moving AKCEA-TTR-L_{Rx} forward rapidly to address the larger patient population, which includes hereditary and wild-type ATTR patients.

Akcea is also working closely with us to develop WAYLIVRA to treat two severe and rare, genetically defined diseases, familial chylomicronemia syndrome, or FCS, and familial partial lipodystrophy, or FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. We estimate that FCS and FPL each affect 3,000 to 5,000 people globally. The clinical development program for WAYLIVRA consists of three Phase 3 studies called APPROACH, BROADEN and COMPASS. In the first quarter of 2017, we and Akcea reported positive Phase 3 data from the APPROACH study in patients with FCS. In December 2016, we and Akcea reported positive results from the Phase 3 COMPASS study in patients with triglycerides above 500 mg/dL. Based on the positive data from these Phase 3 studies, Akcea filed for marketing authorization for WAYLIVRA in the U.S., EU and Canada in the third quarter of 2017. The FDA set a PDUFA date of August 30, 2018 for WAYLIVRA. In May 2018, an FDA advisory committee voted in favor of WAYLIVRA for the treatment of FCS. Akcea is prepared to launch WAYLIVRA this year, assuming approval.

In addition to commercializing TEGSEDI and preparing to commercialize WAYLIVRA, Akcea is focused on developing their other clinical-stage drugs: AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx}, each of which could potentially treat multiple patient populations. Moving these drugs into Akcea allows us to retain substantial value from them and ensures our core focus remains on innovation. As of August 2018, we owned approximately 75 percent of Akcea.

We are addressing a broad spectrum of diseases that affect millions of people, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease. We also are addressing rare diseases, such as acromegaly, amyotrophic lateral sclerosis, beta-thalassemia and Huntington's disease. We anticipate at least four drugs will enter pivotal studies before the end of 2019, representing our next wave of commercial opportunities, including IONIS-HTT_{Rx}, for patients with Huntington's disease, danvatirsen for patients with head and neck cancer, AKCEA-TTR-L_{Rx}, our LICA version of TEGSEDI for patients with all forms of TTR amyloidosis and AKCEA-APO(a)-L_{Rx} for patients with high Lp(a) who are at risk for cardiovascular disease. We are also focusing on our Ionis-owned drugs that have the potential to move quickly toward the market, including IONIS-GHR-L_{Rx} for patients with acromegaly and IONIS-TMPRSS6-L_{Rx} for people with beta thalassemia.

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our products. Our partners bring substantial resources and expertise that augment and build upon our internal capabilities. We have a strategic partnership with Biogen through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas.

In April 2018, we and Biogen entered into a new strategic collaboration to develop novel antisense drug candidates for a broad range of neurological diseases. We received $1 billion from Biogen, comprised of $625 million to purchase our stock at a 25 percent cash premium and $375 million in an upfront payment. We believe this collaboration provides us with the opportunity to continue to build a strong pipeline for Biogen and for our own account. We also have partnerships with AstraZeneca, Bayer, GSK, Janssen, Novartis and Roche. Each of these companies brings significant expertise and global resources to develop and potentially commercialize the drugs under these partnerships. Lastly, we also work with a group of companies that can develop our drugs and utilize our technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Through our partnerships, we have created a broad and sustaining base of research and development, or R&D, revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Moreover, we have the potential to earn more than $20 billion in future milestone payments and licensing fees from our current partnerships. In late 2016, we began adding commercial revenue from SPINRAZA royalties to our existing R&D revenue base. Looking forward, we have the potential to increase our commercial revenue from SPINRAZA royalties from the continued growth we expect in the U.S., EU and in other markets globally. As a result of the EU's approval of TEGSEDI, we expect to add product sales from TEGSEDI to our commercial revenue this year. We will further increase our commercial revenue if TEGSEDI is approved in additional markets and from WAYLIVRA, assuming it is approved. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through royalties, which can further increase our commercial revenue.

Financial Highlights

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Total revenue	$ 117,747	$ 112,273	$ 262,165	$ 228,073
Total operating expenses	$ 168,028	$ 105,823	$ 315,748	$ 202,138
Income (loss) from operations	$ (50,281)	$ 6,450	$ (53,583)	$ 25,935
Net income (loss)	$ (56,573)	$ (3,085)	$ (67,381)	$ 5,878
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (40,358)	$ (3,085)	$ (41,775)	$ 5,878

Our revenue for the six months ended June 30, 2018 was $262 million and increased compared to the same period in 2017, primarily from increased commercial revenue from SPINRAZA royalties. In addition to revenue from SPINRAZA, we plan to add product revenue from TEGSEDI and WAYLIVRA this year, assuming WAYLIVRA is approved.

Our operating expenses for the six months ended June 30, 2018 were $316 million and increased compared to $202 million for the same period in 2017. The increase in operating expenses was primarily due to higher SG&A expenses as we prepare to commercialize TEGSEDI and WAYLIVRA in 2018. Our SG&A expenses also increased in the first half of 2018 compared to 2017 because of fees we owed under our in-licensing agreements related to SPINRAZA. As sales for SPINRAZA grow, our in-licensing expenses also increase but not at the same rate. We earn tiered royalties on annual SPINRAZA sales and pay nominal fixed third-party royalties that are not tiered. R&D expenses accounted for a smaller portion of the increase in operating expenses. R&D expenses increased primarily from increases in medical affairs expenses and drug development costs related to several drugs including AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. These increases reflect the investment we are making in advancing and expanding our pipeline. As this year progresses, we expect our operating expenses to continue to increase primarily related to the commercialization of TEGSEDI and WAYLIVRA.

During the first half of 2018, we received more than $1.2 billion in payments from our partners, primarily from Biogen for our 2018 strategic neurology collaboration to develop novel antisense drugs for a broad range of neurological diseases.

Recent Events

Business Highlights *(Q2 2018 and subsequent activities)*

- *TEGSEDI – approved in the EU for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)*
  - On track for post-summer launch in the EU
  - On track for approval and launch in the U.S. in 2018
  - License agreement with PTC Therapeutics accelerates access to TEGSEDI in Latin America
  - Results from the TEGSEDI pivotal study published in the *New England Journal of Medicine*
  - Akcea's commercial organization staffed; patient support program and supply chain in place

- *WAYLIVRA – potential first treatment for people with FCS*
  - U.S. FDA Division of Metabolism and Endocrinology Products Advisory Committee voted in favor of approving WAYLIVRA
  - On track for approval and launch in the U.S. and EU in 2018
  - License agreement with PTC Therapeutics accelerates access to WAYLIVRA in Latin America
  - Akcea's commercial organization staffed; patient support program and supply chain in place

- *SPINRAZA – the first and only approved treatment for people with SMA*
  - SPINRAZA, commercialized by Biogen, continues to generate growth, with global sales of $423 million in the second quarter of 2018, a 250 percent increase from the second quarter of 2017
  - 10 percent of adults with SMA in the U.S. are currently on SPINRAZA treatment, a 20 percent increase from last quarter. Adult patients represent 60 percent of the U.S. SMA patient population
  - More than 5,000 people with SMA are now on SPINRAZA, representing a 28 percent increase from last quarter
  - Access outside the U.S. is expanding with reimbursement in 24 countries; Biogen expects reimbursement in at least four more countries by the end of 2018

Pipeline Progress

- EU granted PRIME designation to IONIS-HTT_{Rx} (RG6042), potentially providing accelerated assessment for the treatment of people with Huntington's disease
- European Medicines Agency granted Orphan Drug Designation to IONIS-$MAPT_{Rx}$ for the treatment of people with frontotemporal dementia
- We earned a $7.5 million milestone payment when the FDA approved Achaogen's ZEMDRI™ (plazomicin) for the treatment of people with complicated urinary tract infections

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments require us to make 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 our audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating the impact of the Tax Act and our net deferred income tax asset valuation allowance;
- Determining the fair value of convertible debt without the conversion feature; and
- Valuing premiums received under our collaborations

These critical accounting policies and estimates are included in our Annual Report on Form 10-K for the year ended December 31, 2017 in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations.”

In the first quarter of 2018, we updated the following critical accounting policy:

- Assessing the propriety of revenue recognition and associated deferred revenue.

Our updated critical accounting policy is as follows:

Revenue Recognition

Adoption of New Revenue Recognition Accounting Standard (Topic 606)

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. This guidance supersedes the revenue recognition requirements we previously followed in Accounting Standards Codification, or ASC, Topic 605, *Revenue Recognition*, or Topic 605, and created a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. Under Topic 606, an entity will recognize revenue when it transfers control of promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. Further, an entity will recognize revenue upon satisfying the performance obligation(s) under the related contract. We adopted Topic 606 on January 1, 2018 under the full retrospective approach, which required us to revise our prior period revenue. Under Topic 606, we were required to review all of our ongoing collaboration agreements in which we recognized revenue after January 1, 2016. We were required to assess what our revenue would have been for the period from January 1, 2016 to December 31, 2017 under Topic 606. As a result of this analysis, we determined that the cumulative revenue we would have recognized under Topic 606 decreased by $53.6 million. We recorded this amount as a cumulative adjustment to our accumulated deficit as of December 31, 2017. We have labeled our prior period financial statements “as revised” to indicate the change required under the accounting rules.

The following tables summarize the adjustments we were required to make to amounts we originally reported in 2017 to adopt Topic 606 (in thousands, except per share amounts):

Condensed Consolidated Balance Sheet

	At December 31, 2017		
	As Previously Reported under Topic 605	**Topic 606 Adjustment**	**As Revised**
Current portion of deferred revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred revenue	$ 72,708	$ 35,318	$ 108,026
Accumulated deficit	$ (1,187,398)	$ (53,636)	$ (1,241,034)
Noncontrolling interest in Akcea Therapeutics, Inc.	$ 87,847	$ (3,580)	$ 84,267
Total stockholders’ equity	$ 418,719	$ (53,439)	$ 365,280

Condensed Consolidated Statement of Operations

	Three Months Ended June 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 22,366	$ —	$ 22,366
Licensing and other royalty revenue	557	765	1,322
Total commercial revenue	22,923	765	23,688
Research and development revenue under collaborative agreements	81,229	7,356	88,585
Total revenue	$ 104,152	$ 8,121	$ 112,273
Income (loss) from operations	$ (1,671)	$ 8,121	$ 6,450
Net income (loss)	$ (11,206)	$ 8,121	$ (3,085)
Net income (loss) per share, basic and diluted	$ (0.09)	$ 0.07	$ (0.02)

	Six Months Ended June 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 27,577	$ —	$ 27,577
Licensing and other royalty revenue	4,103	(191)	3,912
Total commercial revenue	31,680	(191)	31,489
Research and development revenue under collaborative agreements	182,776	13,808	196,584
Total revenue	$ 214,456	$ 13,617	$ 228,073
Income from operations	$ 12,318	$ 13,617	$ 25,935
Net income (loss)	$ (7,739)	$ 13,617	$ 5,878
Net income (loss) per share, basic and diluted	$ (0.06)	$ 0.11	$ 0.05

Condensed Consolidated Statement of Cash Flows

	Six Months Ended June 30, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (7,739)	$ 13,617	$ 5,878
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Deferred contract revenue	$ 69,205	$ (13,617)	$ 55,588
Cash and cash equivalents at beginning of period	$ 84,685	$ —	$ 84,685
Cash and cash equivalents at end of period	$ 132,991	$ —	$ 132,991

During the three and six months ended June 30, 2017, our revenue increased $8.1 million and $13.6 million, respectively, under Topic 606, compared to Topic 605. The change in our revenue was primarily due to:

- A change in how we recognize milestone payments: Topic 606 requires us to amortize more of the milestone payments we achieve, rather than recognizing the milestone payments in full in the period in which we achieved the milestone event as we did under Topic 605. This change resulted in an increase of $17.1 million and $27.3 million for the three and six months ended June 30, 2018, respectively.

- A change in how we calculate revenue for payments we are recognizing into revenue over time: Under Topic 605, we amortized payments into revenue evenly over the period of our obligations. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. Each period, we will review our “inputs” such as our level of effort expended or costs incurred relative to the total expected inputs to satisfy the performance obligation. For certain collaborations, such as Novartis and Bayer, the input method resulted in a change to the revenue we had previously recognized using a straight-line amortization method. This change resulted in a decrease of $9.7 million and $13.5 million for the three and six months ended June 30, 2018, respectively.

Our updated revenue recognition policy reflecting Topic 606 is as follows:

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. As a result of the EU's approval of TEGSEDI, we expect to add product sales from TEGSEDI to our commercial revenue this year. We will further increase our commercial revenue if TEGSEDI is approved in additional markets and from WAYLIVRA, assuming it is approved. We will also recognize future sales milestone payments and royalties we earn under our partnerships as commercial revenue.

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.

Our collaboration agreements are detailed in Note 6, *Collaborative Arrangements and Licensing Agreements.* Under each collaboration note we discuss our specific revenue recognition conclusions, including our significant performance obligations under each collaboration.

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 is probable.

2. Identify the performance obligations

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

Often times when we enter into a collaboration agreement in which we provide our partner with an option to license a drug 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 drug in the future or to provide additional goods and services as requested by our partner are not material rights. These items are contingent upon future events that may not occur. When a partner exercises its option to license a drug 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 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. 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.

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 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 on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- 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 number of internal hours we estimate 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.

We do not reallocate the transaction price after the start of an agreement to reflect subsequent changes in stand-alone selling prices.

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 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 will recognize each period. The approach requires numerous estimates and 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 in the period in which the counterparty sells the related product, which in certain cases may require us to estimate our royalty revenue. We recognize royalties from SPINRAZA sales in the period Biogen records the sale of SPINRAZA. Our accounting for SPINRAZA royalties did not change as a result of adopting Topic 606.

Research and development revenue under collaboration agreements:

Upfront Payments

When we enter into a collaboration agreement with 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 new SMA collaboration with Biogen, we received a $25 million upfront payment in December 2017. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $25 million upfront payment using an input method over the estimated period of time we are providing R&D services. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion. Under Topic 605, we amortized upfront payments evenly over the period of our obligation.

Milestone Payments

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the third quarter of 2017, we initiated a Phase 1/2a clinical study of IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease. We earned a $10 million milestone payment from Biogen related to the initiation of this study. Under Topic 606, we allocated this payment to our R&D services performance obligation. We are recognizing revenue from this milestone payment over our estimated period of performance. Under Topic 605, this milestone payment was recognized in full in the third quarter of 2017, which was the period in which we achieved the milestone event.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event. For example, in the second quarter of 2017, we earned a $50 million milestone payment from Biogen for the EU approval of SPINRAZA. Our revenue recognition of milestone payments we earn based on our partners' activities did not change as a result of adopting Topic 606.

License Fees

We generally recognize as revenue the total amount we determine to be the 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. Our recognition of license fees did not change as a result of adopting Topic 606.

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 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 at their standalone 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 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 IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, 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*, for further discussion of our accounting treatment for our Bayer collaboration. Our allocation of the consideration we received for the Bayer amendment did not change as a result of adopting Topic 606. However, the method in which we are recognizing revenue related to our R&D services performance obligation did change. We are amortizing revenue related to our R&D services performance obligation using the input method under Topic 606.

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. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the 2018 strategic neurology collaboration with Biogen.

Results of Operations

Revenue

Whenever we refer to prior period results, they reflect the impact of Topic 606, which we adopted in the first quarter of 2018.

Total revenue for the three and six months ended June 30, 2018 was $117.7 million and $262.2 million, respectively, compared to $112.3 million and $228.1 million for the same periods in 2017 and was comprised of the following (amounts in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017 (as revised)	2018	2017 (as revised)
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 56,653	$ 22,366	$ 97,734	$ 27,577
Licensing and other royalty revenue	545	1,322	1,487	3,912
Total commercial revenue	57,198	23,688	99,221	31,489
R&D revenue:				
Amortization from upfront payments	33,761	26,315	61,090	47,253
Milestone payments	11,522	59,149	18,418	78,720
License fees	820	369	62,579	64,518
Other services	14,446	2,752	20,857	6,093
Total R&D revenue	60,549	88,585	162,944	196,584
Total revenue	$ 117,747	$ 112,273	$ 262,165	$ 228,073

The increase in revenue in the first half of 2018 compared to the same period in 2017 was primarily due to the increase in commercial revenue from SPINRAZA royalties, which increased over 250 percent. Revenue from amortization of upfront payments also increased due to $11 million of amortization from our 2018 strategic neurology collaboration with Biogen. We expect that the quarterly amortization from this collaboration will be nearly $14 million beginning in the third quarter. In the second quarter and year to date 2017, revenue included the $50 million milestone payment from Biogen for SPINRAZA approval in the EU. License fees in the first half of 2018 were $62.6 million primarily from AstraZeneca for the license of IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L$_{Rx}$ compared to $64.5 million primarily from Bayer for the license of IONIS-FXI-L$_{Rx}$.

Operating Expenses

Operating expenses for the three and six months ended June 30, 2018 were $168.0 million and $315.7 million, respectively, and increased compared to $105.8 million and $202.1 million for the same periods in 2017. Our operating expenses increased year over year principally due to higher SG&A expenses as we prepare to commercialize TEGSEDI and WAYLIVRA. Our SG&A expenses also increased year over year because of fees we owed under our in-licensing agreements related to SPINRAZA. As sales for SPINRAZA grow, our in-licensing expenses also increase but not at the same rate. We earn tiered royalties on annual SPINRAZA sales and pay nominal fixed third-party royalties that are not tiered. R&D expenses accounted for a smaller portion of the increase in operating expenses. R&D expenses increased primarily due to increases in medical affairs expenses and drug development costs related to several drugs including AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. These increases reflect the investment we are making in advancing and expanding our pipeline. As this year progresses, we expect our operating expenses to continue to increase primarily related to the commercialization of TEGSEDI and WAYLIVRA.

Our operating expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Ionis Core	$ 64,124	$ 66,065	$ 147,601	$ 126,685
Akcea Therapeutics	69,618	21,460	110,670	87,750
Elimination of intercompany activity	409	(2,960)	(4,850)	(54,467)
Subtotal	134,151	84,565	253,421	159,968
Non-cash compensation expense related to equity awards	33,876	21,258	62,327	42,170
Total operating expenses	$ 168,027	$ 105,823	$ 315,748	$ 202,138

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 is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research, Development and Patent Expenses

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Research, development and patent expenses	$ 82,594	$ 67,366	$ 166,979	$ 133,882
Non-cash compensation expense related to equity awards	19,236	16,140	38,918	32,262
Total research, development and patent expenses	$ 101,830	$ 83,506	$ 205,897	$ 166,144

Our research, development and patent expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Ionis Core	$ 45,419	$ 53,758	$ 109,407	$ 108,587
Akcea Therapeutics	37,215	16,568	62,872	80,663
Elimination of intercompany activity	(41)	(2,960)	(5,300)	(54,467)
Subtotal	82,593	67,366	166,979	133,882
Non-cash compensation expense related to equity awards	19,236	16,140	38,918	32,262
Total research, development and patent expenses	$ 101,829	$ 83,506	$ 205,897	$ 166,144

For the three and six months ended June 30, 2018, our total research, development and patent expenses were $82.6 million and $167.0 million, respectively, and increased compared to $67.4 million and $133.9 million for the same periods in 2017. All amounts exclude non-cash compensation expense related to equity awards.

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.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipelines. Our antisense drug discovery expenses are part of our Ionis Core business segment.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 13,590	$ 13,162	$ 27,495	$ 25,760
Non-cash compensation expense related to equity awards	4,449	3,746	8,825	7,709
Total antisense drug discovery expenses	$ 18,039	$ 16,908	$ 36,320	$ 33,469

Antisense drug discovery expenses for the three and six months ended June 30, 2018 were $13.6 million and $27.5 million, respectively, and were slightly higher compared to $13.2 million and $25.8 million for the same periods in 2017. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
SPINRAZA	$ —	$ 5,154	$ —	$ 10,802
WAYLIVRA	6,049	5,944	12,450	10,202
TEGSEDI	5,195	5,324	11,031	12,110
Other antisense development projects	20,514	11,011	41,167	21,428
Development overhead expenses	12,100	10,519	24,078	20,822
Total antisense drug development, excluding non-cash compensation expense related to equity awards	43,858	37,952	88,726	75,364
Non-cash compensation expense related to equity awards	7,406	6,346	15,498	12,802
Total antisense drug development expenses	$ 51,264	$ 44,298	$ 104,224	$ 88,166

Antisense drug development expenses were $43.9 million and $88.7 million for the three and six months ended June 30, 2018, respectively, and increased compared to $38.0 million and $75.4 million for the same periods in 2017. During the first half of 2018, our development expenses for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} increased compared to the same period in 2017. We completed enrollment of its Phase 2 clinical study of AKCEA-APO(a)-L_{Rx} during the first quarter of 2018. We also initiated a Phase 2 clinical study of AKCEA-APOCIII-L_{Rx} in patients with hypertriglyceridemia and established cardiovascular disease in the first quarter of 2018. Slightly offsetting these increases were decreased expenses for SPINRAZA and TEGSEDI. Specifically, we have transitioned all further development of SPINRAZA to Biogen and we completed our Phase 3 TEGSEDI trial in people with hATTR with polyneuropathy in 2017. All amounts exclude non-cash compensation expense related to equity awards.

Our antisense drug development expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Ionis Core	$ 19,023	$ 26,422	$ 46,649	$ 54,133
Akcea Therapeutics	24,835	11,530	42,077	70,526
Elimination of intercompany activity	—	—	—	(48,394)
Subtotal	43,858	37,952	88,726	76,265
Non-cash compensation expense related to equity awards	7,406	6,346	15,498	13,358
Total antisense drug development expenses	$ 51,264	$ 44,298	$ 104,224	$ 89,623

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 products 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 product. Although we may characterize a product 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 products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products 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 product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous drugs in preclinical and early stage clinical research, the fluctuations in expenses from drug to drug, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Medical Affairs

Our medical affairs function is responsible for performing further research regarding our drugs to ensure appropriate medical use. In addition, members of our medical affairs team educate the medical community about the diseases our drugs are designed to treat.

Expenditures in our medical affairs function include personnel costs and outside services.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 8,428	$ 1,116	$ 13,560	$ 2,017
Non-cash compensation expense related to equity awards	1,224	654	1,990	1,210
Total medical affairs expenses	$ 9,652	$ 1,770	$ 15,550	$ 3,227

Medical affairs expenses were $8.4 million and $13.6 million for three and six months ended June 30, 2018, respectively, and were higher compared to $1.1 million and $2.0 million for the same periods in 2017. The increase was primarily due to the build-out of our medical affairs teams and associated activities to educate the medical community on FCS and hATTR. We expect these costs to continue to increase this year as we continue to build-out these teams. All amounts exclude non-cash compensation expense related to equity awards.

Our medical affairs expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Ionis Core	$ 951	$ —	$ 4,297	$ —
Akcea Therapeutics	7,477	1,116	9,263	2,017
Subtotal	8,428	1,116	13,560	2,017
Non-cash compensation expense related to equity awards	1,224	654	1,990	1,210
Total medical affairs expenses	$ 9,652	$ 1,770	$ 15,550	$ 3,227

Manufacturing and Operations

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

Our manufacturing and operations expenses were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 9,689	$ 8,288	$ 21,998	$ 17,093
Non-cash compensation expense related to equity awards	2,386	1,745	4,788	3,450
Total manufacturing and operations expenses	$ 12,075	$ 10,033	$ 26,786	$ 20,543

Manufacturing and operations expenses were $9.7 million and $22.0 million for the three and six months ended June 30, 2018, respectively, compared to $8.3 million and $17.1 million for the same periods in 2017. Manufacturing and operations expenses increased for the first half of 2018. Since accounting rules require us to expense launch supplies prior to obtaining approval, the increase in manufacturing expenses was primarily from the manufacturing of commercial supply of TEGSEDI in the first half of 2018. All amounts exclude non-cash compensation expense related to equity awards.

Our manufacturing and operations expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Ionis Core	$ 6,086	$ 7,728	$ 17,728	$ 15,832
Akcea Therapeutics	3,603	3,490	9,499	7,274
Elimination of intercompany activity	—	(2,930)	(5,229)	(6,013)
Subtotal	9,689	8,288	21,998	17,093
Non-cash compensation expense related to equity awards	2,386	1,745	4,788	3,450
Total manufacturing and operations expenses	$ 12,075	$ 10,033	$ 26,786	$ 20,543

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 thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Personnel costs	$ 3,094	$ 2,714	$ 6,197	$ 5,566
Occupancy	2,143	2,076	3,902	3,954
Patent expenses	531	495	1,232	994
Depreciation and amortization	99	57	200	124
Insurance	396	327	1,262	673
Other	766	1,179	2,407	2,337
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	7,029	6,848	15,200	13,648
Non-cash compensation expense related to equity awards	3,771	3,649	7,817	7,091
Total R&D support expenses	$ 10,800	$ 10,497	$ 23,017	$ 20,739

R&D support expenses for the three and six months ended June 30, 2018 were $7.0 million and $15.2 million, respectively, and were slightly higher compared to $6.8 million and $13.6 million for the same periods in 2017. R&D support expenses increased primarily related to costs associated with the expansion of our business. All amounts exclude non-cash compensation expense related to equity awards.

Our R&D support expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Ionis Core	$ 5,769	$ 6,446	$ 13,238	$ 12,862
Akcea Therapeutics	1,300	432	2,033	846
Elimination of intercompany activity	(41)	(30)	(71)	(60)
Subtotal	7,028	6,848	15,200	13,648
Non-cash compensation expense related to equity awards	3,771	3,649	7,817	7,091
Total R&D support expenses	$ 10,799	$ 10,497	$ 23,017	$ 20,739

Selling, General and Administrative Expenses

Selling, general and administrative expenses include costs associated with the pre-commercialization and commercialization activities for our drugs and costs to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of pre-commercialization, commercialization, 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 selling, general and administrative expenses (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 51,558	$ 17,199	$ 86,442	$ 26,086
Non-cash compensation expense related to equity awards	14,640	5,118	23,409	9,908
Total selling, general and administrative expenses	$ 66,198	$ 22,317	$ 109,851	$ 35,994

Selling, general and administrative expenses were $51.6 million and $86.4 million for the three and six months ended June 30, 2018, respectively, and increased compared to $17.2 million and $26.1 million for the same periods in 2017. The increase in SG&A expenses was principally due to the cost of preparing to commercialize TEGSEDI and WAYLIVRA, and from fees we owed under our in-licensing agreements related to SPINRAZA. We project our expenses will increase as we launch TEGSEDI and continue to prepare to launch WAYLIVRA. All amounts exclude non-cash compensation expense related to equity awards.

Our selling, general and administrative expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Ionis Core	$ 18,705	$ 12,307	$ 38,194	$ 18,098
Akcea Therapeutics	32,403	4,892	47,798	7,988
Elimination of intercompany activity	450	—	450	—
Subtotal	51,558	17,199	86,442	26,086
Non-cash compensation expense related to equity awards	14,640	5,118	23,409	9,908
Total selling, general and administrative expenses	$ 66,198	$ 22,317	$ 109,851	$ 35,994

Akcea Therapeutics, Inc.

The following table sets forth information on operating expenses (in thousands) for our Akcea Therapeutics business segment:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Development and patent expenses	$ 37,215	$ 16,568	$ 62,872	$ 80,663
General and administrative expenses	32,403	4,892	47,798	7,988
Total operating expenses, excluding non-cash compensation expense related to equity awards	69,618	21,460	110,670	87,750
Non-cash compensation expense related to equity awards	12,126	3,942	18,509	7,122
Total Akcea Therapeutics operating expenses	$ 81,744	$ 25,402	$ 129,179	$ 94,872

Operating expenses for Akcea were $69.6 million and $110.7 million for the three and six months ended June 30, 2018, respectively, and increased compared to $21.5 million and $87.8 million for the same periods in 2017.

In the first half of 2017, $48.4 million of development and patent expenses was for one-time sublicensing expenses related to the Novartis collaboration recorded in the first quarter of 2017. $33.4 million of these expenses were non-cash and the remaining $15 million was paid to us. Excluding the $48.4 million of one-time expenses, Akcea's development and patent expenses increased $30.6 million in the first half of 2018 compared to the same period in 2017 as Akcea made investments in advancing its pipeline, including AKCEA-APO(a)-L_{Rx}, which is now fully enrolled with data expected in the second half of 2018, and AKCEA-APOCIII-L_{Rx}.

For each period presented, we allocated a portion of Ionis' R&D support expenses, which are included in development and patent expenses in the table above, to Akcea for work we performed on behalf of Akcea.

Akcea's G&A expenses increased in the first half of 2018 compared to the same period in 2017, primarily due to Akcea continuing to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch TEGSEDI and WAYLIVRA this year, assuming WAYLIVRA approval. For each period presented, we allocated a portion of Ionis' G&A expenses, which were included in Akcea's G&A expenses in the table above, to Akcea for work we performed on Akcea's behalf.

We anticipate Akcea's operating expenses will continue to increase in the second half of 2018, as Akcea launches TEGSEDI and continues to prepare to launch WAYLIVRA.

All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three and six months ended June 30, 2018 was $5.1 million and $8.7 million, respectively, compared to $2.5 million and $4.7 million for the same periods in 2017. The increase in investment income was primarily due to our significantly higher average cash balance and an improvement in the market conditions during the first half of 2018 compared to the same period in 2017. We expect our investment income to increase in the second half of 2018 because we added $1 billion to our cash balance in June 2018 from our 2018 strategic collaboration with Biogen.

Interest Expense

Interest expense for the three and six months ended June 30, 2018 was $11.1 million and $22.1 million, respectively, compared to $11.8 million and $23.1 million for the same periods in 2017.

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent notes, non-cash interest expense related to the long-term financing liability, which was replaced by mortgage debt for our primarily R&D and manufacturing facilities beginning in July 2017 and other miscellaneous debt.

In July 2017, we purchased the building that houses our primary R&D facility and the building that houses our manufacturing facility for $79.4 million and $14.0 million, respectively. As a result of the purchase of our primary R&D facility, we extinguished the financing liability we had previously recorded on our balance sheet. We financed the purchase of the buildings with mortgage debt of $51.3 million with an interest rate of 3.88 percent for our primary R&D facility and mortgage debt of $9.1 million with an interest rate of 4.2 percent for our manufacturing facility. Both mortgages mature in August 2027. The non-cash interest expense for our long-term financing liability was replaced with lower mortgage interest expense.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Convertible notes:				
Non-cash amortization of the debt discount and debt issuance costs	$ 8,693	$ 8,058	$ 17,217	$ 15,960
Interest expense payable in cash	1,714	1,946	3,427	3,660
Non-cash interest expense for long-term financing liability	—	1,676	—	3,352
Interest on mortgage for primary R&D and manufacturing facilities	601	—	1,195	—
Other	105	98	212	169
Total interest expense	$ 11,113	$ 11,778	$ 22,051	$ 23,141

Net Income (Loss)

We had a net loss of $56.6 million for the three months ended June 30, 2018, compared to $3.1 million for the same period in 2017. We had a net loss of $67.4 million for the six months ended June 30, 2018, compared to net income of $5.9 million for the same period in 2017. In 2018 we had a net loss primarily due to increased operating expenses as we prepared to commercialize TEGSEDI and WAYLIVRA, assuming approval of WAYLIVRA.

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

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In April 2018, we received eight million shares of Akcea's stock for the license of TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea and purchased an additional 10.7 million shares of Akcea's stock for $200 million, increasing our ownership percentage to approximately 75 percent. As a result, we adjusted our financial statements to reflect the portion of Akcea we no longer own. Accordingly, our consolidated statement of operations includes a line called "Net loss attributable to noncontrolling interests in Akcea", our noncontrolling interest in Akcea for the three and six months ended June 30, 2018 was $16.2 million and $25.6 million, respectively. We also have a corresponding account on our consolidated balance sheet called "Noncontrolling interest in Akcea Therapeutics, Inc."

Net Income (Loss) Attributable to Ionis Pharmaceuticals, Inc. Common Stockholders and Net Income (Loss) per Share

We had a net loss attributable to our common stockholders' of $40.4 million for the three months ended June 30, 2018, compared to $3.1 million for the same period in 2017. For the six months ended June 30, 2018 we reported a net loss attributable to our common stockholders of $41.8 million, compared to net income attributable to our common stockholders of $5.9 million for the same period in 2017.

For the three months ended June 30, 2018, basic and diluted net loss per share were $0.29, compared to $0.02 for the same period in 2017. For the six months ended June 30, 2018, basic and diluted net loss per share were $0.30, compared to basic and diluted net income per share of $0.05 for the same period in 2017.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Beginning in December 2016 we added commercial revenue from SPINRAZA royalties. From our inception through June 30, 2018, we have earned approximately $2.8 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through June 30, 2018, we have raised net proceeds of approximately $1.7 billion from the sale of our equity securities, not including the $182.4 million Akcea received in net proceeds from its IPO in July 2017. Additionally, we have borrowed approximately $1.4 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

At June 30, 2018, we had cash, cash equivalents and short-term investments of $2.0 billion and stockholders' equity of $817.4 million. In comparison, we had cash, cash equivalents and short-term investments of $1.0 billion and stockholders' equity of $365.3 million at December 31, 2017. Our cash, cash equivalents and short-term investments increased in the first half of 2018 primarily from the $1 billion payment we received from Biogen for our 2018 strategic neurology collaboration.

At June 30, 2018, we had consolidated working capital of $1.8 billion compared to $925.1 million at December 31, 2017. As of June 30, 2018, our debt and other obligations totaled $761.1 million compared to $759.9 million at December 31, 2017.

The following table summarizes our contractual obligations as of June 30, 2018. 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:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Convertible senior notes (principal and interest payable)	$ 709.4	$ 6.9	$ 13.7	$ 688.8	$ —
Building mortgage payments	$ 82.0	$ 2.4	$ 4.8	$ 5.4	$ 69.4
Financing arrangements (principal and interest payable)	$ 12.9	$ 0.3	$ 12.6	$ —	$ —
Other obligations (principal and interest payable)	$ 1.1	$ 0.1	$ 0.1	$ 0.1	$ 0.8
Operating leases	$ 29.0	$ 2.8	$ 6.0	$ 5.2	$ 15.0
Total	$ 834.4	$ 12.5	$ 37.2	$ 699.5	$ 85.2

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.

1 Percent Convertible Senior Notes

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes. As a result, the principal balance of the 2¾ percent notes following the repurchase in November 2014 was $61.2 million.

In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. At June 30, 2018, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At June 30, 2018, we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes
Outstanding principal balance	$ 685.5
Original issue date ($500 million of principal)	November 2014
Additional issue date ($185.5 million of principal)	December 2016
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	10.3

Interest is payable semi-annually for the 1 percent notes. The notes are convertible under certain conditions, at the option of the note holders. We 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 1 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 1 percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Financing Arrangements

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, Morgan Stanley will provide a maximum of $30 million of revolving credit for general working capital purposes. Any loans under the credit agreement have interest payable monthly in arrears at a borrowing rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of June 30, 2018 we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which we used to fund our capital equipment needs consistent with our historical practice to finance these costs.

The credit agreement includes customary affirmative and negative covenants and restrictions. We are in compliance with all covenants of the credit agreement.

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million. We purchased our manufacturing facility in July 2017 for $14.0 million. We financed the purchase of our primary R&D facility and manufacturing facility, with mortgage debt of $51.3 million and $9.1 million, respectively. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages we are only required to make interest payments. Both mortgages mature in August 2027.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2018 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to 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 long-term debt arrangements and, secondarily, 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, 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 consolidated financial statements. Our business strategy incorporates potentially significant international expansion, particularly related to TEGSEDI and WAYLIVRA, therefore we expect that the impact of foreign currency exchange rate fluctuations may become more substantial in the future.

ITEM 4. CONTROLS AND PROCEDURES

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

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of June 30, 2018. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2018.

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 implemented internal controls to ensure we adequately evaluated our contracts and properly assessed the impact of the new revenue recognition accounting guidance we adopted on January 1, 2018 reflected in our financial statements. 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 significant 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

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, which are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead asked the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents infringes those patents, and requesting monetary damages to compensate for such infringement. In the trial for this case held in March 2016, the jury upheld all ten of the asserted claims of the patents-in-suit. The jury then decided that we and Merck are entitled to four percent of $5 billion in past sales of sofosbuvir. Gilead stated it would appeal the jury’s finding of validity. In the meantime, Gilead asserted two additional non-jury defenses: waiver and unclean hands. Although the judge rejected the waiver defense, she granted Gilead’s motion claiming that the patents are unenforceable against it under the doctrine of unclean hands. We believe this ruling is contrary to the relevant law and the facts of the case. Accordingly, in July 2016, together with Merck we appealed the decision to the Court of Appeals for the Federal Circuit. Gilead cross-appealed on the issue of validity. In April 2018, the Court of Appeals issued its ruling affirming the District Court’s finding of unenforceability based on unclean hands. Having upheld the ruling that the patents are unenforceable against Gilead, the court did not reach the question of validity. In July 2018, we and Merck requested an extension of time to file a petition for a hearing before the Supreme Court. The Supreme Court granted that request, setting a deadline of September 21, 2018. Under our agreement with Merck, Merck is responsible for the costs of this suit.

ITEM 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully 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, 2017.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

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

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

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

The degree of market acceptance for our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, 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 drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. For example, in the clinical studies with WAYLIVRA and TEGSEDI, declines in platelet counts were observed in many patients and some patients discontinued the studies because of platelet declines. In addition, in the TEGSEDI NEURO-TTR study, safety signals related to renal function were observed. Therefore, we expect the product label for WAYLIVRA and TEGSEDI will require periodic platelet monitoring and the product label for TEGSEDI will require periodic renal monitoring, which could negatively affect our ability to attract and retain patients for these drugs. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we and Akcea can better maintain patients on TEGSEDI and WAYLIVRA through patient-centric commercial approaches where we and Akcea plan to have greater involvement with physicians and patients, if we and Akcea cannot effectively maintain patients on TEGSEDI or WAYLIVRA, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If we or our partners fail to compete effectively, our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, 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 engage in developing antisense technology. Our competitors may succeed in developing drugs that are:

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

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

Certain of our partners are pursuing other technologies or developing other drugs 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 drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI.

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. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will primarily rely on our partners, and Akcea to provide this capability.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, AVXS-101, RG7916, and LMI070 could compete with SPINRAZA and metreleptin and Gemcabene could compete with WAYLIVRA; patisiran, tafamadis, diflunisal, tolcapone, PRX004 and ALN-TTRsc02 could compete with TEGSEDI.

Following approval, our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI could be subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our drug products, including SPINRAZA, WAYLIVRA and TEGSEDI.

The FDA and foreign regulatory authorities have the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities.

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. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

If we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products including SPINRAZA, WAYLIVRA and TEGSEDI.

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, 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, 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.

If Akcea cannot optimize and maintain effective marketing and sales capabilities or enter into agreements with third parties to market and sell TEGSEDI, we may not generate product revenue from TEGSEDI.

To successfully commercialize TEGSEDI Akcea must successfully manage its marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. Akcea may not be successful in doing so. To commercialize TEGSEDI in the initial indications Akcea plans to pursue, Akcea will need to optimize and maintain a specialty sales force in each global region it expects to market TEGSEDI, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine platelet and renal monitoring and a medical affairs team. Akcea may seek to further penetrate markets by expanding its sales force or through strategic partnerships with other pharmaceutical or biotechnology companies or third-party sales organizations.

Even though certain members of Akcea's management team and other employees have experience commercializing drug products, Akcea has no prior experience marketing, selling or distributing drug products, and there are significant risks involved in building and managing a commercial infrastructure. It will be expensive and time consuming for Akcea to maintain its own sales force and related compliance protocols to market TEGSEDI. Akcea may never successfully optimize or manage this capability and any failure could delay or preclude TEGSEDI's launch. Akcea and its partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel.

Akcea will incur expenses prior to the launch of TEGSEDI to integrate and manage the marketing and sales infrastructure. If regulatory requirements or other factors cause a delay in the commercial launch of TEGSEDI, Akcea would incur additional expenses for having invested in these capabilities earlier than required and prior to realizing any revenue from sales of TEGSEDI. Akcea's sales force and marketing teams may not successfully commercialize TEGSEDI.

To the extent we and Akcea decide to rely on third parties to commercialize TEGSEDI in a particular geographic market, we and Akcea may receive less revenue than if Akcea commercialized TEGSEDI by itself. Further we would have less control over the sales efforts of any other third parties involved in commercializing TEGSEDI.

If Akcea cannot effectively build and manage its distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable third party to perform such functions, the commercial launch and sales of TEGSEDI may be delayed, less successful or precluded. Such events may result in decreased sales and lower revenue, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

If government or other third-party payors fail to provide adequate coverage and payment rates for our drugs, including SPINRAZA, TEGSEDI and WAYLIVRA, 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 payors. The majority of people in the United States who would fit within our target patient populations for our drugs 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 drug products 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 drugs affordable.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. For example, in the United States, recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several U.S. Congressional inquiries and proposed federal legislation designed to, among other things, reform government program reimbursement methodologies for drug products and bring more transparency to drug pricing. Third-party coverage and reimbursement for our products or drugs may not be available or adequate in either the United States or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If Biogen cannot manufacture finished drug product for SPINRAZA or the post-launch supply of the active drug substance for SPINRAZA, SPINRAZA may not maintain commercial success.

Biogen is responsible for the long-term supply of both SPINRAZA drug substance and finished drug product. Biogen may not be able to reliably manufacture SPINRAZA drug substance and drug product to support the long-term commercialization of SPINRAZA. If Biogen cannot reliably manufacture SPINRAZA drug substance and drug product, SPINRAZA may not maintain commercial success, which will harm our ability to generate revenue.

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

We cannot guarantee that any of our drugs, including WAYLIVRA, will be considered safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA and TEGSEDI will be approved in additional markets or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs before they can be approved for sale. We 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 drugs. It is possible that regulatory agencies will not approve our drugs including, WAYLIVRA for marketing or additional marketing authorizations for SPINRAZA or TEGSEDI. 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 drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, the FDA or foreign regulatory authorities could claim that we have not tested WAYLIVRA in a sufficient number of patients to demonstrate WAYLIVRA is safe and effective in patients with FCS or FPL to support an application for marketing authorization, especially since a small number of patients in the APPROACH FCS study experienced severe thrombocytopenia, a condition where the patient has severely low platelet levels. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays.

Failure to receive marketing authorization for our drug, WAYLIVRA, or additional authorizations for SPINRAZA or TEGSEDI, or delays in these authorizations could prevent or delay commercial introduction of the drug, 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 drugs 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 drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our drugs, including the study of WAYLIVRA in patients with FPL. If any of our drugs in clinical studies, including WAYLIVRA, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

Even if our drugs are successful in preclinical and human clinical studies, the drugs 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 drugs in development, may not predict the results of subsequent clinical studies, including the Phase 3 study of WAYLIVRA in patients with FPL. 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 drug on subjects in the trial;
- we 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;

- 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;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

In addition, our current drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, are chemically similar to each other. As a result, a safety observation we encounter with one of our drugs could have, or be perceived by a regulatory authority to have, an impact on a different drug 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 drugs 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 drugs: 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. Similarly, we have an ongoing Phase 3 study of WAYLIVRA in patients with FPL, an ongoing open label extension study of WAYLIVRA in patients with FCS, an ongoing open label extension study of TEGSEDI and expanded access programs for each drug. Adverse events or results from these studies could negatively impact our current or planned marketing approval applications for WAYLIVRA in patients with FCS, for TEGSEDI or the commercial opportunity for each product.

Any failure or delay in the clinical studies, including the Phase 3 study for WAYLIVRA in patients with FPL, could reduce the commercial potential or viability of our drugs.

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

To successfully commercialize any of our drugs, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. We and Akcea will rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAYLIVRA. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, 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 may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

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

We depend on third parties to conduct our clinical studies for our drugs 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 drugs and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our drugs, including WAYLIVRA and TEGSEDI. 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 or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our drugs, including authorizations for WAYLIVRA or additional authorizations for SPINRAZA and TEGSEDI.

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of June 30, 2018, we had an accumulated deficit of approximately $1.3 billion and stockholders’ equity of approximately $817.4 million. Most of the 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. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

Our ability to use our net operating loss carryovers and certain other tax attributes may be limited.

As described above, we have incurred net losses. 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.

As of December 31, 2017, we had federal and California net operating loss carryforwards of approximately $561.1 million and $887.1 million, respectively. The federal net operating loss carryforwards will begin to expire, if not utilized, beginning in 2024. These net operating loss carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under the Tax Cut and Jobs Act of 2017, or the Tax Act, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the newly enacted federal tax law. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, 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. It is possible that we have experienced an ownership change limitation. 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 is materially limited, it would harm our future operating results by effectively increasing our future tax obligations.

Since corporate partnering is a significant part of our strategy to fund the development 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 our unpartnered drugs. 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 drugs could suffer.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs 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 on 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 authorization; and
- manufacture, market and sell our drugs.

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

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

- pursue alternative technologies or develop alternative products that may be competitive with the drug 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 drugs than it does for its own drugs.

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 drugs, including SPINRAZA.

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 drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' expectations, including milestones related to SPINRAZA, WAYLIVRA and TEGSEDI, the price of our securities could decrease.

If we cannot protect our patents 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 and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. 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.

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 sometimes need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business. For example, in November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court for the Northern District of California. Intellectual property lawsuits may be costly and may not be resolved in our favor.

If a third party claims that our drugs 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 United States 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.

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of June 30, 2018, we had cash, cash equivalents and short-term investments equal to $2.0 billion. If we do not meet our goals to successfully commercialize our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI, or to license our drugs 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 for SPINRAZA and TEGSEDI;
- marketing approvals for WAYLIVRA and additional approvals for TEGSEDI;
- the profile and launch timing of our drugs, including WAYLIVRA and TEGSEDI;
- 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; and
- competing technological and market developments, including the introduction by others of new therapies that address our markets.

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 drugs.

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.

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 June 30, 2018, the market price of our common stock ranged from $39.07 to $65.51 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, governmental regulation, marketing authorization, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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, WAYLIVRA and TEGSEDI. 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 drug products, 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.

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 affected. We manufacture the finished drug product for WAYLIVRA and TEGSEDI at third-party contract manufacturers.

If a natural or man-made disaster strikes our research, development or manufacturing facilities or otherwise affects our business, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we and our contract manufacturers use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities or our contract manufacturers may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, 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 and operations would suffer in the event of computer system failures.

Despite the implementation of security measures, our internal computer systems, and those of our clinical research organizations, manufacturers, commercial partners and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If issues were to arise and cause interruptions in our operations, it could result in a material disruption of our drug programs. For example, the loss of clinical study data from completed or ongoing clinical studies could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development or commercialization of our drugs, including SPINRAZA, WAYLIVRA and TEGSEDI could be harmed or delayed.

Provisions in our certificate of incorporation, other agreements 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.

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 10.3 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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.

The comprehensive tax reform bill could adversely affect our business and financial condition.

The Tax Act significantly revises the Internal Revenue Code of 1986, as amended. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35 percent to a flat rate of 21 percent, limitation of the tax deduction for interest expense to 30 percent of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80 percent of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

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.

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have in the past experienced periods of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. 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.

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	New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement, dated April 19, 2018, by and between Ionis Pharmaceuticals, Inc. and Biogen MA Inc. Portions of this exhibit have been omitted and separately filed with the SEC.
10.2	Stock Purchase Agreement, dated April 19, 2018, by and between Ionis Pharmaceuticals, Inc. and Biogen MA Inc.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended June 30, 2018, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

* 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/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 7, 2018
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	August 7, 2018

Exhibit 10.1

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)(4), 240.24B-2

NEW STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

IONIS PHARMACEUTICALS, INC.

AND

BIOGEN MA INC.

Dated April 19, 2018

Table of Contents

NEW STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

This NEW STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 19th day of April, 2018 (the "***Execution Date***") by and between **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Ionis***"), and **BIOGEN 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 is interested in entering into a strategic relationship with Ionis to explore potential targets for the treatment of neurological and neuromuscular diseases, mood disorders, psychological disorders, ocular diseases and diseases of the inner ear, and to create antisense drugs to such targets;

WHEREAS, Biogen and Ionis are parties to an ongoing existing discovery and development collaboration in relation to certain neurological diseases, including ALS, pursuant to that certain Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement dated October 20, 2017, as amended or restated (the "***Neurology II Agreement***");

WHEREAS, the Parties now desire to enter into a new strategic collaboration in neurological diseases (including neurodegenerative and neuropsychiatric diseases), mood disorders, psychological disorders, ocular diseases and diseases of the inner ear, comprising (a) a research program focused on the identification, validation and applications of novel targets implicated in such diseases and novel therapeutic approaches directed to such targets, (b) a broad core technology research program focused on enhancing the Parties' knowledge of the use of antisense oligonucleotides in the central and peripheral nervous systems, and the eye and the ear, (c) a targeted drug discovery and development effort and (d) the exclusive opportunity for Biogen to select collaboration targets from among all available targets reaching target sanction status in Ionis' research programs directed at such diseases;

WHEREAS, with regard to targets that reach target sanction status and that Biogen selects as collaboration targets for development, Biogen desires to (a) have Ionis identify development candidates for each such collaboration target, (b) develop development candidates through completion of the IND-enabling toxicology studies and (c) receive an exclusive option to obtain from Ionis an exclusive license under this Agreement to develop, manufacture and commercialize collaboration products directed to such collaboration targets in the Field; and

WHEREAS, as partial consideration for Ionis' grant of the Options, licenses and other rights to Biogen under this Agreement, Biogen desires to subscribe for and purchase from Ionis, and Ionis desires to issue and sell to Biogen, certain shares of common stock pursuant to the terms and subject to the conditions set forth in the Stock Purchase Agreement.

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.

1.1.1. The intent of the Collaboration is for the Parties to conduct (a) a research program focused on the identification and validation of and applications for novel Neurology Targets, (b) a drug discovery and development effort in Neurological Disease with respect to those Strategies directed to Neurology Targets selected to be Collaboration Programs and (c) a broad core technology research program focused on enhancing the Parties' knowledge of the use of ASOs in the central and peripheral nervous systems, and the eye and the ear. This Agreement also provides Biogen the exclusive opportunity to select as Collaboration Programs any Strategy directed to any Ionis Neurology Target that Ionis is independently researching, up through Target Sanction.

1.1.2. Once one or more Strategies directed to a Neurology Target reach Target Sanction, one or more of such Strategies directed to such Neurology Target may be selected as Collaboration Programs under this Agreement (and upon selection of one or more Strategies directed to a Neurology Target as Collaboration Programs, such Neurology Target will be a Collaboration Target). Unless not feasible, Ionis will generate at least one Development Candidate for each Collaboration Program, with the goal of generating up to five Compounds that may be suitable Development Candidates for each Collaboration Program. Biogen may select one or more of the Compounds generated by Ionis as Development Candidates to be the subject of further Development activities under the applicable Collaboration Program, as further set forth in Section 1.8.

1.1.3. For Development Candidates selected by Biogen to be the subject of further Development activities under a Collaboration Program, Ionis provides to Biogen an exclusive option under Section 3.1.2(a) to be granted an exclusive license from Ionis to further Develop and Commercialize Products under such Collaboration Program, each of which options is exercisable as set forth in Section 3.1.2(a).

1.1.4. The Parties have agreed to form (a) a collaboration steering committee to oversee the Collaboration under this Agreement, (b) a joint research committee reporting to the CSC to oversee the Core Research Program, the Neurological Disease Research Program and each Development Candidate Identification Plan and (c) one or more joint development committees reporting to the CSC to oversee Development activities for Development Candidates.

1.1.5. 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. **Research Programs**. Subject to and in accordance with the terms of this Agreement, during the Research Term, Ionis and Biogen will conduct two research programs, each under a separate mutually agreed plan. The first research program will cover research focused on enhancing the Parties' knowledge of the use of ASOs in the central and peripheral nervous systems, and the eye and the ear, including with respect to pharmacokinetics and pharmacodynamics, [***] of ASOs (such program, the "***Core Research Program***" and the plan for such program, the "***Core Research Plan***"). A draft of the Core Research Plan has been mutually agreed upon by the Parties in writing on or prior to the Effective Date. The second research program will focus on the identification and validation of Strategies directed to High Interest Targets, which Strategies are eligible to become Collaboration Programs and which High Interest Targets, upon designation of one or more Strategies as Collaboration Programs, will become Collaboration Targets (such program, the "***Neurological Disease Research Program***" and the plan for such program, the "***Neurological Disease Research Plan***"). The Neurological Disease Research Plan will itself be comprised of individual plans that set forth the target validation activities to be conducted by the Parties in order to achieve Target Sanction for each Strategy directed to a High Interest Target designated for such activities under Section 1.2.3(d) (each such individual plan for each Strategy, a "***Target Sanction Plan***"). Notwithstanding the foregoing, neither Party will be required to complete any activities under the Core Research Plan or Neurological Disease Research Plan (or any individual Target Sanction Plan included therein) if such Party in good faith believes that such activities are not technically feasible given the then-current state of the art.

1.2.1. **Research Term**. The term for the conduct of the Core Research Program and the Neurological Disease Research Program will begin on the Effective Date and will end on the 10th anniversary of the Effective Date, as such term may be extended in accordance with this Agreement (the "***Research Term***"). Notwithstanding the foregoing:

(a) with respect to the Neurological Disease Research Program, (i) subject to subclause (iii) of this Section 1.2.1(a), Ionis will not be required to begin target validation activities for any Strategy directed to a High Interest Target under the Neurological Disease Research Program unless the activities proposed under the applicable Target Sanction Plan for such Strategy are reasonably able to be completed on or before the end of the Research Term, (ii) if any target validation activities that are Ionis Activities or Biogen Activities are ongoing under the Neurological Disease Research Plan on the date that would otherwise be the end of the Research Term, then if requested by Biogen, Ionis and Biogen will complete such activities, respectively, in accordance with the Neurological Disease Research Plan, and the Research Term will be extended until the completion thereof, and (iii) the Research Term may be automatically extended to the Research Term Extension Date under Section 1.8.1(d), in which case Biogen may propose new Strategies and add new targets to the High Interest Target List (solely to the extent the applicable target validation activities could reasonably be completed by the Research Term Extension Date), and (unless Biogen exercises its step-in rights to perform target validation activities pursuant to Section 1.8.1(d)) Ionis shall commence new target validation activities for such new Strategies directed to such High Interest Targets, in each case, in accordance with this Agreement; and

(b) The Research Term may be further extended by written agreement of the Parties.

1.2.2. **Core Research Program**. The Core Research Program activities will initially be focused on investigating and optimizing delivery of ASOs to the central and peripheral nervous systems and the eye and the ear. Ionis will use Commercially Reasonable Efforts to conduct the Ionis Activities under the Core Research Program, and Biogen will use Commercially Reasonable Efforts to conduct the Biogen Activities under the Core Research Program. The Neurology JRC will update the Core Research Plan as needed during the Research Term. If either Party desires that any activities contemplated by the Parties under the Core Research Program should be performed by a Third Party, then the Parties will discuss through the Neurology JRC and agree upon the appropriate Third Party to conduct such activities, and how the costs of such Third Party activities should be allocated between the Parties.

1.2.3. **Neurological Disease Research Program**. The Neurological Disease Research Program activities will focus primarily on identifying and validating Strategies directed to High Interest Targets.

(a) ***High Interest Targets***. Under the Neurological Disease Research Plan, Biogen will establish a prioritized list of Neurology Targets that are designated by Biogen as high interest targets and added to such list in accordance with Section 1.2.3(b), which Neurology Targets, in accordance with Section 1.2.3(b)(v), may include one or more gene targets that are already defined as "High Interest Targets" or "Collaboration Targets" under the Neurology II Agreement using a different Strategy directed to such High Interest Target or Collaboration Target than the approach to such gene target being pursued under the Neurology II Agreement (each such target, a "***High Interest Target***" and such list the "***High Interest Target List***"). With respect to the High Interest Target List (i) at any given time during the Research Term such list may not include more than [***] High Interest Targets for which at least one Strategy directed to such High Interest Target has not achieved Target Sanction, and (ii) no targets may be added to the High Interest Target List unless target validation activities for the applicable Strategies directed to such targets can reasonably be completed before the expiration of the Research Term, taking into account the target validation activities already being conducted under the Neurological Disease Research Program under Section 1.2.3(d) and the number of FTEs available to perform activities as described in Section 1.11. Without limiting the foregoing, if, on or after the [***] anniversary of the date a High Interest Target was added to the High Interest Target List, such target remains or becomes an Inactive Target, then, unless the Parties mutually agree through the Neurology JRC that such High Interest Target may remain on the High Interest Target List, such High Interest Target shall automatically be removed from the High Interest Target List and will no longer be a High Interest Target. However, during the remainder of the Research Term, such target will remain a Neurology Target and Biogen may again add such target to the High Interest Target List in accordance with this Section 1.2.3(a).

(b) ***Addition of High Interest Targets***.

(i) Biogen will present an updated list of gene targets, if any, that it desires to add to the High Interest Target List at each meeting of the Neurology JRC. At any other time during the Research Term, subject to the restrictions set forth in Section 1.2.3(a), Biogen may request to add one or more targets to the High Interest Target List by written notice to Ionis. The date of such presentation to the Neurology JRC or such notice to Ionis shall be the "***HIT Request Date***." Within [***] days of the HIT Request Date, Ionis will notify Biogen in writing in accordance with this Section 1.2.3(b) whether it accepts such additional gene targets as High Interest Targets (a "***High Interest Target Acceptance Notice***").

(ii) Subject to the limitations set forth in Section 1.2.3(a), Ionis may not refuse to add a gene target proposed by Biogen to the High Interest Target List, unless (A) the HIT Request Date for the applicable gene target [***], as indicated by a written notice already provided by Ionis to Biogen pursuant to Section 1.8.5(b), or (B) within the [***]-day period after the HIT Request Date (the "***High Interest Target Designation Period***"), (1) [***], (2) Ionis notifies Biogen in writing that such proposed gene target is not a Neurology Target as of the HIT Request Date [***] or (3) meets [***], and in each case of (A) and (B), the applicable proposed gene target will not be a High Interest Target hereunder.

(iii) If Ionis fails to provide a High Interest Target Acceptance Notice for one or more High Interest Targets, or any notification of rejection under Section 1.2.3(b)(ii) by the earlier of [***] days following the expiration of the applicable High Interest Target Designation Period or [***] days following receipt of written notice from Biogen of such failure to accept or reject such High Interest Targets by the end of the applicable High Interest Target Designation Period, then such gene targets will automatically be deemed to be a High Interest Targets upon expiration of such period.

(iv) For clarity, Biogen may add any Ionis Neurology Target to the High Interest Target List so long as Biogen requests to add such Ionis Neurology Target to the High Interest Target List at least [***]months prior to the Estimated Target Sanction Date for a given Strategy directed to such target, as indicated by a notification already provided by Ionis to Biogen in writing (or at a meeting of the Neurology JRC as reflected in the minutes of such meeting) pursuant to Section 1.8.5(b). Biogen may also remove any target from the High Interest Target List during the Research Term if no target validation activities for any Strategy directed to such High Interest Target have been initiated under the Neurological Disease Research Plan, or by Ionis independently (as presented by Ionis to the Neurology JRC). If target validation activities have been initiated for any Strategies directed to a High Interest Target, then Biogen may not remove such High Interest Target from the High Interest Target List until all such target validation activities for such Strategies are complete and Target Sanction has not been reached for such Strategies directed to such High Interest Target.

(v) If Biogen desires to pursue a new Strategy against a gene target that is already defined as a "High Interest Target" or a "Collaboration Target" under the Neurology II Agreement, then Biogen may add such gene target to the High Interest Target List under this Agreement in accordance with this Section 1.2.3(b) and, in either case, such gene target will be deemed a High Interest Target as of the date of presentation thereof to the Neurology JRC or notice thereof to Ionis (as applicable). For clarity, such a designation will not affect the terms applicable to any Collaboration Program directed to such gene target that is at such time already being pursued under the Neurology II Agreement (i.e., any new Strateg(ies) against such gene target will be governed by the terms of this Agreement and the Strategy directed to such gene target already being pursued under the Neurology II Agreement will remain subject to the terms of the Neurology II Agreement). Further, such new Strategy directed to such High Interest Target under this Agreement would not be subject to Section 2.2 of the Neurology II Agreement (Right of First Negotiation for Follow-On Compounds).

(c) ***Multi-Indication Targets***. No later than the end of the [***] days following the addition of a particular High Interest Target to the High Interest Target list, Ionis may notify Biogen in writing that Ionis believes, in good faith based upon published scientific literature or the results of Ionis' internal research efforts, that such High Interest Target may have therapeutic benefit beyond Neurological Disease (each such High Interest Target, a "***Multi-Indication Target***", and each such notice a "***Multi-Indication Target Notice***"). If Ionis delivers a Multi-Indication Target Notice to Biogen, such Multi-Indication Target Notice will (i) include materials supporting Ionis' belief that such High Interest Target may have therapeutic benefit beyond Neurological Disease and (ii) specify whether Ionis in good faith believes such Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If within [***] days of its receipt of a Multi-Indication Target Notice Biogen notifies Ionis in writing that Biogen wishes to remove the applicable Multi-Indication Target from the High Interest Target List, then such Multi-Indication Target will not be a High Interest Target but will continue to be a Neurology Target unless and until its status changes by operation of this Agreement. If Biogen does not so notify Ionis that it wishes to remove the applicable Multi-Indication Target from the High Interest Target List within such [***] day period, then within [***] days after Biogen's receipt of the applicable Multi-Indication Target Notice, Biogen will notify Ionis whether it agrees with Ionis' determination as to whether the applicable Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If Biogen and Ionis agree with respect to such determination, then the agreed upon designation will be binding upon the Parties with respect to such Multi-Indication Target and the provisions of clauses (b)-(e) of APPENDIX 3 will apply with respect to such Multi-Indication Target. If Biogen does not agree with such determination, then the Multi-Indication Target will be designated as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target in accordance with Section 1.2.3(e) upon the Neurology JRC agreeing to conduct target validation activities for one or more Strategies directed to such Multi-Indication Target under the Neurological Disease Research Plan (which shall occur prior to the commencement of such activities). For the avoidance of doubt, if Ionis fails to deliver a Multi-Indication Target Notice within [***] days after the addition of a particular High Interest Target to the High Interest Target List, then such High Interest Target will not be a Multi-Indication Target hereunder.

(d) ***Target Validation under the Neurological Disease Research Program***.

(i) ***Generally***. The Parties agree that the focus of activities during the Research Term is to validate Strategies directed to Neurology Targets as potential therapeutic approaches to therapeutic targets in Neurological Disease, with the goal of achieving Target Sanction for one or more Strategies directed to High Interest Targets and to perform all pre-clinical development work required to achieve the validation of such Strategies directed to such High Interest Targets. Biogen will have final decision-making authority with respect to [***]. It is the intention of the Parties that, at any given time during the Research Term, Ionis will be performing activities under [***] Target Sanction Plans. The Neurology JRC will determine the number of Strategies for which activities under Target Sanction Plans will be conducted during each Calendar Year of the Research Term based on the number of Target Sanction Plans under which the Neurology JRC determines that, using the number of FTEs provided for under Section 1.11 and Commercially Reasonable Efforts, Ionis will be able to (A) [***], and (B) [***]. Notwithstanding anything to the contrary set forth in this Agreement, but subject to Section 1.2.1(a)(i), unless otherwise agreed by the Neurology JRC, at any given time during the Research Term, as part of the Ionis Target Sanction Diligence Obligations, Ionis will be performing activities under at least [***] Target Sanction Plans, subject to a reasonable allowance for an appropriate ramp-up and wind-down of such activities at the beginning and end of the Research Term, and subject to Biogen designating for target validation activities a sufficient number of Strategies directed to High Interest Targets on the High Interest Target List to permit Ionis to work on [***] Target Sanction Plans at a given time.

(ii) ***Strategies***.

(A) At any time during the Research Term (subject to Section 1.2.1(a)(i)), Biogen may request or Ionis may propose, in each case in writing or through the Neurology JRC that Ionis evaluate one or more Strategies directed to any (1) High Interest Target (whether such proposed Strategy is the first Strategy directed to such High Interest Target or whether the Parties are already pursuing one or more Strategies directed to such High Interest Target), (2) Collaboration Target or (3) in accordance with Section 1.4.3, an Ionis Neurology Target. For clarity, the Parties intend that at the time that Biogen proposes a High Interest Target under Section 1.2.3(b), Biogen will also propose (but need not commence target validation activities with respect to) at least one Strategy directed to such proposed High Interest Target, and in such case, the High Interest Target Designation Period, and the Strategy Acceptance Period will run concurrently.

(B) The Parties will discuss, at the Neurology JRC at which such Strategy is proposed (or the first scheduled Neurology JRC meeting following notification by Biogen to Ionis that it wishes to evaluate a specified Strategy) and agree as to whether to accept each proposed Strategy directed to a High Interest Target or Collaboration Target (as applicable). Notwithstanding the foregoing, Ionis may only withhold its consent to accept a particular Strategy directed to a High Interest Target or Collaboration Target (as applicable) at the Neurology JRC if, following Ionis' evaluation of such Strategy, it has in good faith determined that [***] and in all other cases where the Neurology JRC is unable to agree, Biogen has final decision-making authority as to [***]. If Ionis fails to provide written notice that it accepts such proposed Strategy (the "***Strategy Acceptance Notice***"), or any notification of rejection under this Section 1.2.3(d)(ii) within [***] days following the date that Ionis first received the request from Biogen (or the date of the Neurology JRC meeting at which such Strategy was considered) (the "***Strategy Acceptance Period***"), then such Strategy will automatically be deemed to be accepted with respect to such High Interest Target, upon expiration of such Strategy Acceptance Period. If, at any time during the Research Term, Ionis subsequently determines in good faith that a Strategy previously rejected by Ionis as [***], then Ionis shall promptly notify Biogen.

(C) The Parties will discuss through the Neurology JRC whether to pursue target validation activities for each accepted Strategy directed to a High Interest Target or Collaboration Target (as applicable), and in what order to pursue such activities; *provided that* Biogen has final decision making authority [***]. The date that the Neurology JRC designates for the initiation of target validation activities for an accepted Strategy directed to a High Interest Target or Collaboration Target (as applicable) (or the date on which Biogen uses its [***]) shall be the "***Strategy Initiation Date***." Following the Strategy Initiation Date for a Strategy, subject to Section 1.2.3(d)(i), the Parties will promptly conduct each approved Strategy under a separate Target Sanction Plan. Ionis will be eligible to receive a separate Target Designation Milestone Payment (and all subsequent milestone payments, as applicable) for each Target Sanction Plan for each separate Strategy. At any time prior to the Strategy Initiation Date, Biogen may propose a new Strategy to replace an accepted Strategy, and such new Strategy will be subject to the approval process set forth in Section 1.2.3(d)(ii)(B).

(iii) ***Determination of Approaches as Separate Strategies***. The Parties will decide through the Neurology JRC whether a proposed approach to a gene target will be considered distinct, such that it is eligible for designation as a separate Strategy and separate Target Sanction Plan (and separate Collaboration Program) under this Agreement, from any other Strategy for which the Parties are considering or pursuing target validation activities with respect to the same High Interest Target or Collaboration Target at such time under the Collaboration. If the Parties disagree as to whether two proposed approaches to a High Interest Target are distinct approaches, then so long as each such proposed approach falls within one of the subclauses ((a) through (f)) of the definition of Strategy, such proposed approaches will be distinct Strategies *unless*, (i) the activities in connection with the primary approach are proposed to be [***] the secondary approach, and (ii) (A) such secondary approach [***] the primary approach and (B) the scientific work [***] the two approaches (for example, [***] the secondary approach [***] the primary approach). Out-of-pocket expenses payable to Third Parties and incurred by Ionis directly in the course of pursuing [***] approach will not be included in the [***] calculation under the foregoing sentence, and [***] for such reasonable out-of-pocket expenses. If the Parties cannot agree as to whether a proposed approach to a gene target is distinct from any other Strategy for which the Parties are considering or pursuing target validation activities with respect to the same High Interest Target or a Collaboration Target at such time under the Collaboration (i.e., that the proposed approach is not a separate Strategy and a Party believes that it falls within a Strategy already being considered or for which target validation activities are already being pursued for the same target under the Collaboration) within [***] days after the date on which the Parties started discussing such matter, then the Parties will refer such matter for review and resolution by the CSC. If the CSC is unable to resolve such matter within [***] days following such referral, then such proposed approach shall not be pursued under the Collaboration unless and until the Parties mutually agree upon the terms upon which such approach can be progressed, such agreement not to be unreasonably withheld, conditioned or delayed. Notwithstanding anything to the contrary set forth in this Agreement, and without limiting Section 6.11.7, if Biogen believes that such proposed approach is a distinct approach from any other Strategy being pursued under the Collaboration at such time, and Ionis agrees that such approach is [***], then Biogen will have final decision-making authority to determine that such approach is a distinct approach and a separate Strategy to pursue under this Agreement.

(iv) ***Target Sanction Plans***. Ionis will submit a draft of each Target Sanction Plan to the Neurology JRC for its review and approval as soon as reasonably practicable after the Strategy Initiation Date. No later than [***] days after the Strategy Initiation Date for a given Strategy, the Parties will finalize a separate Target Sanction Plan for such Strategy, *provided that* if the next scheduled meeting of the Neurology JRC is not within such [***]-day period, then the Parties may mutually agree to postpone finalization of the Target Sanction Plan to the date of such meeting of the Neurology JRC. Upon approval of such Target Sanction Plan, the Neurological Disease Research Plan shall be updated to include such Target Sanction Plan. If the Neurology JRC cannot agree upon a final Target Sanction Plan within such [***]-day period following the applicable Strategy Initiation Date, or at such meeting of the Neurology JRC at which the Target Sanction Plan was considered, then either Party may refer the matter to the CSC for resolution. If the CSC cannot agree on a final Target Sanction Plan for any Strategy (or any update thereto) within an additional [***] days after the matter is so referred, then [***] will have final decision-making authority with respect to those elements of the applicable Target Sanction Plan to which the Neurology JRC or the CSC (as applicable) cannot agree; *provided*, *however*, that in its exercise of its final decision-making authority, [***] may not allocate to [***] any costs or obligations under any Target Sanction Plan without [***] written consent. Thereafter, the Parties will update each Target Sanction Plan as reasonably required until activities under such Target Sanction Plan have been completed (but no less than once every 12 months) and submit such updates to the Neurology JRC for its review and approval. The final Target Sanction Plan will include a summary of any [***] that the Parties (taking into account the recommendations of the [***]) consider are related to the applicable target or Strategy, or that may be [***] conduct of the activities under such Target Sanction Plan or the Development and Commercialization of Products directed to such High Interest Target or Collaboration Target (as applicable). The [***] will also make non-binding recommendations at the time the Target Sanction Plan is considered by the Neurology JRC in relation to any activities in such draft Target Sanction Plan that Ionis proposes should be conducted [***] and the Neurology JRC will consider such recommendations in good faith, but shall have no obligation to make any modification to the Target Sanction Plan as a result of such consideration.

(v) ***Performance of Target Validation Activities***. Ionis (and Biogen, where applicable) will use Commercially Reasonable Efforts to conduct activities to support Target Sanction in accordance with each Target Sanction Plan during each year of the Research Term (the "***Ionis Target Sanction Diligence Obligations***"). Each Target Sanction Plan will identify which Party will be responsible for the activities related to validation of the applicable Strategy directed to the applicable High Interest Target or Collaboration Target (as applicable). It is anticipated that (A) Biogen will perform the [***] work required under any Target Sanction Plan if at the applicable time Biogen already has in place at Biogen or through its collaborators the appropriate [***] and the ability to conduct such [***] work, and (B) Ionis will conduct all other such [***] work. Neither Party will be required to conduct work using [***]. Each Party will be responsible for the cost of the work that it conducts under the Neurological Disease Research Program as more specifically detailed in Section 1.12 and Section 1.13.

(e) ***Target Validation for Multi-Indication Targets***. If the Neurology JRC agrees to conduct target validation activities under the Neurological Disease Research Plan with respect to any Strategy directed to a Multi-Indication Target that the Parties did not agree to designate as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target pursuant to Section 1.2.3(c), then within [***] days after such agreement the CSC will meet to determine whether such target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If the CSC agrees on the appropriate classification for such Multi-Indication Target, then the provisions of clauses (b)-(e) of APPENDIX 3 will apply with respect to such Multi-Indication Target. If the members of the CSC cannot unanimously agree on the appropriate classification for a Multi-Indication Target at the applicable meeting, then such classification will be made pursuant to clause (a) of APPENDIX 3.

(f) ***Other Neurology Targets***. Subject to the terms of this Agreement, including the provisions of Section 1.4 and Section 2.1.1(b) (with respect to Ionis' obligations to Biogen in connection with Ionis Neurology Targets) and Section 1.8.5(b) (with respect to [***]), during the Research Term, either Party may work outside of the Collaboration on any Neurology Target that is not (i) a High Interest Target for which target validation activities are planned under the then-current Neurological Disease Research Plan, or (ii) a Collaboration Target. Notwithstanding Section 1.4, if, during the Research Term in the course of conducting work outside of the Collaboration under this Section 1.2.3(f) with respect to any High Interest Target, Ionis achieves Target Sanction with respect to any Strategy directed to such High Interest Target (as an Ionis Neurology Target), then Ionis will deliver under Section 1.3 a Target Sanction Data Package for such Strategy directed to such High Interest Target to the Neurology JRC for review as soon as reasonably practicable and Section 1.3 (and for clarity, not Section 1.4) will apply with respect to such Strategy and such Target Sanction Data Package.

1.3. Process for Designating Strategies as Collaboration Programs.

1.3.1. Target Sanction Data Packages. As soon as reasonably practicable after the Parties complete the activities in the agreed upon Target Sanction Plan for a particular Strategy directed to a High Interest Target or Collaboration Target, Ionis will deliver a Target Sanction Data Package to the Neurology JRC for review. Each time Ionis delivers to the Neurology JRC a Target Sanction Data Package under this Section 1.3, if requested by Biogen, Ionis will promptly provide to Biogen any additional supporting data in Ionis' possession that is reasonably necessary for Biogen to make a decision as to whether to designate such Strategy as a Collaboration Program and, if requested by Biogen, the Parties will schedule a meeting of the Neurology JRC within [***] days following delivery of such Target Sanction Data Package in order to obtain additional information in relation to the Target Sanction Data Package. On or before the date that is the later of (a) [***] days following such meeting of the Neurology JRC or (b) [***] days after Biogen's receipt of the applicable Target Sanction Data Package (such date, for each Strategy, the "***Collaboration Program Designation Date***") if Biogen desires to further progress Development activities with respect to such Strategy directed to such High Interest Target or Collaboration Target, then Biogen may designate such Strategy directed to such High Interest Target as a "***Collaboration Program***" under this Agreement, in which case, Biogen will make the Target Designation Milestone Payment for such Collaboration Program in accordance with Section 6.2 and thereafter Section 1.6 will apply. For clarity, in requesting additional supporting information in connection with a Target Sanction Data Package, Biogen may not request Ionis to perform any additional experiments or studies, or generate any additional data beyond that which is set forth in the applicable Target Sanction Plan.

1.3.2. **Collaboration Targets**. If at the time of such designation of such Strategy as a Collaboration Program, the Parties are not pursuing any other Collaboration Programs directed to the applicable High Interest Target, then such High Interest Target that is the subject of such newly-designated Collaboration Program will be a Collaboration Target for purposes of this Agreement (and, for clarity, if at the time of designation of such Strategy as a Collaboration Program the Parties are pursuing other Collaboration Programs directed to the applicable High Interest Target, such that the High Interest Target is already a Collaboration Target for purposes of this Agreement, then such target will remain a Collaboration Target). Biogen may also request at any time during the Research Term that Ionis evaluate one or more alternative Strategies directed to a Collaboration Target under a new Target Sanction Plan pursuant to Section 1.2.3(d)(ii), as long as at the time of such request, such Collaboration Target remains an Active Target.

1.3.3. **High Interest Targets that Become Limited Availability Neurology Targets**. With respect to a Strategy directed to a High Interest Target that has not yet been designated as a Collaboration Target, if, (a) on or before the Collaboration Program Designation Date for such Strategy Biogen does not designate such Strategy as a Collaboration Program or request that Ionis evaluate one or more alternative Strategies directed to such High Interest Target under a new Target Sanction Plan, and (b) Biogen has not made such designation or evaluation request by the earlier of [***] days following such Collaboration Program Designation Date or [***] days following receipt of written notice from Ionis of such failure to designate or make an evaluation request (the "***Collaboration Program Final Deadline***"), then the Strategy that was the subject of the Target Sanction Data Package for which Biogen failed to make such election will be deemed an "***Ionis Strategy***" solely with respect to such High Interest Target. In addition, if as of the Collaboration Program Final Deadline such High Interest Target is or becomes an Inactive Target, then such target will no longer be a High Interest Target and will instead be deemed a "***Limited Availability Neurology Target***." The provisions of Section 1.5, Section 2.1.1(b)(ii) and Section 2.1.1(e) will apply with respect to any such Ionis Strategy or Limited Availability Neurology Target.

1.4. **Process for Designating Strategies for Ionis Neurology Targets as Collaboration Programs**.

1.4.1. **Target Sanction Data Packages for Ionis Neurology Targets**. Subject to Section 1.2.3(f), if, during the Research Term in the course of conducting work outside of the Collaboration with respect to any Ionis Neurology Target, Ionis achieves Target Sanction with respect to any Strategy directed to such Ionis Neurology Target, then Ionis will deliver a Target Sanction Data Package for such Strategy directed to such Ionis Neurology Target to the Neurology JRC for review as soon as reasonably practicable. Each time Ionis delivers to the Neurology JRC a Target Sanction Data Package for a Strategy under this Section 1.4, if requested by Biogen, Ionis will promptly provide any additional supporting data in Ionis' possession that is reasonably necessary for Biogen to make a decision as to whether to designate such Strategy as a Collaboration Program. For clarity, in requesting additional supporting information in connection with a Target Sanction Data Package, Biogen may not request Ionis to perform any additional experiments or studies, or generate any additional data.

1.4.2. **Designation of Ionis Neurology Targets as Collaboration Programs**. Within [***] days after the date on which Ionis delivered the applicable Target Sanction Data Package to the Neurology JRC (for each Strategy, the "***Ionis Collaboration Program Designation Date***"), if Biogen desires to progress Development activities with respect to such Strategy directed to such Ionis Neurology Target, Biogen shall by written notice to Ionis designate such Strategy as a Collaboration Program and shall make the Target Designation Milestone Payment for such Collaboration Program in accordance with Section 6.2. Upon such designation, such Ionis Neurology Target will become a Collaboration Target for purposes of this Agreement, and Section 1.6 will apply. If Biogen does not so designate the Strategy for which Ionis presented the Target Sanction Data Package as a Collaboration Program, then Section 1.4.3 will apply.

1.4.3. **Alternative Strategies for Ionis Neurology Targets**. Biogen may, in accordance with this Section 1.4.3, request that Ionis evaluate one or more alternative Strategies directed to such Ionis Neurology Target instead of the Strategy for which the Target Sanction Data Package was presented to Biogen pursuant to Section 1.4.1. If (a) Biogen requests that Ionis evaluate one or more alternative Strategies directed to such Ionis Neurology Target instead of the Strategy for which the Target Sanction Data Package was presented to Biogen prior to the Ionis Collaboration Program Designation Date, (b) Ionis reasonably believes that [***] Section 1.2.3(d)(ii)(B), and (c) Biogen pays within [***] days of such acceptance the Target Designation Milestone Payment for the Strategy for which Ionis already presented a Target Sanction Data Package pursuant to Section 1.4.1 as if Biogen was intending to progress such Strategy as a Collaboration Program, then upon such payment, (i) such Ionis Neurology Target will be added to the High Interest Target List and become a High Interest Target, (ii) the process set forth in Section 1.2.3(d) will govern with respect to such accepted Strategy and any subsequent target validation activities for other Strategies directed to such High Interest Target and (iii) the process set forth in Section 1.3 (including the payment of the Target Designation Milestone Payment for such Strategy if subsequently designated as a Collaboration Program) will govern with respect to any subsequent Target Sanction Data Packages for such other Strategies directed to such High Interest Target. At any time during the Research Term until the date on which the applicable High Interest Target becomes an Inactive Target, Biogen may also elect to commence Development Candidate identification activities (as set forth in Section 1.8.2) for the original Strategy that was the subject of the original Target Sanction Data Package (as an Ionis Neurology Target) and for which Biogen already paid the Target Designation Milestone Payment.

1.4.4. **Ionis Neurology Targets that Become Limited Availability Neurology Targets**. If Biogen does not designate the Strategy presented by Ionis in its Target Sanction Data Package for an Ionis Neurology Target as a Collaboration Program under Section 1.4.2 by the applicable Ionis Collaboration Program Designation Date, or does not request that Ionis evaluate one or more alternative Strategies directed to such Ionis Neurology Target by the applicable Ionis Collaboration Program Designation Date and pay the applicable Target Designation Milestone Payment to designate such Ionis Neurology Target as a High Interest Target in accordance with Section 1.4.3, then such Ionis Neurology Target will be deemed a "***Limited Availability Neurology Target***," the Strategy that was the subject of such Target Sanction Data Package will be deemed an "***Ionis Strategy***" solely with respect to such Limited Availability Neurology Target and the provisions of Section 1.5 and Section 2.1.1(b)(ii) will apply with respect to such Limited Availability Neurology Target and such Ionis Strategy. If, however, Biogen requests that Ionis evaluate one or more such alternative Strategies directed to such Ionis Neurology Target and pays the Target Designation Milestone Payment as set forth in Section 1.4.3, then such target will become a High Interest Target. If such High Interest Target subsequently fails to reach Target Sanction for all such alternative Strategies and within [***] days after the date of such failure Biogen does not elect to commence Development Candidate identification activities (as set forth in Section 1.8.2) for the original Strategy that was the subject of the original Target Sanction Data Package (as an Ionis Neurology Target) under Section 1.4.3, or if such High Interest Target otherwise subsequently becomes an Inactive Target, then, in either case, such target will thereafter be deemed a "***Limited Availability Neurology Target***" and all of the Strategies that were the subject of Target Sanction Data Packages for such target delivered under Section 1.4.1 (whether originally as an Ionis Neurology Target or subsequently as a High Interest Target) will be deemed an "***Ionis Strategy***."

1.5. Process for Designating Limited Availability Neurology Targets as High Interest Targets.

1.5.1. Limited Availability Neurology Targets Generally. If Ionis by itself or with a Third Party has continued to use Commercially Reasonable Efforts to research and develop at least [***] compound or product for an Ionis Strategy directed to a Limited Availability Neurology Target for more than [***] months following the date on which the Target Sanction Data Package was delivered, then such Limited Availability Neurology Target will no longer be a Neurology Target under this Agreement, and each Party shall be free to pursue any Strategy directed to such target independently or with any Third Party. Notwithstanding the foregoing, if prior to the expiration of Ionis' exclusivity obligations under Section 2.1.1(b)(ii) with respect to a Limited Availability Neurology Target, Ionis has not granted rights to such Limited Availability Neurology Target to a Third Party (or if such Third Party's rights to such Limited Availability Neurology Target have terminated), and Ionis ceases all research, development or commercialization activities in relation to such Limited Availability Neurology Target, then such target may again become, at Biogen's request, a High Interest Target pursuant to Section 1.2.3(a).

1.5.2. Limited Availability Neurology Targets Developed by Ionis. Notwithstanding the foregoing, at any time prior to Ionis granting any rights to a Third Party in connection with any Limited Availability Neurology Target, Biogen may elect, by written notice to Ionis, that Biogen be granted rights to continue activities under this Agreement with respect to any Strategy directed to such Limited Availability Neurology Target that Ionis independently progressed past Target Sanction prior to such cessation. If Biogen delivers such a notification to Ionis, then the Parties will negotiate in good faith the terms upon which Ionis would grant Biogen such rights to such Limited Availability Neurology Target. Notwithstanding the foregoing, if Ionis intends, in good faith, itself or through an affiliated company, to commercialize Product(s) based on such Limited Availability Neurology Target, then it will not be considered a failure of the foregoing obligation to negotiate in good faith.

1.6. Consequences of Designating Collaboration Targets and Collaboration Programs.

1.6.1. Designation of Collaboration Targets. Subject to and in accordance with the terms of this Agreement, Ionis and Biogen will be responsible for conducting activities to discover, Develop and Manufacture Products that are the subject of each Collaboration Program designated under Sections 1.3, 1.4 or 1.5. Upon the License Effective Date with respect to a Collaboration Program, Biogen will be responsible for further Development, Manufacture and Commercialization of all Products that are the subject of such Collaboration Program. It is understood and agreed that there may be more than one Collaboration Program directed to a particular Collaboration Target, and after the first Strategy directed to a High Interest Target is designated as a Collaboration Program (thereby designating such High Interest Target as a Collaboration Target) additional Strategies directed to such Collaboration Target may be designated as separate Collaboration Programs throughout the Research Term so long as such target remains a Collaboration Target and is also an Active Target. For clarity, each Strategy designated by Biogen in accordance with Sections 1.3, 1.4 or 1.5 will be the subject of a separate Collaboration Program, subject to its own set of financial terms that apply to each Collaboration Program under ARTICLE 6 (notwithstanding the fact that one or more other Collaboration Programs directed to the same Collaboration Target may be ongoing simultaneously). A Development Candidate Identification Plan will be established for each Collaboration Program in accordance with Section 1.8.2(a).

1.6.2. Ionis Obligations. For each Collaboration Program, Ionis will (a) perform the obligations set forth in Section 1.8.2(b) with respect to generation of Development Candidates, and (b) if agreed by the Parties through the Neurology JDC or if elected by Ionis pursuant to Section 1.8.4(a) (with respect to a Collaboration Program that is a [***]), perform its obligations under Section 1.8.4(c); *provided that* in the case of (a), Ionis will not be required to commence work on more than [***] Collaboration Programs in any rolling [***]-month period unless (i) the Neurology JDC unanimously agrees to reallocate resources to support additional Collaboration Programs, (ii) Ionis is projected to fall under the [***]% Obligation at a Subsequent Measurement Date if it does not commence more than [***] Collaboration Programs during such [***] month period or (iii) the Parties mutually agree otherwise.

1.6.3. Certain Multi-Indication Targets. Notwithstanding the foregoing, if the applicable Collaboration Target is an Equal Multi-Indication Target, then the Parties will not conduct any activities under this Section 1.6 unless and until Ionis and Biogen have agreed on a development plan and enhanced economic provisions to be paid by Biogen for the Non-Neurological Indications pursuant to clause (c) of APPENDIX 3.

1.7. **End of Research Term**. At the end of the Research Term, (a) neither Ionis nor Biogen will have an obligation to perform any further activities under the Core Research Program; (b) if requested by Biogen, Ionis will complete all activities not yet completed under any ongoing Target Sanction Plans, and shall deliver to the Neurology JRC for review as soon as reasonably practical thereafter (i) any outstanding Target Sanction Data Packages, once completed, or (ii) where the activities under any Target Sanction Plan are not successful, the data and results generated by Ionis in completing the activities under each such Target Sanction Plan to the extent not already provided to Biogen; (c) the High Interest Target List will be dissolved except, solely for those High Interest Targets that achieved Target Sanction and for which Ionis has not delivered the deliverables required under subclauses (b)(i) and (b)(ii) of this Section 1.7, the High Interest Target List will dissolve after the expiration or exercise of Biogen's right to designate such targets as Collaboration Targets; (d) if one or more Strategies directed to one or more High Interest Targets have not been designated as Collaboration Programs (such that such High Interest Targets are not Collaboration Targets at such time) on or before the Collaboration Program Final Deadline under Section 1.3 or the Ionis Collaboration Program Designation Date under Section 1.4, then such targets will no longer be Neurology Targets under this Agreement and Ionis' obligations and Biogen's rights under this Agreement with respect to such targets and any ASOs targeting such targets will then terminate; (e) at Ionis' request, Biogen will provide to Ionis the data generated under the Core Research Program and the Neurological Disease Research Program to the extent licensed to Ionis under Section 4.3.4 and not already provided to Ionis; and (f) upon Biogen's request, Ionis will provide to Biogen the data generated under the Core Research Program and the Neurological Disease Research Program to the extent licensed to Biogen under Section 4.3.3 and not already provided to Biogen. For clarity, the expiration of the Research Term will not affect Biogen's rights or Ionis' obligations with respect to Collaboration Targets or the identification of Development Candidates for Collaboration Programs under this Agreement.

1.8. **Research and Development Responsibilities**.

1.8.1. **Development Goals**. Ionis will generate at least [***] Development Candidate for at least [***]% of the Collaboration Programs for which the Development Candidate Generation Period has expired (the "***[***]% Obligation***"). During the Research Term, the Parties will monitor Ionis' progress towards achieving the [***]% Obligation as follows:

(a) No later than the expiration of the Development Candidate Generation Period for the [***] Collaboration Program (the "***First Measurement Date***"), Ionis will have generated at least [***] Development Candidate for at least [***] of such [***] Collaboration Programs. For clarity, the Parties agree to round down to the nearest whole number when making a [***]% calculation (e.g., [***]% of [***] Collaboration Programs equals [***] Collaboration Programs, which rounds down to [***] Collaboration Programs).

(b) During the Research Term, The Parties will thereafter continue to evaluate Ionis' progress toward achieving the [***]% Obligation on each anniversary after the First Measurement Date (each a "***Subsequent Measurement Date***"). By the applicable Subsequent Measurement Date, Ionis will have generated at least [***] Development Candidate for at least [***]% of the total number of Collaboration Programs (i) for which Biogen has paid a Target Designation Milestone Payment and (ii) for which the Development Candidate Generation Period has expired. For example, if (A) a Subsequent Measurement Date falls on January 15, 2022, (B) Biogen has paid the Target Designation Milestone Payments for the [***] Collaboration Program on or before such Subsequent Measurement Date, (C) the Development Candidate Generation Periods (as such periods may be extended pursuant to Section 1.8.1(e)) for [***] of such Collaboration Programs have already expired by such Subsequent Measurement Date, and the Development Candidate Generation Periods for [***] of such Collaboration Programs have not expired by such Subsequent Measurement Date and (D) Ionis has generated at least [***] Development Candidate for [***] out of [***] of such Collaboration Programs for which the Development Candidate Generation Period has expired by such Subsequent Measurement Date, then Ionis will be on track to achieving the [***]% Obligation.

(c) If at the First Measurement Date or any Subsequent Measurement Date, Ionis is not on track to achieve the [***]% Obligation as set forth in Sections 1.8.1(a) or 1.8.1(b), as applicable, then the Parties will discuss at the next Neurology JRC meeting to identify ways in which Ionis might achieve the [***]% Obligation during the remainder of the Research Term.

(d) Notwithstanding the foregoing ((a) through (c)), if (1) Ionis is not on track to achieve the [***]% Obligation as measured on the Subsequent Measurement Date that falls in the [***] year of the Research Term (regardless of whether or not Ionis is using Commercially Reasonable Efforts) and (2) (I) Ionis has not generated at least one Development Candidate for a total of at least [***] Collaboration Programs by such date or (II) Biogen has not exercised its Option for at least [***] Collaboration Programs by such date, then:

(i) the Research Term will automatically extend until the earlier of (A) the [***] anniversary of the Effective Date, or (B) the date on which the Parties have generated at least one Development Candidate for at least [***]% of the Collaboration Programs for which Biogen has paid the Target Designation Milestone Payment (the "***Research Term Extension Date***"); and

(ii) Biogen may elect at its sole discretion at any time during the remainder of the Research Term to assume responsibility for any or all target validation activities and drug discovery activities under this Agreement with respect to existing or new High Interest Targets or Collaboration Targets, in which case Ionis shall within [***] days following the effective date of Biogen's notice electing to exercise its step-in rights under this Section 1.8.1(d)(ii), deliver to one of Biogen or Biogen's designated Affiliate or Third Party contractor (at Biogen's election), all Ionis Manufacturing and Analytical Know-How and Ionis Know-How in Ionis' Control that is necessary (A) to conduct those activities for which Biogen has exercised its step-in rights under this Section 1.8.1(d)(ii) and (B) to Manufacture and supply research grade ASOs sufficient to support such activities, in each case ((A) and (B)), solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf to conduct such assumed activities. In addition, Ionis will provide to Biogen, and its Affiliates and Third Party contractors all Know-How, assistance, assignments and other support reasonably requested by Biogen solely to enable Biogen to assume responsibility for and perform such assumed activities in an efficient and orderly manner. In the event of such a step-in by Biogen, Biogen will assume final decision-making ability with respect to any Neurology Plans that cover the activities for which Biogen elects to assume responsibility under this Section 1.8.1(d)(ii) and Biogen will solely make all decisions with respect to such activities and Neurology Plans for which the Neurology JRC, the applicable Neurology JDC, the JPC, the CSC or any other subcommittees or working groups, or the Parties collectively, would otherwise be permitted or required to make under this Agreement; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis. If Biogen elects to trigger one or more of the remedies set forth in this Section 1.8.3(d)(ii), then all payment obligations with respect to the applicable Collaboration Programs will remain in full force and effect in accordance with ARTICLE 6, except that Biogen will be permitted to offset against subsequent milestone payments payable to Ionis with respect to each assumed Collaboration Program or High Interest Target, those reasonable costs and expenses associated with Biogen's performance of such activities for such Collaboration Program or High Interest Target that would otherwise have been Ionis Activities and the responsibility of Ionis under Section 1.12.

(e) If a Collaboration Program utilizes a novel Strategy that, in a Party's reasonable determination, makes achieving a timeline under this Agreement (such as identification of a Development Candidate within the Development Candidate Generation Period) unlikely (e.g., an [***]), then the Neurology JRC will meet to discuss and agree upon any appropriate revisions to the applicable timelines for such Collaboration Program, including the Development Candidate Generation Period (if applicable).

(f) Except where Ionis has failed to meet the [***]% Obligation due to its failure to satisfy its obligations set forth under subclause (i) or (ii) of Section 1.8.2(b), the remedies set forth in Section 1.8.1(d), shall be Biogen's sole and exclusive remedy for Ionis' failure to meet the [***]% Obligation in accordance with the terms of this Agreement.

1.8.2. Development Candidate Identification.

(a) **Development Candidate Identification Plans**. Within [***] days after the designation of each Collaboration Program, Ionis will submit to the Neurology JRC for its review and approval an initial draft plan to identify Development Candidates under such Collaboration Program, which plan may include activities related to the identification of biomarkers if determined by the Neurology JRC, shall take into account any recommendations of the [***] in relation to [***] considerations for such potential Development Candidates and shall include a list prepared by Biogen of any [***] that the [***] agrees to include in such plan (such plan, as may be modified from time to time to address the discovery, research and optimization activities to be conducted under such Collaboration Program, a "***Development Candidate Identification Plan***"). No later than [***] days after the designation of each Collaboration Program, or if the Parties mutually agree, at the next Neurology JRC meeting, the Parties or the Neurology JRC will agree on all other aspects of such final Development Candidate Identification Plan, which plan (and the Key Criteria set forth therein) will be generally consistent with Ionis' other plans for other gene targets and which plan will include any other activities that should be initiated during the Development Candidate Identification Term, such as natural history studies and endpoint development. Ionis will update each Development Candidate Identification Plan as needed and submit it to the Neurology JRC for its review and approval. In addition, either Party may propose updates to the Development Candidate Identification Plan and submit such proposed updates to the Neurology JRC for its review and approval. If the Neurology JRC cannot agree upon any aspect of a final Development Candidate Identification Plan for a Collaboration Program (or any proposed updates thereto) within [***] days following discussion at the meeting of the Neurology JRC, then either Party may refer the matter to the CSC for resolution. If the CSC cannot agree on any aspect of a final Development Candidate Identification Plan for a Collaboration Program or a proposed update thereto within an additional [***] days after the matter is so referred, then Ionis will have final decision-making authority with respect to any other elements of the applicable Development Candidate Identification Plan to which the Neurology JRC or the CSC (as applicable) cannot agree; *provided*, *however*, that Ionis shall not (i) include any Biogen Background Technology or (ii) allocate to Biogen any costs or obligations, in each case ((i) and (ii)), under any Development Candidate Identification Plan (or update thereto) without Biogen's written consent. Ionis will carry out its drug discovery efforts for each Collaboration Program in accordance with the applicable Development Candidate Identification Plan and in a manner consistent with its internal practices for other gene targets with the goal of identifying Development Candidates for the applicable Collaboration Program as soon as practicable. Notwithstanding anything to the contrary set forth in this Agreement, Ionis will not start work on any Equal Multi-Indication Target unless and until Ionis and Biogen have agreed on a development plan and enhanced economic provisions to be paid by Biogen for Non-Neurological Indications in accordance with APPENDIX 3.

(b) **Development Candidate Identification Diligence**. Ionis shall (i) use Commercially Reasonable Efforts to conduct drug discovery activities according to the applicable Development Candidate Identification Plan, (ii) use Commercially Reasonable Efforts to generate at least one Development Candidate and at least one Related Program Compound for each Collaboration Program for which Ionis conducts identification activities under a Development Candidate Identification Plan (with a goal of generating up to [***] Development Candidates or Related Program Compounds for each such Collaboration Program), and (iii) include within a Development Candidate Data Package as many Compounds as Ionis' RMC considers, in its reasonable judgment, are suitable Related Program Compounds.

(c) **Biomarker, Endpoint and Natural History Work**. If the Neurology JRC agrees to include biomarker work, natural history studies or endpoint development in the Development Candidate Identification Plan, then Biogen shall be responsible for performing such biomarker work natural history studies or endpoint development.

(d) **Development Candidate Identification Term**. On a Collaboration Program-by-Collaboration Program basis, the term for the conduct of the applicable Development Candidate Identification Plan will begin on the date the applicable Strategy directed to a Neurology Target becomes a Collaboration Program and will end upon the earlier of (i) designation of a Development Candidate for such Collaboration Program, and (ii) the date on which Ionis notifies Biogen that Ionis has in good faith determined that the identification of a Development Candidate under the applicable Development Candidate Identification Plan is no longer technically feasible under the then-current state of the art (a "***Technical Failure***" and such term, with respect to the applicable Collaboration Program, the "***Development Candidate Identification Term***").

(e) **Technical Failure Resolution**. If Biogen disagrees with Ionis' determination that a Technical Failure has occurred with respect to any Collaboration Program, then it may refer the matter to Expert Resolution under Section 12.1.4. In the event of any Expert Resolution under this Section 1.8.2(e), Ionis will not be required to conduct any activities under the applicable Development Candidate Identification Plan during the pendency of such proceeding, but the Development Candidate Identification Term will not conclude until such Third Party expert makes a determination that such a Technical Failure has occurred with respect to the applicable Collaboration Program.

(f) **End of Development Candidate Identification Term**. If, at the end of the final Development Candidate Identification Term for all Collaboration Programs directed to a particular Collaboration Target, no potential Development Candidates have been identified for any Collaboration Program directed to such Collaboration Target, and (if the Research Term is still ongoing) more than [***] days have passed since the Parties stopped pursuing or evaluating any other Strategy against such Collaboration Target (a "***Target Technical Failure***" and such date, the "***Target Technical Failure Date***"), then, subject to Section 1.8.2(g), (i) Ionis and Biogen will no longer have an obligation to perform any activities under this ARTICLE 1 with respect to such Collaboration Programs; (ii) such Strategies will no longer be Collaboration Programs and the applicable gene target to which such Strategies are directed will no longer be a Collaboration Target; (iii) except as expressly set forth in Section 1.8.2(g) with respect to Ionis' obligation to present Carryover Development Candidates to Biogen, Ionis' obligations and Biogen's rights under this Agreement with respect to such gene target and any ASOs targeting such gene target that is the subject of such Collaboration Programs will then terminate; (iv) upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program to the extent licensed to Ionis under Section 4.3.4; and (v) upon Biogen's request, Ionis will provide to Biogen any data generated under the Collaboration Program to the extent licensed to Biogen under Section 4.3.3. For each Collaboration Program for which Ionis has identified potential Development Candidates, Ionis will remain obligated to complete all other activities (if any) agreed to by the Parties and included under the applicable Development Candidate Identification Plan for such Collaboration Program with respect to such potential Development Candidates.

(g) **Carryover Development Candidates**. If a Target Technical Failure occurs with respect to a Collaboration Target, and at any time during the [***]-month period after the Target Technical Failure Date for such Collaboration Target (for each such Collaboration Target, the "***Carryover Period***"), Ionis' RMC designates as development candidates ready to start IND-Enabling Toxicology Studies one or more ASOs discovered by Ionis designed to bind to the RNA that encodes such Collaboration Target using any Strategy (each such ASO, a "***Carryover Development Candidate***"), then Ionis will notify Biogen and will provide Biogen with the data package presented to Ionis' RMC in connection with such approval by Ionis' RMC of such Carryover Development Candidate. Biogen will then have [***] days from its receipt of such data package to provide written notice to Ionis electing to deem such Carryover Development Candidates as Compounds and at least one of such Carryover Development Candidates as a Development Candidate under a Collaboration Program and then thereafter continue activities under this Agreement with respect to such Collaboration Program, with such date of written notice deemed the date of Development Candidate designation under Section 1.8.3(d), and all terms of this Agreement will apply to such Collaboration Program (and the applicable target that such Collaboration Program is directed to will again become a Collaboration Target for purposes of this Agreement). For clarity, no additional up-front payment under Section 6.1 and no additional Target Designation Milestone Payment will be due. If Biogen does not provide written notice to Ionis within [***] days of receipt of such data package electing to resume activities under this Agreement with respect to the applicable former Collaboration Target, then Ionis will have no further obligations and Biogen will have no further rights with respect to such Carryover Development Candidate or any of the associated former Collaboration Programs and such Collaboration Target will no longer be a Neurology Target under this Agreement.

1.8.3. **Development Candidates**.

(a) **Development Candidate Data Package; Related Program Compounds**. Unless otherwise mutually agreed by the Parties, Ionis' RMC shall only approve a Compound as a potential Development Candidate for a Collaboration Program if such Compound satisfies the Key Criteria set forth in the applicable Development Candidate Identification Plan for such Collaboration Program. Ionis will provide Biogen, through the Neurology JDC, or by written notice to Biogen if such Neurology JDC meeting is not scheduled within [***] days of such approval by Ionis' RMC, with a complete Development Candidate Data Package for each Collaboration Program within [***] days following the date on which Ionis' RMC approves a potential Development Candidate for such Collaboration Program. Such Development Candidate Data Package will include at least one Compound that Ionis' RMC has approved as a suitable lead Development Candidate for such Collaboration Program and will include any other Compounds that Ionis' RMC considered as possible Development Candidates in connection with its review of Compounds generated under the applicable Development Candidate Identification Plan for the applicable Collaboration Program (all such additional Compounds that are identified by Ionis' RMC as potential backup Compounds, the "***Related Program Compounds***"). In each Development Candidate Data Package, Ionis will identify the Compound included therein that Ionis recommends be selected as the lead Development Candidate for the applicable Collaboration Program. However, Biogen will be under no obligation to accept Ionis' recommendation as to which Compound Biogen should designate as the lead Development Candidate. The Development Candidate Data Package will include a level of detail for the proposed Development Candidate and any Related Program Compounds that Ionis typically has for its other programs, as appropriate for the applicable Collaboration Program. Within [***] days of receipt of a Development Candidate Data Package pursuant to this Section 1.8.3(a), Biogen or an Affiliate will notify Ionis of any omissions or deficiencies that Biogen or its Affiliate believes in good faith cause the Development Candidate Data Package to be incomplete with respect to the any proposed Development Candidate or Related Program Compound described therein ("***Development Candidate Data Package Deficiency Notice***"). Ionis will promptly, and in any event within [***] days of receipt of the Development Candidate Data Package Deficiency Notice, resubmit a complete Development Candidate Data Package to Biogen or its designated Affiliate, including any information that Biogen identified in the Development Candidate Data Package Deficiency Notice. If the Parties do not agree as to whether the Development Candidate Data Package is complete, either Party may refer the matter for resolution by the CSC. If the CSC cannot resolve the dispute within [***] days following the date of such referral, then the dispute will be escalated for resolution by the Executives. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete Development Candidate Data Package. For clarity, in requesting additional supporting information in connection with such a dispute, Biogen may not request Ionis to perform any additional experiments or studies, or generate any additional data, beyond that which is set forth in the applicable Development Candidate Identification Plan.

(b) **Additional Development Candidate Data Package**. Biogen may request that Ionis conduct additional research or drug discovery activities (excluding additional target validation activities) using the same Strategy to generate one or more additional Development Candidate Data Packages for a Collaboration Program for which Ionis has already provided a complete Development Candidate Data Package in accordance with Section 1.8.3(a). If Ionis agrees to perform such activities, then within [***] days of the agreement by the Parties upon a new Development Candidate Identification Plan for such Collaboration Program, Biogen shall pay to Ionis an additional Target Designation Milestone Payment (as if Biogen had just designated such Collaboration Program) to initiate such work, Ionis shall begin work under such Development Candidate Identification Plan pursuant to Section 1.8.2(b) and the remainder of this Section 1.8 shall apply with respect to the performance of such additional development candidate identification activities. Thereafter for purposes of this Agreement, all Compounds contained in such additional Development Candidate Data Package will be considered part of the same Collaboration Program as the prior Development Candidate Data Package for which Biogen paid the additional Target Designation Milestone Payment, and the timelines to designate a Development Candidate for such Collaboration Program, to Initiate IND-Enabling Toxicology Studies for such Collaboration Program and to exercise the Option for such Collaboration Program will restart from the date upon which Ionis delivers the complete additional Development Candidate Data Package to Biogen. After Ionis delivers the initial Development Candidate Data Package for a Collaboration Program, any such efforts to generate one or more additional Development Candidate Data Packages for such Collaboration Program, whether successful or unsuccessful, shall not be included in the calculation of the [***]% Obligation under Section 1.8.1.

(c) **Development Candidate Toxicology Strategy**. On a Development Candidate-by-Development Candidate basis, the applicable Neurology JDC will agree upon a high level pre-clinical toxicology strategy to enable a first-in-human study, which shall be comprised of each of the components set forth on SCHEDULE 1.8.3(c) and shall include any contract research organization ("***CRO***") to be used to conduct the applicable IND-Enabling Toxicology Studies (the "***Toxicology Strategy***") for each Development Candidate Data Package delivered by Ionis in accordance with Section 1.8.3(a). The applicable Neurology JDC will agree upon the Toxicology Strategy with respect to any potential Development Candidates directed to a Collaboration Target, no later than [***] days following the delivery of the Development Candidate Data Package for such potential Development Candidates directed to such Collaboration Target to the Neurology JDC in accordance with Section 1.8.3(a) or, with respect to a Carryover Development Candidate, within [***] days of Biogen's written notice to Ionis electing to deem such Carryover Development Candidate as a Development Candidate under a Collaboration Program pursuant to Section 1.8.2(g). The Neurology JDC may mutually agree to extend any such deadline if the Parties would like more time to discuss the applicable Toxicology Strategy. Notwithstanding the foregoing, in order to facilitate earlier preparation of an agreement on the Toxicology Strategy and earlier commencement of IND-Enabling Toxicology Studies for Development Candidate, where reasonably practicable, Ionis will notify Biogen at least [***] days in advance of its presentation of a Development Candidate Data Package for a Collaboration Program to Ionis' RMC, and the Parties will discuss the preparation of the Toxicology Strategy at the next scheduled meeting of the Neurology JDC. If the Neurology JDC cannot agree upon a Toxicology Strategy within the applicable time period as set forth in this Section 1.8.3(c), then either Party may refer the matter to the CSC for resolution. If the CSC cannot agree on such Toxicology Strategy within [***] days after the matter is so referred, then [***] will have final decision-making authority with respect to any such Toxicology Strategy, *provided that* [***] shall exercise its final decision-making authority no later than [***] Business Days following the earlier of the CSC's determination that it is unable to agree, or the expiration of the [***]-day period allowed for the CSC to agree pursuant to the foregoing sentence.

(d) **Development Candidate Designation**.

(i) Within [***] days following Ionis' delivery of a Development Candidate Data Package with respect to a Collaboration Program to Biogen pursuant to Section 1.8.3(a) (which period will begin upon resolution of any dispute regarding omissions or deficiencies with respect to such Development Candidate Data Package in accordance with Section 1.8.3(a), including the delivery of information to resolve such omissions or deficiencies, if applicable), the Neurology JDC will discuss whether to designate the Compound proposed by Ionis as the Development Candidate (or any Related Program Compounds) as the lead Development Candidate for such Collaboration Program, taking into account the input of the [***] with respect to its [***] assessment of such proposed Development Candidate and Related Program Compounds. Any designation of a Development Candidate for a Collaboration Program by the Neurology JDC will be documented in the written minutes of the Neurology JDC. If the Neurology JDC mutually agrees to designate the Compound recommended by Ionis as the lead Development Candidate or any Related Program Compound as a Development Candidate for a Collaboration Program, then the Parties will conduct the IND-Enabling Toxicology Studies for such selected Development Candidates under the applicable Toxicology Strategy that has been agreed to in accordance with Section 1.8.3(c).

(ii) If the Neurology JDC cannot agree as to whether to designate any Compound proposed by Ionis as the lead Development Candidate or Related Program Compound as Development Candidates within [***] days after the Neurology JDC meets to discuss the applicable Development Candidate Data Package (such [***]-day period for a Collaboration Program, the "***Development Candidate Decision Period***"), then Biogen will have final decision-making authority as to whether to designate any such proposed Development Candidate or Related Program Compound as a Development Candidate for such Collaboration Program and Biogen will notify the Neurology JDC in writing of its determination.

(iii) If the Neurology JDC (or Biogen through the exercise of its final decision-making authority) does not designate any of the Ionis-proposed lead Development Candidate or Related Program Compounds as Development Candidates for a given Collaboration Program within the Development Candidate Decision Period, and Biogen has not cured such failure to designate a Development Candidate within the earlier of [***] days following the missed deadline or [***] days following a written notice from Ionis of the missed deadline (the "***Development Candidate Designation Deadline***"), then, (A) Biogen's Option with respect to such Collaboration Program will terminate; (B) neither Ionis nor Biogen will have an obligation to perform any further activities under this ARTICLE 1 with respect to such Collaboration Program; (C) such program will no longer be a Collaboration Program, (D) unless the applicable Collaboration Target that is the subject of such Collaboration Program is an Active Target, such target shall cease to be a Collaboration Target and shall no longer be a Neurology Target under this Agreement at such time; (E) upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program to the extent licensed to Ionis under Section 4.3.4; (F) upon Biogen's request, Ionis will provide to Biogen any data generated under the Collaboration Program to the extent licensed to Biogen under Section 4.3.3; and (G) with respect to any Ionis-proposed lead Development Candidate and any Related Program Compounds included in the applicable Development Candidate Data Package, effective on the day that the applicable Collaboration Target that such proposed Development Candidates and Related Program Compounds target becomes a Terminated Target, Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, non-exclusive royalty-bearing (in accordance with Section 1.8.3(d)(iv)) license or sublicense, as the case may be, to Biogen Background Technology Controlled by Biogen as of such date solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize such Ionis-proposed lead Development Candidate and such Related Program Compounds, in each case, targeting such Terminated Target, in the Field in the form such Compounds exist as of such date other than Permitted Changes in Form with respect to such lead Development Candidate or Related Program Compounds (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*). Ionis will reimburse Biogen for any amounts owed by Biogen to Third Parties as a result of the grant of any such license to Ionis under, or Ionis' practice of, any Biogen Background Technology; *provided that* Ionis has been notified of the terms of such payment obligations to any such Third Party, and, if Ionis notifies Biogen that it does not wish to be granted a license under any Patent Rights or Know-How that are subject to such payment obligations included in the Biogen Background Technology, then such Patent Rights or Know-How (as applicable) will be excluded from the Biogen Background Technology licensed to Ionis hereunder, and Ionis will have no obligation to reimburse Biogen for any such payments.

(iv) If Ionis or its Affiliates or Sublicensee sells any product that includes any such proposed Ionis-proposed lead Development Candidate or Related Program Compounds, in each case, that Biogen fails to designate as a Development Candidate by the applicable Development Candidate Designation Deadline that is Covered by any Patent Rights within the Biogen Background Technology, then on a country-by-country basis Ionis will pay to Biogen a royalty equal to [***]of net sales of any such product sold by Ionis, its Affiliates or Sublicensees, for so long as such product is Covered by such Patent Rights within the Biogen Background Technology in such country. For the purpose of the foregoing royalty calculation, "net sales" will be calculated in accordance with the definition of "Net Sales" as set forth in APPENDIX 1, applied *mutatis mutandis* to such calculation. The provisions of Sections 6.12, 6.13, 6.14 and 6.15 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 1.8.3(d)(iv). If the Parties are unable to agree as to the [***] under this Section 1.8.3(d)(iv) within a period of [***] days after the applicable Development Candidate Designation Deadline, then either Party may refer the matter to Expert Resolution under Section 12.1.4.

(v) If at the time of the Development Candidate Designation Deadline, the applicable Collaboration Target is an Active Target, then Biogen's rights in such Collaboration Target in connection with all other Strategies and Collaboration Programs for such Collaboration Target shall remain unaffected and each Party's rights and obligations under Section 2.1 shall continue in full force and effect.

(e) [***] Development Candidates. If, in conducting activities under a given Development Candidate Identification Plan and with respect to a proposed Development Candidate, Ionis utilizes or incorporates a [***], then Ionis shall identify the applicable Development Candidate or Related Program Compound in the Development Candidate Data Package as a "***[***] Compound***". Ionis shall have the right to elect, by notice to be included within the Development Candidate Data Package for a Collaboration Program, to conduct the IND-Enabling Toxicology Studies for one or more [***] Compounds that are included in such Development Candidate Data Package, should such [***] Compounds be designated by Biogen as Development Candidates (each such Development Candidate, a "***[***] Development Candidate***").

1.8.4. IND-Enabling Toxicology Studies.

(a) IND-Enabling Toxicology Study Design. Biogen shall have the right to make the final decision regarding which and how many of the proposed lead Development Candidate or Related Program Compounds for any Collaboration Program are to be advanced into IND-Enabling Toxicology Studies as Development Candidates, subject to the Parties agreeing upon the Toxicology Strategy under Section 1.8.3(c), and the requirements of this Section 1.8.4(a). Subject to the IND-Enabling Toxicology Study Completion Date and the Option Deadline, Biogen shall have the right to make the final decision regarding the timing and the order in which to conduct the IND-Enabling Toxicology Studies for Development Candidates. For clarity, Biogen may designate additional Development Candidates at a later date if Biogen wishes to conduct IND-Enabling Toxicology Studies on additional Compounds. The applicable Neurology JDC shall agree upon the study design and any amendments to the Toxicology Strategy for each IND-Enabling Toxicology Study for each Development Candidate (which study design will be in the form of a draft study protocol for the relevant *in vivo* studies to be conducted under the Toxicology Strategy) at least [***] days prior to the anticipated first dosing of the first animal in such IND-Enabling Toxicology Study. Notwithstanding the foregoing, if the Neurology JDC cannot agree upon a study design for an IND-Enabling Toxicology Study or any amendment to a Toxicology Strategy within the applicable time period as set forth in this Section 1.8.4(a), then either Party may refer the matter to the CSC for resolution. If the CSC cannot agree on the study design for an IND-Enabling Toxicology Study or any amendment to a Toxicology Strategy within [***] days after the matter is so referred, as applicable, then Biogen will have final decision-making authority with respect to any such IND-Enabling Toxicology Study design or such Toxicology Strategy amendment, *provided that* Biogen shall exercise its final decision-making authority by the date that is [***] Business Days following the earlier of (i) the CSC's determination that it is unable to agree, or (ii) the expiration of the [***]-day period allowed for the CSC to agree pursuant to the foregoing sentence. Biogen will conduct the IND-Enabling Toxicology Studies under the applicable Toxicology Strategy and study design. Notwithstanding the foregoing, (A) Ionis shall have the right to elect, by providing written notice in the applicable Development Candidate Data Package for a Collaboration Program pursuant to Section 1.8.3(e), to conduct the IND-Enabling Toxicology Studies for any [***] Compounds that are included in the Development Candidate Data Package for such Collaboration Program that Biogen elects to designate as Development Candidates and advance to IND-Enabling Toxicology Studies, and (B) if the Parties agree through the Neurology JDC, then Ionis may conduct IND-Enabling Toxicology Studies for any other Development Candidate for which Ionis provided a notice of interest in the applicable Development Candidate Data Package, in each case of (A) and (B), at [***] and in accordance with Sections 1.8.4(c) and 1.8.4(d). In conducting any IND-Enabling Toxicology Studies under this Section 1.8.4 for those categories of IND-Enabling Toxicology Studies listed on SCHEDULE 1.8.4(a), the Parties will not use a CRO to conduct any such IND-Enabling Toxicology Studies that is not either (i) an "*Approved CRO*" listed on SCHEDULE 1.8.4(a) with respect to the applicable category of IND-Enabling Toxicology Studies, or (ii) approved in writing by the other Party, such approval not to be unreasonably withheld, conditioned or delayed. If the members of the Neurology JDC unanimously agree, then the Parties may add or remove CROs to or from the "*Approved CRO*" list and categories of IND-Enabling Toxicology Studies by adding such updated list of Approved CROs to the minutes of the Neurology JDC meeting at which such changes were discussed.

(b) **Biogen Performance of IND-Enabling Toxicology Studies**. Biogen will Initiate the first IND-Enabling Toxicology Study for a Development Candidate targeting each Collaboration Target within [***] days following the later of (i) Neurology JDC's agreement on (or Biogen's determination thereof in the exercise of its final decision-making authority) the Toxicology Strategy under Section 1.8.3(c), and (ii) the date Biogen receives the Development Candidate Data Package under Section 1.8.3(a) (such date, the "***IND-Enabling Toxicology Strategy Date***"), in each case for the applicable Development Candidate targeting such Collaboration Target, unless Ionis is responsible for conducting such IND-Enabling Toxicology Study pursuant to Section 1.8.4(a). If Biogen is responsible for conducting the first IND-Enabling Toxicology Study for the first Development Candidate targeting a Collaboration Target, and Biogen fails to Initiate such first IND-Enabling Toxicology Study within [***] days following the IND-Enabling Toxicology Strategy Date for such Collaboration Program, and Biogen has not cured such failure by Initiating such IND-Enabling Toxicology Study within the earlier of [***] days following the missed deadline or [***] days following receipt of written notice from Ionis of the missed deadline, then Biogen will be deemed to have terminated this Agreement under Section 10.3.2 solely with respect to such Collaboration Program (but not with respect to the applicable Collaboration Target, to the extent that such Collaboration Target is an Active Target at such time). Notwithstanding the foregoing, (i) the Neurology JDC may extend such [***]-day period for any length of time by unanimous agreement of its members, (ii) if there is a delay in Initiating such IND-Enabling Toxicology Study caused by a condition reasonably outside of the control of the Party responsible for conducting such IND-Enabling Toxicology Study (including a delay by a Third Party vendor, or a change in the Party that is responsible for conducting such IND-Enabling Toxicology Study), then, so long as such Party is taking reasonable steps to cure such condition, in each case, such [***]-day period will be tolled for so long as such condition continues, or solely in the case of a change in the Party conducting the IND-Enabling Toxicology Study, such [***]-day period will restart from the date upon which the change in the conducting Party occurs, (iii) if the Party responsible for conducting the IND-Enabling Toxicology Study conducts a pre-IND meeting or other similar meeting with a Regulatory Authority, and the feedback received from such Regulatory Authority results in a material change to the applicable Toxicology Strategy or study design, then such [***]-day period will be tolled for a reasonable period while such Party is working to make such changes and (iv) if either Party in good faith believes that, due to the novelty of the applicable Strategy, or new scientific or technological information or an advance in the state of the art with respect to the Development Candidate, Collaboration Program or Collaboration Target at issue, additional work should be conducted prior to the Initiation of such IND-Enabling Toxicology Study, then the applicable [***]-day period will be tolled for a reasonable period to take account of such novel Strategy, new scientific or technical information or advance in the state of the art, up to a maximum of [***] days while such additional work is performed (each of (i) through (iv), an "***IND Delay Condition***").

(c) **Ionis Performance of IND-Enabling Toxicology Studies**. If Ionis elects to, or the Neurology JDC determines that Ionis will, conduct an IND-Enabling Toxicology Study for a Development Candidate directed to a Collaboration Target under Section 1.8.4(a) (each, an "***Ionis-Conducted IND-Enabling Toxicology Study***"), then Ionis will Initiate such Ionis-Conducted IND-Enabling Toxicology Study within [***] days following Biogen's decision to proceed with IND-Enabling Toxicology Studies for such Development Candidate, and Ionis will use Commercially Reasonable Efforts to conduct each Ionis-Conducted IND-Enabling Toxicology Study pursuant to the applicable Toxicology Strategy and IND-Enabling Toxicology Study design determined in accordance with Section 1.8.4(a) (collectively, the "***Ionis IND Study Diligence Obligations***"). If Ionis fails to Initiate an Ionis-Conducted IND-Enabling Toxicology Study within [***] days following Biogen's decision to proceed with IND-Enabling Toxicology Studies for such Collaboration Program, and Ionis has not cured such failure by Initiating such Ionis-Conducted IND-Enabling Toxicology Study within the earlier of [***] days following the missed deadline or [***] days following receipt of written notice from Biogen of the missed deadline, then Biogen will have the right, at its sole discretion, to conduct such IND-Enabling Toxicology Studies instead of Ionis. Notwithstanding the foregoing, Ionis' diligence obligations under this Section 1.8.4(c) (whether for the first or a subsequent IND-Enabling Toxicology Study under a Collaboration Program or for a Collaboration Target) will be tolled for the period during which any IND Delay Condition exists to the same extent as Biogen's diligence obligations may be extended or tolled under Section 1.8.4(b).

(d) **Ionis IND-Enabling Toxicology Costs**. Prior to the commencement of any Ionis-Conducted IND-Enabling Toxicology Studies, Ionis shall provide a good faith detailed estimate of Ionis' fully burdened cost (including any [***]) expected to be incurred in connection with conducting such IND-Enabling Toxicology Studies and the Parties shall agree, through the Neurology JDC, upon a budget for such IND-Enabling Toxicology Studies (such Neurology JDC-approved costs, the "***Ionis IND-Enabling Toxicology Costs***"). Ionis shall submit invoices to Biogen for (i) the amount that is [***] of the total amount of the Ionis IND-Enabling Toxicology Costs promptly following the first animal dose in the applicable Ionis-Conducted IND-Enabling Toxicology Study, (ii) [***] of the total amount of such Ionis IND-Enabling Toxicology Costs promptly following the date on which [***] in such Ionis-Conducted IND-Enabling Toxicology Study, and (iii) the final [***] of the total amount of such Ionis IND-Enabling Toxicology Costs once Ionis sends to Biogen [***] with respect to such Ionis-Conducted IND-Enabling Toxicology Study. In each case, Biogen shall pay to Ionis [***] set forth in any such invoice within [***] days following Biogen's receipt of such invoice. For clarity, Ionis will not be responsible for conducting any activities in connection with Ionis-Conducted IND-Enabling Toxicology Studies, and the Ionis IND Study Diligence Obligations shall not apply to, any activities that it is unable to perform as a result of the Parties' inability to agree upon the Ionis IND-Enabling Toxicology Costs applicable to such activities directly due to a delay by Biogen's finance in approving such costs.

1.8.5. **Briefing the Neurology JRC, Neurology JDC and CSC; Conduct of Research and Development**.

(a) At each regularly scheduled meeting of the Neurology JRC, the Parties will provide progress updates on (i) the Neurological Disease Research Program and progress toward achieving Target Sanction under each Target Sanction Plan; (ii) activities conducted under the Core Research Program; (iii) progress under each Development Candidate Identification Plan; and (iv) subject to Section 1.8.5(b), the progress of any Ionis Neurology Targets (including the estimated date on which each Ionis Neurology Target will achieve Target Sanction), in each case, together with a summary of data associated with each Party's Research or Development activities for each Collaboration Program. At each Neurology JDC meeting, the Parties will provide progress updates on their respective Development activities under each Collaboration Program, together with a summary of data associated with each Party's Development activities for the applicable Collaboration Program. At each CSC meeting, the Parties will provide any information reasonably requested by the members of the CSC in advance of such meeting.

(b) Without limiting Ionis' reporting obligations under Section 1.8.5(a), Ionis will provide an Annual update at a meeting of the Neurology JRC of the Ionis Neurology Targets for which Ionis is currently conducting target validation activities (and the Strategies that are the subject of such activities) and all Ionis Neurology Targets on which Ionis plans to conduct target validation activities (and the Strategies that will be the subject of such activities, if known) in the upcoming year. In addition, no later than the date that is [***] months away from the date on which Ionis in good faith believes that any Strategy directed to any Ionis Neurology Target will achieve Target Sanction status, Ionis shall provide notice to Biogen through the Neurology JRC (which notice shall be reflected in the meeting minutes thereof), or provide to Biogen a written notice listing the applicable Strategy and Ionis Neurology Target and the estimated date of achievement of each such Target Sanction (such estimated date of achievement, the "***Estimated Target Sanction Date***"). Prior to Ionis providing such Annual update, Ionis will first provide to the Neurology JRC a list of the Ionis Neurology Targets (without any detail of the applicable Strategies or other target validation activities) on which Ionis is or intends to conduct target validation activities during the following year, and Biogen shall inform Ionis of any Ionis Neurology Target on such list that is already the subject of a Prioritized Biogen Research Program using any Strategy for treatment of a Neurological Disease (each, a "***Biogen Excluded Targets***"), and effective as of the date of such notice, such Biogen Excluded Target will no longer be a Neurology Target under this Agreement, and each Party may work independently or with any Third Party with respect to the discovery, research, development, and commercialization of products including Oligonucleotides designed to bind to the RNA that encodes such Biogen Excluded Target.

1.8.6. Manufacturing and Supply for Collaboration Programs.

(a) Before the License Effective Date with respect to a Strategy or Collaboration Program, Ionis, at [***] expense, will supply research-grade ASOs sufficient to support the Research and Development activities under each such Strategy or Collaboration Program as set forth in the applicable Target Sanction Plan or Development Candidate Identification Plan (as applicable), and unless otherwise agreed by the Parties, Biogen shall be responsible, at [***] expense, for the CMC responsibilities for, and for supplying Development Candidate API (on its own or, subject to Section 4.1.2, through a CMO) sufficient to support IND-Enabling Toxicology Studies pursuant to the applicable Toxicology Strategy. Notwithstanding the foregoing, unless otherwise agreed by the Parties through the Neurology JDC, Ionis shall be responsible for the CMC responsibilities for, and for supplying Development Candidate API (on its own or through a CMO reasonably acceptable to Biogen) sufficient to support, any Ionis-Conducted IND-Enabling Toxicology Studies in accordance with the applicable Toxicology Strategy and IND-Enabling Toxicology Study design. The Parties may also mutually agree through the Neurology JDC that Ionis shall be responsible for the CMC responsibilities for, and for supplying Development Candidate API (on its own or through a CMO reasonably acceptable to Biogen) sufficient to support, any IND-Enabling Toxicology Studies conducted by Biogen. Biogen will pay Ionis an amount equal to [***] that is set forth within an invoice within [***] days following Biogen's receipt of such invoice from Ionis.

1.8.7. **Collaborations with Academics and Non-Profit Institutions**. Each Party (the "***Contracting Party***") may engage one or more academic or non-profit institutions to conduct work under any Neurology Plan or on any High Interest Target or Collaboration Target. Notwithstanding the foregoing, no later than [***] days prior to the anticipated date of finalization of the applicable Neurology Plan, the Party preparing such Neurology Plan shall provide the Neurology JRC or Neurology JDC and the JPC with a list of the academic or non-profit institutions with which such Party proposes to conduct activities under such Neurology Plan, and the nature and scope of such activities. The [***] may provide the Neurology JRC or Neurology JDC, as applicable, with recommendations on the [***] considerations arising from such proposed academic or non-profit collaborations, and the Parties, through the Neurology JRC or Neurology JDC, as applicable, shall consider in good faith such recommendations prior to finalizing the Neurology Plan and such collaborations. Furthermore, with respect to any such academic or non-profit institution engaged to conduct such activities with respect to a High Interest Target or Collaboration Target where such engagement begins after the date such High Interest Target or Collaboration Target is placed on the High Interest Target List or designated, as applicable, (a) the Contracting Party shall provide the other Party with an opportunity to comment on the proposed terms of any agreement or amendment to an existing agreement to be entered into with such institution, and (b) so long as the other Party provides the Contracting Party such comments within [***] days after receiving a draft of such agreement from the Contracting Party, the Contracting Party will obtain the other Party's prior written consent to the terms of such agreement or amendment, such consent not to be unreasonably withheld, conditioned or delayed. The Contracting Party will not be responsible for any activities under a Neurology Plan that it is unable to perform as a result of the other Party's refusal to consent to the terms of any agreement with any such academic or non-profit institution.

1.8.8. **Collaboration Diligence Obligations Pre-License Effective Date**. If (a) Ionis fails to fulfill its obligations under Section 1.2.3(d)(i) to work on at least [***] Target Sanction Plans at any given time during the Research Term (allowing for an appropriate ramp-up and wind-down of such activities at the beginning and end of the Research Term, and Biogen designating for target validation activities a sufficient number of Strategies directed to High Interest Targets on the High Interest Target List to permit Ionis to work on [***] Target Sanction Plans at a given time), (b) Ionis, in Biogen's reasonable determination, fails to perform the obligations set forth under Section 1.8.2(b) or (c) Ionis, in Biogen's reasonable determination, breaches the Ionis Target Sanction Diligence Obligations set forth in Section 1.2.3(d)(v), or the Ionis IND Study Diligence Obligations set forth in Section 1.8.4(c), then in each case ((a) through (c)), then within [***] days of Biogen's written request, Ionis and Biogen will meet to discuss and attempt in good faith to resolve the matter and attempt to devise a mutually agreeable plan to address the applicable failure of Ionis to comply with its diligence obligations. Following such meeting, Biogen may deliver notice to Ionis pursuant to Section 10.3.5(a) if Biogen thereafter believes that Ionis is in material breach of this Agreement.

1.9. **Additional Biogen Research & Development Activities Pre-License Effective Date**. The Parties may agree to allocate additional Research or Development activities under a Collaboration Program to Biogen prior to the License Effective Date for such Collaboration Program (for example, if Biogen would like to test a Compound in a new indication). To the extent any such Research or Development activities are allocated to Biogen in accordance with the preceding sentence, such activities will be Biogen Activities and Biogen will use its Commercially Reasonable Efforts to conduct such Research or Development activities in accordance with the applicable Neurology Plan.

1.10. **Biogen Step-In Rights**.

1.10.1. On each anniversary of the Effective Date during the Research Term, Ionis will provide Biogen with the percentage personnel turnover in Ionis' [***] group for the previous [***]-month period (or, during the [***] years after the Effective Date, the shorter period between the Effective Date and such anniversary). If, during the course of any [***]-month (or [***]) period during the Research Term, Ionis has experienced voluntary turnover of [***]% or more in Ionis' [***] group and Biogen reasonably believes that such turnover will negatively affect Ionis' ability to meet its obligations under the Neurology Plans (a "***Precipitous Ionis Turnover***"), (a) promptly following written notice of such belief from Biogen, the Parties will meet and discuss in good faith whether Ionis will be able to meet its obligations and timelines under this Agreement on a going-forward basis and (b) within [***] days following such meeting, if Biogen still reasonably believes that such Precipitous Ionis Turnover will negatively affect Ionis' ability to meet its obligations under the Neurology Plans, and provides written notice to Ionis thereof, then Biogen may, on a Strategy-by-Strategy or Collaboration Program-by-Collaboration Program basis with respect to the Strategy or Collaboration Program to which the failure relates, or for this Agreement in its entirety, assume responsibility for any or all target validation activities, drug discovery activities or Ionis-Conducted IND-Enabling Toxicology Studies for the applicable existing or new Strategies or Collaboration Programs directed to existing or new High Interest Targets or Collaboration Targets. If Biogen elects to take over any such activities in accordance with this Section 1.10, then (i) Biogen will assume final decision-making ability with respect to any Neurology Plans that cover the activities for which Biogen elects to assume responsibility under this Section 1.10 and Biogen will solely make all decisions with respect to such activities and Neurology Plans for which the Neurology JRC, the applicable Neurology JDC, the JPC, the CSC or any other subcommittees or working groups, or the Parties collectively, would otherwise be permitted or required to make under this Agreement; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis and (ii) upon Biogen's request, Ionis shall provide Biogen and its Third Party contractors with reasonable assistance, consulting services and other support reasonably requested by Biogen to assist Biogen in assuming complete responsibility for such activities in an efficient and orderly manner. If Biogen elects to trigger one or more of the remedies set forth in this Section 1.10, then all payment obligations with respect to the applicable Collaboration Programs will remain in full force and effect in accordance with ARTICLE 6, except that Biogen will be permitted to offset against subsequent milestone payments payable to Ionis for each Strategy or Collaboration Program for which Biogen assumed responsibility those reasonable costs and expenses associated with Biogen's performance of such activities for such Strategy or Collaboration Program that would otherwise have been Ionis Activities and the responsibility of Ionis under Section 1.12.

1.10.2. If Biogen elects to take over all target validation activities and drug discovery activities with respect to a Collaboration Program in accordance with Section 1.10.1 following a Precipitous Ionis Turnover, or in accordance with Section 1.8.1(d)(ii) or Section 12.5.1(b)(ii) (a "***Biogen Step-In***"), then on a Collaboration Program-by-Collaboration Program basis with respect to each Collaboration Program for which Biogen exercises a Biogen Step-In, if Biogen has not generated a Development Candidate for such Collaboration Program before (a) the [***] anniversary of the date on which Biogen exercised the Biogen Step-In, if such date occurred before Biogen's payment of the Target Designation Milestone Payment for such Collaboration Program, or (b) the [***] anniversary of the date on which Biogen exercised the Biogen Step-In, if such date occurred after Biogen's payment of the Target Designation Milestone Payment for such Collaboration Program, then, in either case of ((a) or (b)) the relevant Collaboration Program shall no longer be a part of the Collaboration, Section 2.1.1(e) will not apply to the High Interest Target to which such Collaboration Program was directed and Biogen will have no further rights and Ionis will have no further obligations, in each case, with respect to such Collaboration Program.

1.10.3. If Biogen exercises a Biogen Step-In, then, with respect to those Biogen Activities that Biogen is performing pursuant to the exercise of such Biogen Step-In, as applicable, Biogen will provide written notice to Ionis when Biogen commences target validation activities under this Agreement for a new Strategy directed to a High Interest Target and when Biogen completes activities under a particular Target Sanction Plan (or earlier ceases target validation activities for a particular Strategy). In addition, in such case, Biogen will provide written notice to Ionis when Biogen commences Development Candidate generation activities for a Collaboration Program under a Development Candidate Identification Plan (or earlier ceases Development Candidate generation activities for a Collaboration Program). In addition, notwithstanding anything to the contrary set forth in this Agreement, if Biogen exercises a Biogen Step-In, then Biogen may not at any given time perform target validation activities under this Agreement for more than [***] Strategies in total during the Research Term (including those Strategies directed to High Interest Targets pursued by Ionis at any time during the Research Term).

1.11. **Resource Allocations**. During the Research Term, Ionis will dedicate [***] FTEs to perform the activities that are allocated to it under the Core Research Plan and Neurological Disease Research Plan (once agreed). Biogen will be responsible for devoting, in its reasonable discretion, resources toward specific research efforts allocated to Biogen under the Core Research Program and Neurological Disease Research Program. Ionis will update the Neurology JRC at each meeting thereof on the utilization of Ionis' [***] FTEs and provide the Neurology JRC with summaries of resource and FTE utilization, in a format agreed to by the Alliance Managers under SCHEDULE 1.14.9, within [***] days following the end of each fiscal quarter in a format mutually agreed to by each Party's Alliance Managers. Biogen may also choose to supplement Ionis' efforts under the Core Research Plan or the Neurological Disease Research Plan with its own scientists at various points throughout the Research Term. After the conclusion of the Research Term, Ionis will provide sufficient resources to perform its obligations under each Collaboration Program as reasonably determined by Ionis.

1.12. Research and Development Costs Paid by Ionis.

1.12.1. Research Programs. During the Research Term, and during the period in which Ionis is completing ongoing activities under Target Sanction Plans (if any) pursuant to Section 1.7(b), Ionis will be responsible for all Ionis Activities under the Core Research Program and the Neurological Disease Research Program and all costs and expenses associated with its performance of such activities.

1.12.2. Collaboration Programs. On a Collaboration Program-by-Collaboration Program basis, Ionis will be responsible for all Ionis Activities under the Neurology Plans for such Collaboration Program and, except as otherwise provided under Section 1.8.4, Section 1.8.6, Section 1.13.1, Section 1.13.3, and Section 5.2.2, all costs and expenses associated with its performance of such activities. For clarity, Ionis shall not have the right to use, in any such activities, any resources or funding provided to Ionis by Biogen under the Ionis/Biogen Additional Agreements.

1.13. Research and Development Costs Paid by Biogen.

1.13.1. Before the License Effective Date.

(a) Research Programs. During the Research Term, Biogen will be responsible for all Biogen Activities under the Core Research Program and Neurological Disease Research Program, and all costs and expenses associated with its performance of such activities.

(b) Collaboration Programs. During the Option Period, on a Collaboration Program-by-Collaboration Program basis, Biogen will be responsible for any Biogen Activities under the Neurology Plans for such Collaboration Program, including Phase 0, natural history studies, biomarker and endpoint development, and, except as otherwise provided under Section 1.8.6, all costs and expenses associated with its performance of such activities.

1.13.2. After the License Effective Date. After the License Effective Date with respect to the applicable Collaboration Program, Biogen will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Products under such Collaboration Program, including (a) any work performed by Ionis at Biogen's request, or any Clinical Studies conducted by Ionis, in each case, in accordance with Section 5.2.2, (b) any other activities under the Integrated Product Plan that the Parties mutually agree should be conducted by Ionis and (c) all supply chain planning and decision-making.

1.13.3. **Additional Activities Approved by Biogen Prior to the License Effective Date**. On a Collaboration Program-by-Collaboration Program basis, prior to the License Effective Date with respect to such Collaboration Program, if Biogen desires that either Ionis or a Third Party perform additional activities under this Agreement that are not otherwise required hereunder ("***Other Activities***"), then if Ionis agrees to perform such activities, Biogen will pay the costs of conducting such work, including the cost of Ionis' time incurred in performing such work at the then-applicable Ionis FTE Rate ("***FTE Costs***"), plus any reasonable out-of-pocket expenses incurred by Ionis in performing such work (such costs, collectively, "***Biogen-Approved Costs***"). Ionis will permit Biogen to review, negotiate (with Ionis) and approve all Biogen-Approved Costs prior to conducting any Other Activities. In advance of each [***], Ionis will provide Biogen with a good faith estimate of the Biogen-Approved Costs anticipated to be incurred in such [***]. Ionis will invoice Biogen directly for any such approved Biogen-Approved Costs incurred by Ionis and Biogen shall pay all undisputed amounts set forth in any invoices submitted pursuant to this Section 1.13.3 for such approved Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen. In the case where Other Activities 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.

1.14. **Research and Development Management**.

1.14.1. **Collaboration Steering Committee**. The Parties will establish a Collaboration steering committee ("***CSC***") with the powers, roles and responsibilities set forth on SCHEDULE 1.14.1 and in this Section 1.14.1 to oversee the Collaboration. The CSC will consist of up to four representatives appointed by Ionis and up to four representatives appointed by Biogen. The Neurology JRC and Neurology JDC under this Agreement will report to the CSC. The CSC will determine the CSC operating procedures at its first meeting, including the CSC's policies for replacement of CSC members, policies for participation by additional representatives or consultants invited to attend CSC meetings, and the location of meetings, which will be codified in the written minutes of the first CSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending CSC meetings. Any decision that may be made by the Neurology JRC or Neurology JDC may be made by the CSC and such decision by the CSC will have the same effect as if made by the Neurology JRC or the Neurology JDC under this Agreement. The CSC may delegate any of its functions specified in Section 1.14.2 below to a Neurology JDC by agreeing to and codifying such delegation in the minutes of the CSC.

1.14.2. **Role of the CSC**. Without limiting any of the foregoing, subject to Section 1.14.7, the CSC will perform the following functions, some or all of which may be addressed directly at any given CSC meeting:

(a) approve the terms on which Biogen would develop and commercialize a Multi-Indication Product as contemplated in APPENDIX 3;

(b) determine whether an approach to a gene target is a distinct approach such that it is a separate Strategy after the matter is so referred to the CSC for resolution, as described in Section 1.2.3(d)(iii);

(c) determine the final Target Sanction Plan for any Strategy (or any update thereto) after the matter is so referred to the CSC for resolution, as described in Section 1.2.3(d)(iv);

(d) determine the primary disease association of a Multi-Indication Target, as described in Section 1.2.3(e);

(e) determine the final Development Candidate Identification Plan for a Collaboration Program or a proposed update thereto after the matter is so referred to the CSC for resolution, as described in Section 1.8.2(a);

(f) determine whether there are omissions or deficiencies in a Development Candidate Data Package after the matter is so referred to the CSC for resolution, as described in Section 1.8.3(a);

(g) determine the Toxicology Strategy for each potential Development Candidate and the study design for each IND-Enabling Toxicology Study for a Development Candidate after the matter is so referred to the CSC for resolution, as described in Section 1.8.3(c) and Section 1.8.4(a);

(h) appoint a Neurology JDC for each Collaboration Program under this Agreement, whether by creating a new Neurology JDC or assigning an existing Neurology JDC to oversee such Development Candidate, as described in Section 1.14.5;

(i) review and assess reports provided by the Neurology JRC and the Neurology JDCs;

(j) provide input to the [***] as appropriate to facilitate the preparation of [***] strategies (but, for clarity, not with respect to any [***] determinations, which will be made solely by the JSC pursuant to Section 7.1.3(g));

(k) review and provide input on the IPPs as appropriate, as described in Section 5.2.5;

(l) determine the need for or content to any press release, presentation or other public disclosure under Section 11.4 that is intended to be jointly issued, after the matter is so referred to the CSC for resolution, as described in Section 11.4.6;

(m) assist with and participate in the resolution of disputes, as described in Section 12.1.1; and

(n) such other review and advisory responsibilities as may be assigned to the CSC by the Parties pursuant to this Agreement.

1.14.3. **Neurology JRC**. The Parties will establish a joint research committee (the "***Neurology JRC***") reporting to the CSC, to provide advice and make recommendations on the conduct of activities under the Core Research Program, Neurological Disease Research Program and each Collaboration Program through Development Candidate designation. The Neurology JRC will consist of up to three representatives appointed by Ionis and up to three representatives appointed by Biogen. Each Party's Neurology JRC representatives shall be chosen by such Party in its sole discretion and may be replaced by such Party in its sole discretion upon written notice to the other Party; *provided that* each Neurology JRC member will have experience and expertise appropriate for the Core Research Program, Neurological Disease Research Program or the stage of development of the Collaboration Programs. Each Party will designate one of its 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 JRC. The co-chairs will be responsible for overseeing the activities of the Neurology JRC consistent with the responsibilities set forth below in this Section 1.14.3. SCHEDULE 1.14.3 sets forth certain Neurology JRC governance matters agreed to as of the Effective Date. The Neurology JRC will determine the Neurology JRC operating procedures at its first meeting, including the Neurology JRC's policies for replacement of Neurology JRC members, policies for participation by additional representatives or consultants invited to attend Neurology JRC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JRC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JRC meetings. Ionis and Biogen will use reasonable efforts to schedule meetings of the Neurology JRC to take place at the same location and on the same dates as meetings of the CSC and Neurology JDCs under this Agreement and the joint research, 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.

1.14.4. **Role of the Neurology JRC**. Without limiting any of the foregoing, subject to Section 1.14.7, the Neurology JRC will perform the following functions, some or all of which may be addressed directly at any given Neurology JRC meeting:

(a) review and approve amendments to the Core Research Plan and the Neurological Disease Research Plan, as described in Sections 1.2.2 and 1.2.3(d)(iv);

(b) review and discuss the potential performance of any activities by Third Parties that are assigned to a Party under the Core Research Program, as described in Section 1.2.2;

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

(d) determine the number of Strategies for High Interest Targets for which activities to support Target Sanction will be conducted under Target Sanction Plans during each year of the Research Term, as described in Section 1.2.3(d)(i);

(e) discuss and determine any proposals by either Party that Ionis evaluate a Strategy against a High Interest Target, Collaboration Target or Ionis Neurology Target, as described in Section 1.2.3(d)(ii)(B);

(f) determine whether to conduct target validation activities under the Neurological Disease Research Plan with respect to any Strategy directed to a Multi-Indication Target that the Parties did not agree to designate as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target, as described in Section 1.2.3(c);

(g) determine whether the Parties will pursue target validation activities for each Strategy directed to a High Interest Target or Collaboration Target, as described in Section 1.2.3(d)(ii)(C);

(h) review and approve each draft Target Sanction Plan, as described in Section 1.2.3(d)(iv);

(i) determine whether a approach to a gene target is a distinct approach such that it is a separate Strategy, as described in Section 1.2.3(d)(iii);

(j) review the overall progress of Ionis' efforts to achieve Target Sanction with respect to each High Interest Target that has not achieved Target Sanction status;

(k) review and discuss Target Sanction Data Packages for Strategies directed to a High Interest Target or Ionis Neurology Target, as described in Sections 1.3 and 1.4;

(l) track Ionis' progress towards meeting the [***]% Obligation and identify ways to ensure that Ionis achieves the [***]% Obligation, as described in Section 1.8.1(c);

(m) if applicable, revise performance metrics to account for extra work entailed in pursuing a novel Strategy, as described in Section 1.8.1(e);

(n) determine a Development Candidate Identification Plan for each Collaboration Program (and approve any updates thereto), as described in Section 1.8.2(a);

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

(p) review the Parties' updates with respect to Research and Development efforts and the progress of Ionis Neurology Targets, as described in Section 1.8.5(a), and discuss Ionis' Annual update of all Strategies directed to each Ionis Neurology Target for which Ionis is currently conducting target validation activities and all Ionis Neurology Targets on which Ionis plans to conduct target validation activities in the upcoming year as described in Section 1.8.5(b);

(q) review proposed collaborations with academic and non-profit institutions and discuss the [***] recommendations of the [***] with respect thereto, as described in Section 1.8.7;

(r) review and determine the appropriate allocation of Ionis' resources to the Core Research Plan, the Neurological Disease Research Plan and each Development Candidate Identification Plan, as described in Section 1.11;

(s) monitor progress of each Collaboration Program and maintain a calendar of anticipated milestone achievement dates for each Collaboration Program;

(t) establish teams and committees to oversee and manage activities under the Core Research Program, Neurological Disease Research Program and each Collaboration Program up to Development Candidate designation as it deems necessary; and

(u) such other review and advisory responsibilities as may be assigned to the Neurology JRC by the CSC pursuant to this Agreement.

1.14.5. **Joint Development Committees**. The CSC will appoint a joint development committee (each, a "***Neurology JDC***") for each Collaboration Program approximately [***] days prior to the date on which Ionis' RMC expects to designate the first potential Development Candidate under such Collaboration Program. Members of a Neurology JDC for a Collaboration Program may be, but need not be, the same members as the members on any other Neurology JDC for other Collaboration Programs. Each Neurology JDC will report to the CSC and will consist of an equal number of representatives appointed by Ionis and Biogen. Each Party's Neurology JDC representatives shall be chosen by such Party in its sole discretion and may be replaced by such Party in its sole discretion upon written notice to the other Party; *provided that* each Neurology JDC member will have experience and expertise appropriate for the stage of Development of the Collaboration Programs. Each Party will designate one of its 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 JDC. The co-chairs will be responsible for overseeing the activities of the Neurology JDC consistent with the responsibilities set forth below in this Section 1.14.5. SCHEDULE 1.14.5 sets forth certain Neurology JDC governance matters agreed to as of the Effective Date. Each Neurology JDC will determine its operating procedures at its first meeting, including the Neurology JDC's policies for replacement of Neurology JDC members, policies for participation by additional representatives or consultants invited to attend Neurology JDC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JDC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JDC meetings. If practical, Ionis and Biogen will use reasonable efforts to schedule meetings of each Neurology JDC to take place at the same location and on the same dates as meetings of the other Neurology JDCs, the Neurology JRC and the CSC under this Agreement and the joint research, 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.

1.14.6. **Role of the Neurology JDCs**. Without limiting any of the foregoing, subject to Section 1.14.7, each Neurology JDC will perform the following functions, some or all of which may be addressed directly at any given Neurology JDC meeting:

(a) review each Development Candidate Data Package and determine whether to designate the proposed lead Development Candidate or any of the Related Program Compounds as Development Candidates for such Collaboration Program, as described in Sections 1.8.3(a) and 1.8.3(d);

(b) establish a Toxicology Strategy for each potential Development Candidate and approve the study design for each IND-Enabling Toxicology Study, as described in Sections 1.8.3(c) and 1.8.4(a);

(c) determine whether Ionis is the more appropriate Party to conduct certain IND-Enabling Toxicology Studies, as described in Section 1.8.4(a);

(d) update the "*Approved CRO*" list set forth on SCHEDULE 1.8.4(a), as described in Section 1.8.4(a);

(e) determine whether (and for how long) to extend or toll the [***]-day period during which each Party must Initiate the first IND-Enabling Toxicology Study for the applicable Development Candidate, as described in Sections 1.8.4(b) and 1.8.4(c);

(f) determine the Party responsible for the CMC responsibilities for Development Candidate API batch to be used for IND-Enabling Toxicology Studies, as described in Section 1.8.6(a);

(g) review and discuss the Program Determination provided by Biogen for each Collaboration Program, as described in Sections 6.5.2 and 6.5.3;

(h) review the Draft Reports for all IND-Enabling Toxicology Studies, as described in Section 3.1.1;

(i) determine whether Ionis is the more appropriate Party to conduct certain Clinical Studies or other activities under the Integrated Product Plan for a Collaboration Program, as well as the terms, budget and frequency of payments to be made to Ionis in connection with such activities, as described in Section 5.2.2;

(j) approve cost estimates for activities to be conducted by Ionis pursuant to Section 1.8.4(d), Section 1.8.6, and Section 5.2.2;

(k) review proposed collaborations with academic and non-profit institutions and discuss the [***] recommendations of the [***] with respect thereto, as described in Section 1.8.7;

(l) review the overall progress of the Development activities and Clinical Studies under the applicable Integrated Product Plan and Clinical Studies with respect to a particular Development Candidate through [***];

(m) establish teams and committees to oversee and manage activities under each Collaboration Program after Development Candidate designation as it deems necessary; and

(n) such other review and advisory responsibilities as may be assigned to the Neurology JDC by the CSC pursuant to this Agreement.

1.14.7. Decision Making.

(a) **Committee Decision Making**. Decisions by each of the CSC, Neurology JRC, Neurology JDC and the JPC, will be made by unanimous consent with each Party's representatives having, collectively, one vote. At any given meeting of any such committee, 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 any such committee 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 CSC, Neurology JRC or Neurology JDC, as applicable, has not reached unanimous consensus.

(b) **Implementation**. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the CSC, the Neurology JRC and Neurology JDC (as applicable) regarding the conduct of the Core Research Program, Neurological Disease Research Program and each Collaboration Program. Subject to Biogen's right to assume final decision-making responsibility under Section 1.8.1(d)(ii), Section 1.10, Section 10.4, Section 12.5.1 and Section 12.5.2, prior to the License Effective Date with respect to a Collaboration Program, (i) Ionis will have the final decision-making authority regarding [***], (ii) Ionis will have the final decision-making authority, subject to Section 1.2.3(d)(iv), with respect to [***], and (iii) Ionis will have the final decision-making authority, subject to Section 1.8.2, with respect to [***]. Prior to the License Effective Date with respect to a Collaboration Program, Biogen will have the final decision-making authority (A) subject to Section 1.2.3(d), regarding [***] and [***], (B) subject to Section 1.8.3(c) and Section 1.8.4(a), with respect to [***] and [***], (C) subject to Section 1.8.3(d), regarding [***], (D) subject to Section 1.8.3(d), regarding [***] and [***], (E) the [***] and [***]. After the License Effective Date with respect to a particular Collaboration Program, Biogen will have sole decision-making authority regarding [***] of Products for such Collaboration Program, *provided*, *however*, that Biogen will consider in good faith Ionis' recommendations made to the Neurology JDC in relation to such matters, and [***]. Except as otherwise expressly stated in this Agreement, the CSC, the Neurology JRC and Neurology JDC 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.

1.14.8. Committee Activities Following the License Effective Date.

(a) Neurology JDC and CSC Meetings after the License Effective Date. On a Collaboration Program-by-Collaboration Program basis, following the License Effective Date with respect to a Collaboration Program until the applicable Neurology JDC is terminated in accordance with Section 1.14.8(c) the Neurology JDC for each Collaboration Program and the CSC will meet no more than [***] each [***] months, in accordance with each Party's scheduling obligations set forth in Section 1.14.5, solely for the purpose of information exchange and without any decision-making authority. Notwithstanding anything to the contrary in this Section 1.14.8(a), if the Parties engage in discussions regarding any Collaboration Program in a meeting of any other Neurology JDC or other development or steering governing forum under any of the Ionis/Biogen Additional Agreements, where such discussions (i) are included in the agenda for such meeting or documented in the written minutes of such meeting, or (ii) otherwise address topics other than procedure and scheduling, then such discussions shall be deemed to be in lieu of the Neurology JDC meeting or CSC meeting, as applicable, contemplated under this Section 1.14.8(a) for the [***]-month period in which such discussions occurred.

(b) Ionis' Obligation to Participate in the Neurology JRC, Neurology JDC and CSC. On a Collaboration Program-by-Collaboration Program basis, Ionis' obligation to participate in (i) the Neurology JRC, will terminate at the end of the Development Candidate Identification Term, (ii) the Neurology JDC, will terminate upon the License Effective Date (or the earlier termination or expiration of the Option) for the applicable Collaboration Program and (iii) the CSC will terminate upon the termination of Ionis' obligation to participate in the applicable Neurology JDC. After any such termination, for each such governing body, Ionis will have the right, but not the obligation, to participate in such meetings upon Ionis' request, until such governing body is terminated in accordance with Section 1.14.8(c). Notwithstanding the foregoing, Biogen's obligations to provide Ionis with information or reports with respect to a Product shall continue in accordance with Section 5.2.5.

(c) Termination of the Neurology JRC, Neurology JDC and CSC. On a Collaboration Program-by-Collaboration Program basis, solely with respect to this Agreement and not any Ionis/Biogen Additional Agreement, unless the applicable Collaboration Program is earlier terminated, (i) the Neurology JRC will terminate upon the designation of one or more Development Candidates with respect to such Collaboration Program under Section 1.8.3(d), (ii) the Neurology JDC will terminate upon the Completion of the first Pivotal Clinical Trial with respect to such Collaboration Program and (iii) the CSC will terminate upon the expiration of the Full Royalty Period with respect to all Products under such Collaboration Program. On a Collaboration Program-by-Collaboration Program basis, the Neurology JRC, the Neurology JDC and the CSC and any other subcommittees or working groups established pursuant to this Agreement will terminate upon the termination of such Collaboration Program.

1.14.9. 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 CSC, the Neurology JRC and Neurology JDC, and performing the activities listed in SCHEDULE 1.14.9.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1. Exclusivity; Right of First Negotiation.

2.1.1. Exclusivity Covenants.

(a) The Parties' Exclusivity Covenants during the Research Term for High Interest Targets. 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 10.6.3 or Section 10.6.4, neither it nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to the discovery, research, development, manufacture or commercialization in the Field of an Oligonucleotide that is designed to bind to the RNA that encodes a High Interest Target, from the Effective Date until the earlier to occur of (i) the date such target is removed from the High Interest Target List by Biogen or ceases to be a High Interest Target by operation of this Agreement, or (ii) the date on which the High Interest Target List is dissolved in accordance with Section 1.7.

(b) Ionis' Exclusivity Covenants during the Research Term for Ionis Neurology Targets and Limited Availability Neurology Targets.

(i) Ionis agrees that neither it nor any of its Affiliates will work for the benefit of any Third Party (including the grant of any license to any Third Party that would diminish Biogen's rights under Section 1.2.3(f) and Section 1.3 or Section 1.4 or prevent Ionis from granting Biogen a license under Section 4.1.1) with respect to the discovery, research, development, manufacture or commercialization in the Field of an Oligonucleotide that is designed to bind to the RNA that encodes an Ionis Neurology Target from the Effective Date until the earlier to occur of (A) the date such target ceases to be a Neurology Target by operation of this Agreement, (B) the date such target becomes a Limited Availability Neurology Target, in which case Section 2.1.1(b)(ii) will apply or (C) the expiration of the Research Term in accordance with Section 1.7.

(ii) Ionis agrees that neither it nor any of its Affiliates will work for the benefit of any Third Party (including the grant of any license to any Third Party that would diminish Biogen's rights under Section 1.5.1 or prevent Ionis from granting Biogen a license under Section 4.1.1) with respect to the discovery, research, development, manufacture or commercialization in the Field of an Oligonucleotide that is designed to bind to the RNA that encodes a Limited Availability Neurology Target, other than through the use of an Ionis Strategy directed to such Limited Availability Neurology Target, from the date such target becomes a Limited Availability Neurology Target until the earlier to occur of (A) the date on which Ionis has continued to use Commercially Reasonable Efforts to research and develop at least one compound or product for such Ionis Strategy directed to such Limited Availability Neurology Target for more than [***] months following the date on which the Target Sanction Data Package was delivered or (B) the expiration of the Research Term. Notwithstanding the foregoing, if a Limited Availability Neurology Target becomes a High Interest Target or a Collaboration Target pursuant to Section 1.5, then the terms of this Agreement applicable to High Interest Targets or Collaboration Targets, respectively, will govern the Parties' obligations with respect to such target as of the date of such designation.

(c) **The Parties' Exclusivity Covenants during the Option Period for Collaboration Targets**. 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 10.6.3 or Section 10.6.4, neither it nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development, manufacture or commercialization in the Field of an Oligonucleotide that is designed to bind to the RNA that encodes a Collaboration Target from the date such gene target was designated a Collaboration Target under this Agreement through the expiration or earlier termination of the applicable Option Periods for all Collaboration Programs directed to such Collaboration Target.

(d) **The Parties' Exclusivity Covenants after the License Effective Date**. 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 10.6.3 or Section 10.6.4, if Biogen timely exercises an Option in accordance with this Agreement, then neither Ionis nor Biogen nor their respective Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to:

(i) discovery, research or development in the Field of an Oligonucleotide that is designed to bind to the RNA that encodes the applicable Collaboration Target related to such Option until the earlier of (A) the [***] directed to such Collaboration Target for which Biogen exercises the Option and (B) [***] directed to such Collaboration Target for which Biogen exercised an Option (the "***Exclusivity Release Date***"); *provided that* if, as of the Exclusivity Release Date for the first Collaboration Program for such Collaboration Target, the Parties have commenced [***] activities and are at such time conducting activities under this Agreement with respect to any one or more additional Strategies or Collaboration Programs for which Biogen has paid the Target Designation Milestone Payment directed to such Collaboration Target (i.e., the Parties are progressing more than one Strategy for such Collaboration Target), then the Exclusivity Release Date will be tolled for such Collaboration Target until the date upon which the last Collaboration Program directed to such Collaboration Target reaches the earlier of the dates set forth in (A) and (B) above;

(ii) on a country-by-country basis, commercialization in the Field of an Oligonucleotide that is designed to bind to the RNA that encodes such Collaboration Target until [***] or termination of this Agreement with respect to all Collaboration Programs directed to such Collaboration Target.

(e) **Failure to Designate a High Interest Target as a Collaboration Target**. If, after a Strategy directed to a High Interest Target achieves Target Sanction, (i) such High Interest Target becomes a Limited Availability Neurology Target pursuant to the penultimate sentence of Section 1.3.3 and (ii) Biogen has not paid to Ionis an amount equal to the Target Designation Milestone Payment for such Limited Availability Neurology Target, then for a period ending on the date when (A) [***], and (B) [***], neither Biogen nor its Affiliates will work for or with any Third Party (including the grant of any license to any Third Party) to discover, research, develop, manufacture or commercialize an Oligonucleotide designed to bind to the RNA encoding such High Interest Target. If Biogen elects not to pay Ionis [***], then the exclusivity obligations set forth in this Section 2.1.1(e) shall instead expire [***] months following the date on which Ionis delivers to Biogen the Target Sanction Data Package for such Limited Availability Neurology Target.

2.1.2. Limitations and Exceptions to Ionis' Exclusivity Covenants. Notwithstanding anything to the contrary in this Agreement, Ionis' or its Affiliates' practice of the following will not violate Section 2.1.1 or clause (d) of APPENDIX 3:

(a) The discovery, research, development, manufacture or commercialization of (i) Gene-Editing Products or messenger RNA or (ii) Duplex Products solely to the extent agreed by the Parties in writing;

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

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

(d) The discovery, research, development, manufacture or commercialization of an Ionis Multi-Indication Compound to the extent permitted under APPENDIX 3;

(e) The discovery, research, development, manufacture or commercialization of a Pre-Existing Competitive Product in accordance with Section 12.5.2(d) and Section 12.6; or

(f) The limited continuation of discovery, research, development, manufacture or commercialization of Acquired Competitive Product(s) as permitted under Section 12.5.3(a) and in accordance with Section 12.5.3(a) and Section 12.6.

2.1.3. Limitations and Exceptions to Biogen's Exclusivity Covenants. Notwithstanding anything to the contrary in this Agreement, Biogen's or its Affiliates' practice of the following will not violate Section 2.1.1 or clause (b) of APPENDIX 3:

(a) The discovery, research, development, manufacture or commercialization of (i) Gene-Editing Products or messenger RNA or (ii) Duplex Products solely to the extent agreed by the Parties in writing;

(b) the discovery, research, development, manufacture or commercialization of a Pre-Existing Competitive Product in accordance with Section 12.5.2(d) and Section 12.6; or

(c) the limited continuation of discovery, research, development, manufacture or commercialization of Acquired Competitive Product(s) as permitted under Section 12.5.3(a) and in accordance with Section 12.5.3(a) and Section 12.6.

2.1.4. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes a Collaboration Target with the intent of treating a Neurological Disease. Ionis and Biogen are subject to exclusivity obligations under Section 2.1; however, the Parties acknowledge and agree that, except as otherwise provided herein with respect to Ionis Neurology Targets and Limited Availability Neurology Targets, each Party and its Affiliates (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) a High Interest Target to the extent Section 2.1.1(a) still applies or (b) a Collaboration Target, in each case for any indication, even if such products are designed to treat a Neurological Disease.

2.2. Differentiated Compounds.

2.2.1. With respect to any Differentiated Compound designated by Ionis' RMC as a development candidate ready to start IND-Enabling Toxicology Studies, which determination shall be based on criteria substantially similar to the criteria Ionis' RMC uses to designate development candidates under other similar programs, Ionis will notify Biogen of such determination and will provide Biogen with the data package presented to Ionis' RMC to approve such development candidate (a "***Differentiated Compound Notice***"). If, within [***] days after Biogen's receipt of a Differentiated Compound Notice, Biogen delivers written notice to Ionis of Biogen's election to enter into an amendment to this Agreement to include such Differentiated Compound within the scope of this Agreement, then upon such election the Parties will enter into an amendment to this Agreement to include such Differentiated Compound within the scope of this Agreement on the terms set forth in this Agreement; *provided that* (a) for Differentiated Compounds discovered during the Research Term, the up-front payment for such Differentiated Compound will be [***] and (b) for Differentiated Compounds discovered after the Research Term has ended, (i) the Parties shall mutually agree on an additional up-front payment for such Differentiated Compound (taking into consideration the value of any advancements in Ionis' technology used in such Differentiated Compound and the cost of Ionis' work to advance such Differentiated Compound to the development candidate stage, which up-front payment will not exceed [***] for each Differentiated Compound) and (ii) if the scope of work to discover such Differentiated Compound is materially larger than under any of the Development Candidate Identification Plans agreed to pursuant to this Agreement as of the date of such notice, then Biogen will [***] (but in no event will the total amount paid by Biogen to Ionis under clause (b)(i) and clause (b)(ii) of this Section 2.2.1 exceed [***], and in no event will Biogen be required to pay a Target Designation Milestone Payment for such Differentiated Compounds) and (c) Biogen will pay to Ionis [***] in accordance with the principles set forth in Section 6.11.2, Section 6.11.3, Section 6.11.4 and Section 6.11.5.

2.2.2. If Biogen does not provide Ionis with written notice within such [***]-day period of Biogen's election to enter into such an amendment, or provides written notice to Ionis that it does not elect to enter into such an amendment, or if the Parties fail to mutually agree on an up-front payment (if applicable) within [***] days of Biogen's election with respect to any such Differentiated Compound, then Ionis may initiate negotiations with a Third Party regarding a license to such Differentiated Compound; *provided*, *however*, that any such Third Party shall be subject to the restrictions set forth in Section 2.1.1(d)(ii) with respect to any product containing a Differentiated Compound; and *provided*, *further*, that Ionis will not enter into any such license with any Third Party unless [***].

2.2.3. Notwithstanding anything to the contrary in this Section 2.2, if, with respect to any Differentiated Compound that was the subject of the license previously discussed between Biogen and Ionis, after the end of such [***]-day negotiation period and prior to Ionis entering into a license with a Third Party, any new material data (such as significant new GLP toxicology data or Clinical Study data) is generated regarding such Differentiated Compound, then Ionis will provide Biogen with an additional Differentiated Compound Notice and, if Biogen or one of its Affiliates delivers written notice to Ionis within [***] days after Biogen's receipt of such Differentiated Compound Notice indicating that Biogen or one of its Affiliates desires to negotiate with Ionis regarding a license to make, use or sell such Differentiated Compound, Ionis and Biogen or one of its Affiliates will negotiate in good faith with each other until the [***] day following the date of the Differentiated Compound Notice (or such other period as mutually agreed by the Parties) regarding a mutually satisfactory agreement with respect to such license, which may (but shall not be required to) take the form of an amendment to this Agreement and may (but shall not be required to) be on the terms set forth in this Agreement.

ARTICLE 3.
EXCLUSIVE OPTION

3.1. Option.

3.1.1. **IND-Enabling Toxicology Study Completion Notice**. On a Development Candidate-by-Development Candidate basis, within [***] days following the date the Draft Reports from the IND-Enabling Toxicology Studies for such Development Candidate are available to the Party responsible for conducting such IND-Enabling Toxicology Studies, such Party shall provide the other Party (through the Neurology JDC) with such Draft Reports for such IND-Enabling Toxicology Studies. Within [***] days following the date the Draft Reports from the IND-Enabling Toxicology Studies for such Development Candidate are available to Ionis, Ionis shall provide to Biogen the IND-Enabling Toxicology Data Package for such Development Candidate. Within [***] days of receipt of the IND-Enabling Toxicology Data Package for such Development Candidate, Biogen or an Affiliate will notify Ionis of any omissions or deficiencies that Biogen or its Affiliate believes in good faith cause the IND-Enabling Toxicology Data Package to be incomplete (each, an "***IND-Enabling Toxicology Deficiency Notice***"). Ionis will promptly, and in any event within [***] days of receipt of each IND-Enabling Toxicology Deficiency Notice, resubmit a complete IND-Enabling Toxicology Data Package for the applicable Development Candidate to Biogen or its designated Affiliate, including any information required to be included in the IND-Enabling Toxicology Data Package that Biogen identified in the IND-Enabling Toxicology Deficiency Notice. If the Parties do not agree as to whether the IND-Enabling Toxicology Data Package is complete, then either Party may refer the matter for resolution by the Executives. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon all information to be provided to Biogen in furtherance of a "complete" IND-Enabling Toxicology Data Package.

3.1.2. Option and Option Deadline.

(a) 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***"). Subject to Biogen's right to cure in accordance with Section 3.1.2(e) and subject to tolling or extension under Section 3.1.2(b) or Section 3.1.2(c), as applicable, the Option with respect to a Collaboration Program will be available to Biogen and its Affiliates until 5:00 pm (Eastern Time) on the date that is the earlier of (i) [***] following the IND-Enabling Toxicology Studies Completion Date for such Collaboration Program (the "***IND-Enabling Toxicology Trigger Date***") and (ii) the [***]-month anniversary of the date on which Biogen designated the first Development Candidate for such Collaboration Program under Section 1.8.3(d) (the "***Development Candidate Outside Date***," and the earlier to occur of (i) and (ii), the "***Option Deadline***"). For clarity, the Option Deadline shall in no way serve to limit Biogen's obligations under Section 5.1.1.

(b) Notwithstanding Section 3.1.2(a), the Option Deadline may be tolled as follows:

(i) if on the date of the IND-Enabling Toxicology Trigger Date for a given Collaboration Program, Biogen is progressing an additional Collaboration Program directed to the same Collaboration Target, then the Option Deadline for such leading Collaboration Program will be tolled until the earlier of (A) the date that the last such additional Collaboration Program for such Collaboration Target reaches the IND-Enabling Toxicology Trigger Date, (B) the date when Biogen terminates activities with respect to the last of such additional Collaboration Programs, or (C) the Development Candidate Outside Date for such leading Collaboration Program. The Option Deadline for any such additional Collaboration Program will be determined under Section 3.1.2(a).

(ii) if Biogen notifies Ionis in writing prior to the Option Deadline for a Collaboration Program that it wishes to perform separate IND-Enabling Toxicology Studies on an additional Related Program Compound included in a Development Candidate Data Package for such Collaboration Program, but that was not previously the subject of IND-Enabling Toxicology Studies for such Collaboration Program (the "***Separate IND-Enabling Toxicology Notice***"), then each such additional Related Program Compound shall thereafter be a Development Candidate for the purposes of this Agreement (to the extent not already designated as such) and the Option Deadline for such Collaboration Program shall toll until the earlier of (A) the IND-Enabling Toxicology Trigger Date for such additional Development Candidates, or (B) the Development Candidate Outside Date for the first Development Candidate under such Collaboration Program. If Biogen delivers a Separate IND-Enabling Toxicology Notice, then, subject to the IND Delay Conditions, Biogen shall Initiate the IND-Enabling Toxicology Study for the Development Candidate that is the subject of such notice within [***] days following the date of such notification, unless such IND-Enabling Toxicology Study is an Ionis-Conducted IND-Enabling Toxicology Study, in which case Section 1.8.4(c) shall apply to the conduct of such study.

For clarity, nothing in Section 3.1.2(b) shall toll the Option Deadline for any Collaboration Programs directed to a given Collaboration Target beyond the Development Candidate Outside Date for the first Development Candidate for the first Collaboration Program directed to such Collaboration Target.

(c) Notwithstanding Section 3.1.2(a), the Option Deadline may be extended as follows:

(i) by the Parties for any length of time by written agreement;

(ii) if (A) Biogen notifies Ionis in writing prior to the Option Deadline for a Collaboration Program that Biogen desires to analyze the results of Pre-Clinical Studies for one or more additional Development Candidates directed to the same Collaboration Target, and accordingly Biogen reasonably determines that additional work should be conducted on any such additional Development Candidates or (B) either Party in good faith believes that, due to the novelty of a Strategy, new scientific or technological information or an advance in the state of the art with respect to the Development Candidate, Collaboration Program or Collaboration Target at issue, additional work should be conducted prior to the Initiation of an IND-Enabling Toxicology Study for the applicable Collaboration Program or prior to Biogen's exercise of the Option for the applicable Collaboration Program, then in each case ((A) and (B)), the Option Deadline with respect to such Collaboration Program will be subject to a one-time extension, of up to a maximum of [***] additional days to the extent required to perform such additional work; and

(iii) if Biogen determines that an HSR Filing is required to be made under the HSR Act to exercise the Option for such Collaboration Program and notifies Ionis of such determination within [***] days after the applicable IND-Enabling Toxicology Study Completion Date, then the Parties will promptly file an HSR Filing in accordance with Section 3.1.3 and the Option Deadline for such Collaboration Program will be extended until 5:00 pm (Eastern Time) on the later of the fifth Business Day after the HSR Clearance Date and the end of any extension resulting from the application of Section 3.1.2(b) or this Section 3.1.2(c).

(d) If, by the Option Deadline for a Collaboration Program or within the cure period set forth under Section 3.1.2(e), Biogen or its designated Affiliate (1) notifies Ionis in writing that it wishes to exercise the applicable Option and (2) pays to Ionis the applicable Option Fee, Ionis will, and hereby does, grant to Biogen or its designated Affiliate the license set forth in Section 4.1.1 with respect to such Collaboration Program.

(e) If, by the Option Deadline for such Collaboration Program, Biogen or its designated Affiliate has not provided Ionis with both (i) a written notice stating that Biogen is exercising its Option for such Collaboration Program and (ii) the applicable Option Fee, and Biogen has not cured such failure within the earlier of [***] days following such missed Option Deadline or [***] days following receipt of written notice from Ionis of the missed Option Deadline, including payment of interest on the Option Fee over such cure period at the rate set forth in Section 6.15, then Biogen's Option for the applicable Collaboration Program will expire and (A) upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program to the extent licensed to Ionis under Section 4.3.4, (B) upon Biogen's request, Ionis will provide to Biogen any data generated under the Collaboration Program to the extent licensed to Biogen under Section 4.3.3 (and the requesting Party will pay all out-of-pocket direct Third Party costs and expenses incurred in connection with transferring such data, results and information together with the other Party's then-applicable FTE Rate in transferring such data, results and information) and (C) with respect to any Product under the applicable Collaboration Program, effective on the day that the applicable Collaboration Target to which such Collaboration Program is directed becomes a Terminated Target, Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, non-exclusive royalty-bearing (in accordance with Section 3.1.2(f)) license or sublicense, as the case may be, to Biogen Background Technology Controlled by Biogen as of such date solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize such Discontinued Products targeting such Terminated Target, in the Field in the form such products exist as of such date, other than Permitted Changes in Form with respect to such Discontinued Products (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*). Ionis will reimburse Biogen for any amounts owed by Biogen to Third Parties as a result of the grant of any such license to Ionis under, or Ionis' practice of, any Biogen Background Technology; *provided that* Ionis has been notified of the terms of such payment obligations to any such Third Party, and, if Ionis notifies Biogen that it does not wish to be granted a license under any Patent Rights or Know-How that are subject to such payment obligations included in the Biogen Background Technology, then such Patent Rights or Know-How (as applicable) will be excluded from the Biogen Background Technology licensed to Ionis hereunder, and Ionis will have no obligation to reimburse Biogen for any such payments.

(f) If Ionis or its Affiliates or Sublicensee sells any such Discontinued Products that are the subject of a Collaboration Program for which Biogen fails to exercise its Option by the Option Deadline in accordance with Section 3.1.2 and that are Covered by any Patent Rights within the Biogen Background Technology, then on a country-by-country basis Ionis will pay to Biogen a royalty equal to [***] of net sales of any such product sold by Ionis, its Affiliates or Sublicensees, for so long as such Discontinued Product is Covered by such Patent Rights within the Biogen Background Technology in such country. For the purpose of the foregoing royalty calculation, "net sales" will be calculated in accordance with the definition of "Net Sales" as set forth in APPENDIX 1, applied *mutatis mutandis* to such calculation. The provisions of Sections 6.12, 6.13, 6.14 and 6.15 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 3.1.2(f). If the Parties are unable to agree [***] under this Section 3.1.2(f) within a period of [***] days after the applicable Option Deadline, then either Party may refer the matter to Expert Resolution under Section 12.1.4.

(g) If, on or before the Option Deadline for a Collaboration Program (or within the cure period set forth under Section 3.1.2(e)), Biogen or its designated Affiliate does not both (i) notify Ionis in writing that it wishes to exercise the applicable Option for such Collaboration Program and (ii) pay to Ionis the applicable Option Fee for such Collaboration Program, then Biogen will have no further rights to such Collaboration Program.

3.1.3. HSR Compliance.

(a) HSR Filing. If Biogen notifies Ionis pursuant to Section 3.1.2(c)(iii) that an HSR Filing is required for Biogen to exercise an Option under this Agreement for a Collaboration Program, then each of Biogen and Ionis will, within five Business Days after the date of 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 3.1.3(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 [***], as applicable, for the final Product targeting such Collaboration Target.

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, by the [***] day after 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 to a Third Party 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, or supply Development Candidate API and Finished Drug Product for Commercialization, Ionis will, at Biogen's option, either (a) grant a license from Ionis to [***] under the [***] to the extent necessary for [***], which Ionis agrees it will grant to [***] or (b) permit Biogen to grant a sublicense from Biogen to [***]. For the Products, 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 [***] days after written notice from Biogen specifying the details of any such failure, then Biogen will have the right to [***].

4.1.3. Effect of Termination on Sublicenses.

(a) 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.

(b) If this Agreement terminates for any reason, then any Sublicensee of Biogen under Section 4.3.2 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 (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 such Sublicensee and (iii) with respect to Sublicensees of Ionis, such Sublicensee agrees to pay directly to Biogen such Sublicensee's payments under Section 4.3.2 to the extent applicable to the rights sublicensed to it by Ionis. Each Party agrees that it will confirm clause (i) of this Section 4.1.3(b) in writing at the request and for the benefit of the other Party, and if requested, the Sublicensee.

4.1.4. 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 and Biogen Background 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 or to perform Biogen Activities or Ionis Activities, as applicable, 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 owned or Controlled by such Party.

4.1.5. License Conditions; Limitations. Subject to Section 6.11, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are each 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 ((a)-(c)), to the extent the provisions of such obligations or agreements have been specifically disclosed to Biogen in writing (or via electronic data room) prior to the License Effective Date with respect to a Collaboration Program. With respect to each Product for a Collaboration Program, Ionis will promptly disclose to Biogen any Third Party Obligations that Ionis believes apply to such Collaboration Program during the Agreement Term, 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 such 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 from such license granted with respect to such Collaboration Program, such Third Party Patent Rights and Know-How will not be included in the Licensed Technology licensed with respect to the applicable Collaboration Program 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 with respect to a Collaboration Program, then such Third Party Patent Rights and Know-How (and any Third Party Obligations to the extent applicable to the applicable Collaboration Program) will be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement.

4.1.6. **Trademarks for Products**. Biogen or its designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining, and 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. **Assignment to Biogen**. Within [***] days after Biogen has paid to Ionis the milestone payment for [***] for a given Collaboration Program under Section 6.7, and following review and consideration by the Joint Patent Committee (or the Parties if the Joint Patent Committee has been disbanded), 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 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 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.

4.2.2. **Grant Back to Ionis**. 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, which license will be exclusive with respect to such Ionis Product-Specific Patents and non-exclusive with respect to such Jointly-Owned Program Patents (a) for all [***], (b) to conduct its activities with respect to such Collaboration Program under other Development Candidate Identification Plans, Toxicology Strategies and Integrated Product Plans to the extent permitted by this Agreement solely to the extent that Biogen is not responsible for such activities under Section 1.8.1(d)(ii), Section 1.10, Section 10.4, or Section 12.5.1(a), (c) to [***] to the extent permitted by this Agreement and (d) to [***] to the extent permitted under APPENDIX 3.

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 4.3.2 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 (including the activities set forth on SCHEDULE 4.3.1(a)); *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 for such Collaboration Program, (ii) any Biogen Activities that are Development activities with respect to any High Interest Target or Collaboration Target with respect to a Collaboration Program in accordance with this Agreement and (iii) any activities that Biogen is conducting pursuant to its step-in rights under Section 1.8.1(d)(ii), Section 1.10 or Section 12.5.1(a), in each case ((i) through (iii)) 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.

4.3.2. Biogen's Right to Sublicense. Biogen will have the right to grant sublicenses under the license granted under Section 4.3.1(a) above (a) 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 (i) [***] or (ii) [***] and (b) 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 4.3.2, 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 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 4.3.2 within [***] days after the execution thereof. For the avoidance of doubt, Section 4.1.3(b) shall apply to sublicenses granted under this Section 4.3.2.

4.3.3. 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 4.3.3(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 4.3.3(a) and in Section 4.3.3(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 4.3.3(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 4.3.3(a) and 4.3.3(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.

4.3.4. Enabling License 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 4.3.4(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 4.3.4(a) and in Section 4.3.4(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 any 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 in accordance with the definition of "Net Sales" as set forth in APPENDIX 1, applied *mutatis mutandis* to such calculation. The provisions of Sections 6.12, 6.13, 6.14 and 6.15 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 4.3.4. 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 4.3.4(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 4.3.4(a) and 4.3.4(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 Biogen, its Affiliates or Sublicensee 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 remain royalty-free [***]. The provisions of Sections 6.12, 6.13, 6.14 and 6.15 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, then 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. Biogen will have sole ownership of all INDs, NDAs, MAAs, orphan drug designations and other regulatory filings and documentation with respect to the Products under each Collaboration Program. If Biogen requests, then Ionis will assist Biogen in preparing regulatory filings for any 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, utilizing the payment mechanism set forth in Section 5.2.2.

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, 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 rights, title and interests 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 Effective 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.

4.8.1. Technology Transfer to Biogen Following the Effective Date. Within [***] days after the Effective Date, Ionis will deliver to one of Biogen or Biogen's designated Affiliate or Third Party contractor (at Biogen's election), solely for use by Biogen, [***] to conduct any Biogen Activities that are Development activities and any Manufacturing activities permitted under Section 4.3.1(a) with respect to any High Interest Target or Collaboration Target in accordance with this Agreement, all Ionis Manufacturing and Analytical Know-How in Ionis' Control [***] to conduct such Biogen Activities and Manufacturing activities. 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, using the payment mechanism set forth in Section 1.13.3.

4.8.2. Technology Transfer to Biogen after Collaboration Program Designation. On a Collaboration Program-by-Collaboration Program basis, Ionis will promptly, but no later than [***] days after Biogen designates such Collaboration Program hereunder, deliver to one of Biogen or Biogen's designated Affiliate or Third Party contractor (at Biogen's election):

(a) Ionis Know-How. All Ionis Know-How in Ionis' possession that has not previously been provided hereunder, for use solely by Biogen, its Affiliates or a Third Party acting on Biogen's behalf (i) to conduct IND-Enabling Toxicology Studies under Section 1.8.4 and if Biogen exercises the Option for such Collaboration Program, (ii) for use in accordance with the licenses granted under Section 4.1.1 and Section 10.6.2. Ionis will and does hereby assign to Biogen all of Ionis' rights, title and interests in and to all Regulatory Materials (including drafts) that relate to each applicable Development Candidate; *provided that*, (A) 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 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 (1) any non-public data or information, in each case, related solely to the applicable Development Candidate, or (2) any Confidential Information of Biogen, and (B) for clarity, such assignment of Ionis' rights, title and interests 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 (A) 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 and assignment 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 4.8.2(a). 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, using the payment mechanism set forth in Section 1.13.3.

(b) **Ionis Manufacturing and Analytical Know-How**. Solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf to Manufacture Development Candidate 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 or Section 4.3.1. 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(b) to any Third Party Manufacturing Development Candidate API, Clinical Supplies or Finished Drug Product on Biogen's behalf solely to Manufacture Development Candidate 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, using the payment mechanism set forth in Section 1.13.3.

(c) **API and Product**. Upon Biogen's written request, Ionis will sell to Biogen any bulk Development Candidate API, Clinical Supplies and Finished Drug Product, and any [***] relating to a Product in Ionis' possession at the time of the applicable License Effective Date, at a price equal to [***].

(d) **Results**. 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 Patents, 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 processes.

(e) For clarity, the Manufacturing Process Development Terms, and not the enabling licenses set forth in Section 4.3.3 and Section 4.3.4, shall govern with respect to all Results.

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. Development Pre-License Effective Date.

5.1.1. Diligence. Prior to the License Effective Date with respect to a Collaboration Program, (a) Biogen will use Commercially Reasonable Efforts to conduct any Biogen Activities and (b) Ionis will use Commercially Reasonable Efforts to conduct any Ionis Activities, in each case ((a) and (b)), on the timelines set forth in the applicable Neurology Plan.

5.2. Development Post License Effective Date.

5.2.1. Biogen Diligence. Following the License Effective Date with respect to a Collaboration Program, subject to Section 5.2.2, 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 Products under such Collaboration Program. Biogen will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product targeting each Collaboration Target for which Biogen has exercised one or more Options for Collaboration Programs. Biogen will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.2.1 for at least one Product targeting each Collaboration Target for which Biogen has exercised one or more Options for Collaboration Programs directed to such Collaboration Target on the timeline set forth therein (the "***Specific Performance Milestone Events***"). Notwithstanding the foregoing, [***].

5.2.2. **Ionis Diligence**. Notwithstanding Section 5.2.1, following the License Effective Date with respect to a Collaboration Program, the Parties may mutually agree, through the Neurology JDC, that Ionis is the more appropriate Party to conduct certain Clinical Studies or other activities under the Integrated Product Plan for such Collaboration Program, including with respect to [***] Development Candidates or with respect to the Clinical Supply and commercial supplies of Product API and Finished Drug Product. Prior to the commencement of any such Ionis-conducted Clinical Studies or other Development activities, Ionis shall provide a good faith estimate of Ionis' fully burdened cost expected to be incurred in connection with conducting such work (each, a "***Cost Estimate***") and the Parties shall agree, through the Neurology JDC, upon (a) those terms that will govern Ionis' conduct of such activities (including, with respect to Clinical Studies, terms related to regulatory communications, participation in regulatory meetings, and participation in meetings sponsored by Ionis' clinical development group), (b) the budget, based on the applicable Cost Estimate, for Ionis to conduct such Clinical Studies or other specific activities in accordance with the applicable Integrated Product Plan and (c) the frequency of the payments to be made to Ionis in accordance with such Cost Estimate, which budget and payment frequency shall be based on the principles set forth in Section 1.10.2(e) of the Neurology II Agreement. Following agreement of the Parties to the terms set forth in the preceding sentence, such agreed activities will be Ionis Activities and Ionis will use Commercially Reasonable Efforts to conduct such Ionis Activities in accordance with such agreed terms and the Integrated Product Plan. For clarity, unless otherwise mutually agreed, Ionis will not be required to conduct any Development activities for a Development Candidate following the applicable License Effective Date.

5.2.3. **Conduct of Clinical Development**.

(a) Biogen shall be responsible for filing and maintaining all INDs and other communications with Regulatory Authorities for each Collaboration Program consistent with Section 5.3. Notwithstanding the foregoing, with respect to any Clinical Studies being conducted by Biogen for a given Development Candidate, Ionis shall provide such reports and data as reasonably requested by Biogen generated from Ionis' activities, if any, performed under the applicable IPP ("***Ionis Activities Data***") that may be useful in support of an IND for the Development Candidate (including any [***] Development Candidate) under such Collaboration Program; *provided that*, if, after receiving the Ionis Activities Data, Biogen requests that Ionis provide Biogen with additional information outside of the scope of the Ionis Activities Data that Biogen reasonably believes is necessary or useful to support such IND, then, to the extent such additional information is in Ionis' possession and delivering such data to Biogen will not breach any obligation Ionis owes to a Third Party, Ionis will promptly deliver such additional information to Biogen solely for Biogen to use to support such IND. [***].

(b) Subject to Section 5.2.2, Biogen shall be responsible for conducting all Clinical Studies for all Development Candidates under each Collaboration Program at its sole expense. At meetings of the applicable Neurology JDC for a Collaboration Program, Biogen will keep Ionis reasonably informed of the progress and status of each Clinical Study conducted by Biogen for all Products that are the subject of such Collaboration Program.

(c) Unless otherwise agreed by the Parties under Section 5.2.2, Biogen will be responsible for Clinical Supply and commercial supplies of Product API and Finished Drug Product and may contract directly with CMOs with respect to such supply in accordance with Section 4.1.2.

(d) To the extent Ionis conducts all or any part of any Clinical Study pursuant to terms to be agreed by the Parties as set forth under Section 5.2.2, Ionis will keep Biogen informed of the progress and status of such Clinical Study conducted by Ionis at each meeting of the Neurology JDC, or at such other frequency as the Neurology JDC shall require. When Ionis measures the primary endpoint in all cohorts under any Clinical Study, Ionis will notify Biogen in writing of such measurement within [***] days of the conclusion of such Clinical Study. Ionis will present to the Neurology JDC the data generated under the statistical analysis plan for such Clinical Study as soon as practicable after such notice.

5.2.4. **Multi-Indication Targets for Non-Neurological Indications**. Without limiting any of the foregoing, with respect to any plan for the development and commercialization of a Multi-Indication Target that Biogen has agreed to conduct pursuant to a plan mutually-agreed under Appendix 3, Biogen will use Commercially Reasonable Efforts to develop, manufacture and commercialize at least one Product for such Multi-Indication Target in accordance with such agreed plan.

5.2.5. **Integrated Development and Commercialization Plan for Products**. On a Product-by-Product basis, Biogen will prepare a Development and global integrated Product commercialization 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 forecasts (each, an "***Integrated Product Plan***" or "***IPP***"). Biogen will prepare the IPP for each Product no later than [***] after the License Effective Date for the Collaboration Program to which such Product relates. The IPP will include an initial development plan consistent with the initial development plans provided under the Ionis/Biogen Additional Agreements, plus information consistent in scope and content with the information Biogen's senior management uses for internal decision-making for such Product. Schedule 5.2.5 sets forth examples of the types of information Biogen expects will be available to include in the IPP at different stages of development and commercialization of a Product. Once Biogen has prepared such plans, Biogen will update the IPP consistent with Biogen's standard practice and provide such updates to the CSC [***] (or to Ionis after the CSC terminates under Section 1.14.8(c)) until the expiration of the Full Royalty Period with respect to such Product. Biogen and Ionis will meet [***] basis to discuss (through the CSC) the draft of the IPP and Biogen will consider, in good faith, any proposals and comments made by the CSC (or Ionis after the CSC terminates under Section 1.14.8(c)) for incorporation in the final IPP. Members of the Neurology JRC and the Neurology JDC may also attend such yearly meetings. Notwithstanding the foregoing, Biogen's obligations to provide Ionis with information or reports with respect to a Product under this Section 5.2.5 will terminate if [***].

5.2.6. **Investigator's Brochure for Products**. Once prepared, Biogen will provide to Ionis an up-to-date version of the Investigator's Brochure for the applicable Product. Biogen will keep Ionis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions (if any) 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 5.2.6 will terminate with respect to a Product if [***].

5.2.7. **Development Results under Collaboration Programs.** Without limiting the other provisions of this Agreement, on a Collaboration Program-by-Collaboration Program basis, promptly following the availability of the tables, listings and figures generated under the statistical analysis plan and Biogen's completion of the study reports, as applicable, for a non-clinical study or a Clinical Study under any Collaboration Program, Biogen will provide to Ionis (a) all study reports for such non-clinical study or Clinical Study and (b) the applicable tables, listings and figures generated under the statistical analysis plan (for clarity, excluding subsequent *post hoc* analyses) for Clinical Studies conducted by Biogen (or its Affiliates or sublicensees) for the Product that is the subject of such Collaboration Program.

5.2.8. **Applicable Laws**. Each Party will perform its activities under 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.

5.3. **Regulatory Matters; Global Safety Database; Pharmacovigilance Agreement**. Consistent with Section 4.6 and Section 4.8.2, Biogen shall have ownership of all INDs, NDAs, MAAs, Priority Review Vouchers, orphan drug designations and other regulatory filings and documentation with respect to Products under each Collaboration Program and will be responsible for all communications with Regulatory Authorities regarding all such Products. Subject to Section 5.3.2 and Section 5.2.8, Biogen will have sole decision-making authority with respect to the matters set forth in this Section 5.3.

5.3.1. **Participation in Regulatory Meetings**. On a Collaboration Program-by-Collaboration Program basis, Biogen will provide Ionis with as much advance written notice as practicable of any meetings that Biogen has or plans to have with a Regulatory Authority regarding [***] or that directly relate to Ionis' antisense oligonucleotide chemistry platform and will allow two representatives of Ionis to participate in any such meetings at the direction of Biogen; *provided that* (a) where the total number of attendees at such meeting is five or less, Ionis' participation may be limited by Biogen to one representative, and (b) Biogen may exclude Ionis from any portion of such meeting that does not pertain to such Product or to Ionis' antisense oligonucleotide chemistry platform.

5.3.2. **Regulatory Communications**. On a Collaboration Program-by-Collaboration Program basis, following the License Effective Date with respect to a particular Collaboration Program, Biogen will promptly provide Ionis with copies of documents and communications submitted to (including drafts thereof) and received from Regulatory Authorities [***] that materially impact the Development or Commercialization of such Product for Ionis' review and comment, and Biogen will consider in good faith including any comments provided by Ionis to such documents and communications. During such period, Biogen will promptly notify Ionis upon receipt of any such documents or communications from any Regulatory Authority [***] country.

5.3.3. **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.

5.4. Pharmacovigilance Agreement; Global Safety Database.

5.4.1. Pharmacovigilance Agreement. No later than [***] prior to the date on which Biogen reasonably anticipates that it will exercise the Option with respect to a Collaboration Program, the Parties shall enter into a written pharmacovigilance agreement governing each Party's respective obligations with respect to safety-related matters, including matters relating to the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with Products that are the subject of such Collaboration Program, on terms substantially the same as the terms of the safety data exchange agreements entered into by the Parties with respect to the ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs (each as defined in the Neurology II Agreement).

5.4.2. 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 preclinical and clinical development (the "***Ionis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Ionis compounds, 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 reasonable additional 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 in accordance with Section 5.4.2(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 5.4.2(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 five Business Days following identification by Ionis) inform Biogen of such issues and, if requested, provide the data supporting Ionis' conclusions.

5.5. **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 (10) 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 (a) inclusion in filings with Regulatory Authorities for such Products and (b) 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. **Up-Front Fee; Equity Investment**. Within five Business Days following the Effective Date, Biogen will pay to Ionis an up-front fee of $375,000,000. Biogen shall also, in connection with the effectiveness of this Agreement, purchase 11,501,153 shares of common stock of Ionis for an aggregate purchase price of $625,000,000 (representing a price per share equal to 125% of the daily volume-weighted average per share price of such shares on the Nasdaq Global Select Market over the 10 trading day period ending on and including the last trading day prior to the Execution Date) pursuant to and in accordance with the terms set forth in that certain Stock Purchase Agreement to be entered into between the Parties as of the Execution Date.

6.2. **Drug Discovery Milestone Payments**. For each Strategy directed to either (a) a High Interest Target that achieves Target Sanction, and is designated by Biogen as a Collaboration Program pursuant to Section 1.3 or (b) an Ionis Neurology Target that achieves Target Sanction that is designated by Biogen as a Collaboration Program pursuant to Section 1.4 (each such event, the "***Target Designation Milestone***"), Biogen will pay to Ionis a milestone payment equal to $7,500,000 for each such Collaboration Program within (i) [***] following (i) the Collaboration Program Designation Date or Ionis Collaboration Program Designation Date or (ii) if Biogen does not designate such Collaboration Program under Section 1.3 prior to the Collaboration Program Designation Date, within [***] following the Collaboration Program Final Deadline (each such payment, a "***Target Designation Milestone Payment***").

6.3. **Milestone Payments for First Initiation of IND-Enabling Toxicology Studies**. As further consideration for Biogen's Options, on a Collaboration Program-by-Collaboration Program basis, Biogen will pay to Ionis a milestone payment equal to $[***] within [***] following the [***] for a Product under such Collaboration Program (each such event, an "***[***] Milestone***" and each such payment, an "***[***] Payment***").

6.4. **License Fee**. On an Option-by-Option basis, together with Biogen's written notice to Ionis stating that Biogen is exercising such Option for a given Collaboration Program in accordance with this Agreement, Biogen will pay to Ionis a license fee of $[***] for each such Collaboration Program (each such fee, an "***Option Fee***").

6.5. **Collaboration Program Asset Size Determination.**

6.5.1. **Initial Assessment of [***]**. For each Collaboration Program, within [***] months following the [***] for such Collaboration Program, Biogen shall generate a non-binding good faith commercial assessment of the market potential for the anticipated first Product arising from such Collaboration Program. Such commercial assessment will be the same as the assessment Biogen uses for its own internal planning purpose in creating Biogen's board-approved long range plans for Products under such Collaboration Program (the "***Biogen Sales Model***"). Based on such assessment, the applicable Product will be classified as (a) [***] if the market potential for such Product is expected to achieve peak revenue less than $[***] per [***] or (b) [***] per [***] (such determination, the "***[***]***"). Biogen will promptly provide Ionis with written notice of such [***] classification.

6.5.2. **[***] Assessment of [***].** Prior to [***] for any Product that is the subject of a Collaboration Program, Biogen shall generate (or update, as applicable) a good faith commercial assessment of the [***] for such Product based upon the results of Development up to such point. Such commercial assessment will take into account (a) [***] and (b) [***] and will be based on Biogen's updated calculation using the Biogen Sales Model for the first [***] of sales of the applicable Product. Biogen will notify Ionis of its formal designation of the [***] for such Product (such formal designation, together with Biogen's calculation using the Biogen Sales Model and board-approved long range plans for such Products, the "***Program Determination***"). The Program Determination, including the calculations under the Biogen Sales Model and the assumptions upon which such calculation was based may only be used by Ionis to assess the applicable [***] designation (and any adjustment thereto) and may only be disclosed to [***], who are informed of the confidentiality of such information and who agree in writing to maintain such confidentiality in accordance with Ionis' obligations with respect thereto under this Agreement. The Parties will use the Program Determination to calculate the applicable milestone payment due under TABLE 6.7 upon the [***]. Biogen will promptly thereafter present its Program Determination to the Neurology JDC for discussion and review and input by the Neurology JDC, which input Biogen will consider in good faith.

6.5.3. **[***] Assessment of [***]**. If following the Completion (and based on [***]) of such [***], Biogen's good faith commercial assessment of the [***] for the applicable Product changes from [***] to [***], or from [***] to [***], then no later than [***] days following the Completion of such Pivotal Clinical trial (the "***[***] Adjustment Period***"). Biogen will give prompt written notice to Ionis of its desire to change its [***] designation for such Product, including Biogen's updated Program Determination and Biogen Sales Model, and following the date of such notice (a) if [***], and (b) [***].

6.5.4. **Binding Determination**. Any [***] designation made under Section 6.5.3 shall thereafter be binding upon Biogen and dictate those payments due from Biogen pursuant to ARTICLE 6, provided that if Biogen fails to timely deliver written notice to Ionis under this Section 6.5.4 of its desire to change its [***] determination for such Product within the [***] Adjustment Period, then the [***] designation set forth in the Program Determination provided under Section 6.5.2 shall instead be binding upon Biogen and dictate those payments due from Biogen pursuant to ARTICLE 6. For clarity, each [***] designation set forth in a Program Determination shall apply to all Products that are the subject of the applicable Collaboration Program.

6.6. **Annual License Access Fee**.

6.6.1. On a Collaboration Target-by-Collaboration Target basis, commencing on (a) the [***] anniversary of the receipt by Biogen of the data generated under the statistical analysis plan for the first Phase 1 Trial (the "***Phase 1 Readout***") for the first Product directed to such Collaboration Target, if such Product arises from a Collaboration Program with [***] designated as a [***] or (b) the [***] anniversary of the Phase 1 Readout for the first Product directed to such Collaboration Target, if such Product arises from a Collaboration Program with [***] designated as a [***], (such date, (a) or (b), the "***Fee Commencement Date***") and ending upon [***] for a Product directed to such Collaboration Target (the "***Fee End Date***"), Biogen will pay to Ionis an Annual non-refundable, non-creditable license access fee of $[***] (such payment, the "***License Access Fee***"), as follows: a License Access Fee for the given Collaboration Target shall be due to Ionis upon the Fee Commencement Date and each anniversary thereof, and shall be payable within [***] days following the Fee Commencement Date and within [***] days following each anniversary of the Fee Commencement Date until the Fee End Date.

6.6.2. Notwithstanding Section 6.6.1, the Fee Commencement Date and each such subsequent anniversary thereof shall be tolled and Biogen shall not owe the License Access Fee with respect to such Collaboration Target during any period that (a) another Strategy or another Collaboration Program directed to such Collaboration Target is the subject of Research, Development or Commercialization activities under this Agreement at any point between payment of the Target Designation Milestone Payment and the Fee Commencement Date for such Strategy, and (b) the first Product directed to such Collaboration Target is the subject of further activities that a Party has made a good faith determination are reasonably necessary to conduct prior to [***] for such Product, and in the case of this subclause (b), the Fee Commencement Date and each anniversary thereof shall be tolled solely for the length of time reasonably necessary for such additional work to be conducted, *provided that* in the case of this subclause (b), (i) Biogen is using Commercially Reasonable Efforts to conduct such activities and (ii) unless otherwise agreed by the Neurology JDC, the maximum length of such extension shall be [***].

6.6.3. If (a) Biogen has paid the License Access Fee for a Collaboration Program following the [***] anniversary of the Phase 1 Readout based on its non-binding determination under Section 6.5.1 that the first Product under such Collaboration Program is a [***], and Biogen later determines under Section 6.5.2 or Section 6.5.3 that such Product is a [***], and (b) [***] (i.e., between the [***] and [***] anniversaries of the Phase 1 Readout), then upon achievement of the [***] for (i) the [***] or (ii) [***], Biogen may offset the amount of such License Access Fees (solely to the extent such fees would not have been payable to Ionis) against the amount payable to Ionis under Column 2 of TABLE 6.7 (as such amount may be adjusted under Section 6.5.3).

6.6.4. If (a) Biogen has not paid the License Access Fee for a Collaboration Program following the [***] anniversary of the Phase 1 Readout based on its non-binding determination under Section 6.5.1 that the first Product under such Collaboration Program is a [***], and Biogen later determines under Section 6.5.2 or Section 6.5.3 that such Product is a [***], and (b) [***], then within [***] of such determination Biogen shall pay to Ionis the amount of any such unpaid License Access Fees (solely to the extent such fees would have otherwise been payable to Ionis).

6.6.5. If Biogen fails to pay the License Access Fee when due, and Biogen has not cured such failure to pay the License Access Fee within the earlier of [***] days following the missed payment deadline or [***] days following receipt of written notice from Ionis of the missed payment deadline, then the Collaboration Program that triggered the Fee Commencement Date will terminate and, if the Collaboration Target for such Collaboration Program is an Inactive Target, then the rights in such Collaboration Program will revert to Ionis in accordance with Section 10.6.4. For clarity, the License Access Fee will no longer be payable with respect to a Collaboration Target following payment of the milestone payment under Section 6.7 for the first [***] for any Product directed to such Collaboration Target.

6.7. **Post-Option Development Milestone Payments**. On a Collaboration Program-by-Collaboration Program basis, subject to adjustment under Section 6.5.3, Biogen will pay to Ionis the milestone payments as set forth in TABLE 6.7 below when a milestone event (each, a "***Post-Option Development Milestone Event***") listed in TABLE 6.7 is first achieved by Biogen, its Affiliates or Sublicensees for a Product under such Collaboration Program, where the amount of the payment for such Milestone Event will be determined based on whether the applicable Product arises from a Collaboration Program that has been determined by Biogen to be a [***] or a [***] in accordance with Section 6.5:

TABLE 6.7 – Post-Option Development Milestone Events

	Column 1	Column 2
Post-Option Development Milestone Event	Milestone Event payment for the first Product from Collaboration Program designated as [***]	Milestone Event payment for the first Product from a Collaboration Program designated as [***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]

6.8. Limitations on Milestone Payments; Exceptions; Notice.

6.8.1. On a Collaboration Program-by-Collaboration Program basis, each milestone payment set forth in Section 6.2, Section 6.3 and TABLE 6.7 above will be paid only once upon the first achievement of the applicable Milestone Event, and the milestone payments set forth in TABLE 6.7 will be payable under only one of Column 1 or Column 2 upon the first achievement of the applicable Milestone Event, regardless of how many Products under such Collaboration Program achieve such Milestone Event.

6.8.2. If a particular Milestone Event under Section 6.7 is not achieved because Development activities transpired such that achievement of such Milestone Event was unnecessary or did not otherwise occur, then upon achievement of a later Milestone Event under Section 6.7, 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.

6.8.3. Each time Biogen (or its Affiliates or Sublicensees) first achieves a Milestone Event under Section 6.3 or Section 6.7, Biogen will send Ionis a written notice thereof promptly (but no later than five Business Days) following the date of achievement of such Milestone Event and such payment will be due within [***] days of the date such notice was delivered.

6.9. Royalty Payments to Ionis for Products.

6.9.1. Biogen Full Royalty for Products. As partial consideration for the rights granted to Biogen hereunder, subject to the provisions of this Section 6.9.1 and Section 6.9.2, Biogen will pay to Ionis royalties on a Collaboration Program-by-Collaboration Program basis on Annual worldwide Net Sales of all 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 either: (i) TABLE 6.9.1(a) below, where the Collaboration Program is designated a [***] (the "***Biogen [***] Royalty***"), or (ii) TABLE 6.9.1(b) below, where the Collaboration Program is designated a [***] (the "***Biogen [***] Royalty***"). The royalty rates set forth in TABLE 6.9.1(a) and TABLE 6.9.1(b) below shall each be referred to as a "***Biogen Full Royalty***."

TABLE 6.9.1(a) – [***] Royalty Rates

Royalty Tier	Annual worldwide Net Sales of Products for the applicable Collaboration Program ([***])	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 ≥ $[***]	[***]%

TABLE 6.9.1(b) – [***] Royalty Rates		
Royalty Tier	**Annual worldwide Net Sales of Products for the applicable Collaboration Program ([***])**	**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 ≥ $[***]	[***]%

(a) Annual worldwide Net Sales of Products will be calculated by [***]. For clarity, the same royalty rate shall apply to all Products arising from a given Collaboration Program, based on the Program Determination made for Products that are the subject of such Collaboration Program pursuant to Section 6.5.4.

(b) 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 6.12. 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.

(c) For purposes of clarification, any Ionis Product-Specific Patents for a Collaboration Program assigned to Biogen as set forth in Section 4.2.1 will still be considered Ionis Product-Specific Patents for purposes of determining the royalty term and applicable royalty rates under this Section 6.9.

6.9.2. **Application of Royalty Rates for Products**. All royalties set forth under Section 6.9.1 are subject to the provisions of this Section 6.9.2 and are payable as follows:

(a) **Full Royalty Period for Products**. Biogen's obligation to pay to Ionis the applicable 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 for Products**. Subject to Section 6.9.2(g)(i), on a country-by-country and Product-by-Product basis, if, during the Full Royalty Period for a Product, a Loss of Market Exclusivity for a Product in any country has occurred, then the Biogen Full Royalty rate used to pay to Ionis royalties on such Product in such country will be reduced to [***]% of the otherwise applicable Biogen Full Royalty rate.

(c) **Reduced Royalty Period for Products**. Subject to Section 6.9.2(g), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period for a Product and until the end of the Reduced Royalty Period for such Product, in lieu of the applicable royalty rates set forth in TABLE 6.9.1(a) or Table 6.9.1(b), Biogen will pay to Ionis royalty rates (the "***Biogen Reduced Royalty***") on Net Sales of such Product 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) **End of Royalty Obligation for Products**. On a country-by-country and Product-by-Product basis, other than [***], Biogen's obligation to make royalty payments hereunder for a Product in such country will end on the expiration of the Reduced Royalty Period for such Product in such country.

(e) **Royalty Examples**. SCHEDULE 6.9.2(e) attached hereto contains examples of how royalties will be calculated under this Section 6.9.

(f) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.9.2, different royalty rates apply to Net Sales of a Product in different countries, then Biogen will [***] such Net Sales [***]. SCHEDULE 6.9.2(f) attached hereto contains examples of how Net Sales of a Product from different countries at different royalty rates will be [***].

(g) **Limitation on Aggregate Reduction for Royalties for Products**.

(i) **Aggregate Royalty Reductions**. In no event will the aggregate royalty reductions reduce the royalties payable to Ionis on Net Sales of a Product in any given period to an amount that is less than the [***] for such Product; *provided that* Biogen shall have the right to [***].

(ii) **Aggregate Royalty Offsets during Full Royalty Period**. During the Full Royalty Period, unless Section 6.9.2(g)(iv) applies, in no event will the aggregate royalty offsets 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 [***].

(iii) **Aggregate Royalty Offsets during Reduced Royalty Period**. During the Reduced Royalty Period, unless Section 6.9.2(g)(iv) applies, in no event will the aggregate royalty offsets 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 (A) [***].

(iv) **Ionis Additional Core IP Offsets**. During the Full Royalty Period or Reduced Royalty Period, as applicable, in no event will the royalty offsets attributable to Section 6.11.2(b) 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 (A) [***].

6.10. Payments to Biogen for a Discontinued Product.

6.10.1. Reverse Royalty for a Discontinued Product. If Ionis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product that is the subject of a Strategy that was a Collaboration Program for which Biogen has exercised the Option and paid Ionis the applicable Option Fee, then following the First Commercial Sale of such Discontinued Product by Ionis or its Affiliates or Sublicensees, Ionis will pay to Biogen or to its designated Affiliate a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product ("***Reverse Royalties***"). Ionis' obligation to pay to Biogen the Reverse Royalties will [***].

6.10.2. Applicable Royalty Provisions. In addition to this Section 6.10, 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 Section 6.10.1, *mutatis mutandis*, including the provisions of Sections 6.9.2, 6.12, 6.13, 6.14 and 6.15.

6.11. Third Party Rights and Payment Obligations.

6.11.1. Existing Ionis In-License Agreements.

(a) Certain of the Licensed Technology Controlled by Ionis as of the Effective Date that will be licensed to Biogen under Section 4.1.1 on the License Effective Date for a given Collaboration Program were in-licensed or were acquired by Ionis or its Affiliates under agreements entered into prior to the Effective Date with Third Party licensors or sellers 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 Parties' Development, Manufacture and Commercialization of a Product under this Agreement. SCHEDULE 6.11.1 sets forth all Ionis In-License Agreements that as of the Execution Date Ionis believes apply to potential Products, to the extent such potential Products practice the inventions claimed in the Ionis Core Technology Patents in the same manner as Ionis practices such inventions with respect to the products in the Ionis Product Pipeline. As between the Parties, [***] will be responsible for any payment obligations arising under the Ionis In-License Agreements.

(b) If Biogen Controls Patent Rights and any Related Know-How as of the Effective Date that Cover any potential Product under this Agreement (including any Third Party Product IP), in each case, that were in-licensed or were acquired by Biogen or its Affiliates under agreements entered into prior to the Effective Date with Third Party licensors or sellers (all such license or purchase agreements being the "***Biogen In-License Agreements***") and certain milestone or royalty payments and license maintenance fees become payable by Biogen to such Third Parties under the Biogen In-License Agreements based on the Parties' Development, Manufacture and Commercialization of a Product under this Agreement, then as between the Parties, [***] will be solely responsible for any payment obligations arising under such Biogen In-License Agreements. **SCHEDULE 6.11.1** sets forth all Biogen In-License Agreements that as of the Execution Date Biogen believes apply to the use of antisense technology to create contemplated Products in the Field directed to Neurology Targets.

6.11.2. In-License Agreements for Additional Ionis Core IP.

(a) Each Party will promptly notify the other Party if either Party becomes aware of Third Party Patent Rights that such Party reasonably determines is Additional Ionis Core IP. "***Additional Ionis Core IP***" means any Patent Rights that are Controlled by a Third Party that (i) [***] or, (ii) [***], (iii) would not be considered Product-Specific Patents if Controlled by a Party or its Affiliates and (iv) [***]. [***] will have the first right, and the obligation, to negotiate with and seek to acquire rights (whether by purchase, assignment, license or otherwise) or other access to such Additional Ionis Core IP such that [***] such Additional Ionis Core IP [***] of this Agreement. If [***] Additional Ionis Core IP, then such Additional Ionis Core IP (together with any Related Know-How) [***] and Section 4.3.1 and any [***] will be paid solely by [***].

(b) If, however, [***] by the [***] anniversary of [***]. If [***] Additional Ionis Core IP, then, within [***] days of an invoice therefor from [***] will reimburse [***] an amount equal to the Product Specific Payments, other than royalties, payable in consideration for such Additional Ionis Core IP (and any Related Know-How) and paid by [***] under such Third Party agreement. With respect to royalties due on Products that are due as Product Specific Payments in consideration for such Additional Ionis Core IP (and such Related Know-How, if applicable), [***] shall be responsible for payment of all such royalties to the applicable licensor. Subject to Section 6.9.2(g), [***].

(c) Notwithstanding the foregoing, if the Parties do not agree whether certain Third Party Patent Rights constitute Additional Ionis Core IP, then Section 6.11.9 will apply.

6.11.3. In-License Agreements for Required Third Party Core IP.

(a) Each Party will promptly notify the other Party if either Party becomes aware of Third Party Patent Rights that such Party reasonably determines is Third Party Core IP. "***Third Party Core IP***" means Third Party Patent Rights that (i) do not constitute Additional Ionis Core IP, (ii) do not constitute Third Party Product IP, and would not be considered Product-Specific Patents if Controlled by a Party or its Affiliates and (iii) are [***]. Depending on the stage of development of the applicable Product at the time of such notice, to the extent known by a Party at the applicable time, such information will also be included in the applicable Target Sanction Plan or Development Candidate Identification Plan, as applicable.

(b) If the Parties do not agree whether certain Third Party Patent Rights constitute Third Party Core IP, then Section 6.11.8 will apply.

(c) Following such notice, if the Parties agree that such Third Party Patent Rights are Third Party Core IP, or if such Third Party Patent Rights are deemed Third Party Core IP by a Third Party expert pursuant to Section 6.11.8, then [***] shall have the first right, but not the obligation, to negotiate with and seek to acquire rights (whether by purchase, assignment, license or otherwise) or other access to such Third Party Core IP for use in the Collaboration; *provided that* the Parties agree in accordance with Section 6.11.9(a) on the [***] each Party's practice of such Third Party Core IP to Research, Develop, Manufacture and Commercialize Products under this Agreement. Except as expressly set forth in Sections 7.1.3(c)-7.1.3(f), if [***] Third Party Core IP [***], then such Third Party Core IP (together with any Related Know-How) will be included within the Licensed Technology and in the licenses granted to Biogen under Section 4.1.1 and Section 4.3.1 and the Parties will [***]% of all the Product Specific Payments payable in consideration for such Third Party Core IP (and any Related Know-How) as follows: (i) [***] shall be responsible for payment to the applicable Third Party licensor of all Product Specific Payments other than [***], (ii) [***] shall [***] for its [***]% share within [***] days following an invoice from [***] for such amounts and (iii) [***] shall be responsible for paying to the applicable Third Party all [***] due on Products that are due as Product Specific Payments and, subject to Section 6.9.2(g), [***].

(d) If Ionis [***] by the [***] anniversary of [***], then Ionis will so notify Biogen and [***]. Except as expressly set forth in Sections 7.1.3(c)-7.1.3(f), if [***] Third Party Core IP pursuant to [***] Section 6.11.9(a), then [***] days of an invoice therefor from [***] of all the Product Specific Payments, other than [***] payable in consideration for such Third Party Core IP (and any Related Know-How) and paid by [***]. With respect to royalties due on Products that are due as Product Specific Payments in consideration for such Third Party Core IP (and any Related Know-How), [***].

6.11.4. In-License Agreements for Product-Specific Third Party IP.

(a) Each Party will promptly notify the other Party if either Party becomes aware of Third Party Patent Rights that such Party reasonably determines is Third Party Product IP. "***Third Party Product IP***" means Third Party Patent Rights that (i) do not constitute Additional Ionis Core IP, (ii) would be considered Product-Specific Patents if Controlled by a Party or its Affiliates, (iii) do not claim other active ingredients and (iv) are Necessary. Depending on the stage of development of the applicable Product at the time of such notice, to the extent known by a Party at the applicable time, such information will also be included in the applicable Target Sanction Plan or Development Candidate Identification Plan, as applicable.

(b) If the Parties do not agree whether certain Third Party Patent Rights constitute Third Party Product IP, then Section 6.11.8 will apply.

(c) Following such notice, if the Parties agree that such Third Party Patent Rights are Third Party Product IP or if such Third Party Patent Rights are deemed Third Party Product IP by a Third Party expert pursuant to Section 6.11.9, then [***] shall have the first right, but not the obligation, to [***]; *provided that* the Parties agree in accordance with Section 6.11.9(a) on [***] under this Agreement. Except as expressly set forth in Sections 7.1.3(c)-7.1.3(f), if [***] Third Party Product IP [***], then the Parties shall [***] of all the Product Specific Payments payable in consideration for such Third Party Product IP (and any Related Know-How) and paid by [***] as follows: [***] shall be responsible for payment to the applicable Third Party licensor of all such Product Specific Payments, [***] shall reimburse [***] for its [***] for such amounts other than [***] shall be responsible for paying to the applicable Third Party all [***] due on Products that are due as Product Specific Payments and, [***].

(d) If [***] by the [***] anniversary of [***], then Biogen will so notify Ionis and Ionis may seek to acquire such rights or other access. Except as expressly set forth in Sections 7.1.3(c)-7.1.3(f), [***] Third Party Product IP [***] Section 6.11.9(a), then such Third Party Product IP (together with any Related Know-How) will be included within the Licensed Technology and in the licenses granted to Biogen under Section 4.1.1 and Section 4.3.1 and [***] days of an invoice therefor [***] an amount equal to [***]% of all the Product Specific Payments, other than [***], payable in consideration for such Third Party Product IP (and any Related Know-How) [***]. [***] shall be responsible for payment to the applicable Third Party of all [***] due on Products that are due as Product Specific Payments in consideration for such Third Party Product IP (and any Related Know-How) [***].

6.11.5. In-License Agreements for Other Specified Third Party IP.

(a) Biogen will notify Ionis if Biogen becomes aware of [***] Useful Third Party Product IP. "***Useful Third Party Product IP***" means Third Party Patent Rights that (i) do not constitute Additional Ionis Core IP, Third Party Core IP or Third Party Product IP, (ii) [***], (iii) [***] and (iv) are not Necessary, but are [***]. Depending on the stage of development of the applicable Product at the time of such notice, to the extent known by a Party at the applicable time, such information will also be included in the applicable Target Sanction Plan or Development Candidate Identification Plan, as applicable.

(b) Following any notice provided by Biogen in accordance with Section 6.11.5(a), [***] shall have the right, but not the obligation, to [***] and [***] will provide to [***] of such Useful Third Party Product IP to Develop, Manufacture and Commercialize Products under this Agreement. Except as expressly set forth in Sections 7.1.3(c)-7.1.3(f), if [***] Useful Third Party Product IP [***], then [***] shall be responsible for [***]%, and [***] shall be responsible for [***]%, in each case, of all the Product Specific Payments payable in consideration for such Useful Third Party Product IP (and any Related Know-How) and paid by [***] as follows: [***] shall be responsible for payment to the applicable Third Party licensor of all such Product Specific Payments, [***]% of any such Product Specific Payments paid by [***] to the relevant Third Party under any [***] of this Agreement for [***] with respect to Product Specific Payments other than [***], and [***] with respect to Product Specific Payments that are [***] pursuant to [***].

6.11.6. Other Acquisition of Third Party Rights.

(a) Notwithstanding anything to the contrary set forth in this Section 6.11, if, after the Effective Date, (i) either Party Controls Patent Rights as a result of an acquisition by such Party of all of the stock or assets of a Third Party (such acquisition, an "***Acquisition Transaction***" and such intellectual property rights, the "***Third Party Acquisition IP***") and (ii) such Party reasonably believes such Third Party Acquisition IP is Necessary, then such Party will provide the non-acquiring Party notice thereof, including providing details of the applicable Third Party Acquisition IP (and any Related Know-How) and any related payment obligations potentially arising solely as a result of the practice under such intellectual property in connection with the Research, Development, Manufacture or Commercialization of a Product in accordance with this Agreement. The acquiring Party shall [***]% of (A) [***] paid to any Third Parties in connection with the applicable Acquisition Transaction and (B) [***] that are not specifically triggered as a result of the Research, Development, Manufacture or Commercialization of Products in accordance with this Agreement (collectively, "***Acquisition Costs***").

(b) If, following such notice, the non-acquiring Party notifies the acquiring Party in writing that it wishes to include within the scope of the rights licensed to such Party under this Agreement such Third Party Acquisition IP and any Related Know-How, then subject to [***] Section 6.11.6, such Third Party Acquisition IP and Related Know-How will be included within the definition or Licensed Technology (in the case of Third Party Acquisition IP Controlled by Ionis) or the definition of Biogen Technology (in the case of Third Party Acquisition IP Controlled by Biogen) and the following terms will apply:

(i) The Parties will [***] Section 6.11.9(a) based on whether [***] is (A) Additional Ionis Core IP, in which case the payment allocation rules in Section 6.11.2 shall apply, (B) Third Party Core IP, in which case the payment allocation rules in Section 6.11.3 shall apply, (C) Third Party Product IP, in which case the payment allocation rules in Section 6.11.4 shall apply or (D) Useful Third Party Product IP, in which case the payment allocation rules in Section 6.11.5 will apply.

(ii) Each Party will [***] within [***] days following [***]. Except as provided for under Section 6.11.2, [***] shall be responsible for [***] subject to Section 6.9.2(g), [***].

6.11.7. Terms Applicable to Rights in Third Party IP. In each case where a Party has the right to enter into an agreement with a Third Party pursuant to this Section 6.11 for the grant of rights under Third Party Core IP, Third Party Product IP, or Useful Third Party Product IP, as applicable, such Party will negotiate with the applicable Third Party and seek to acquire such rights, unless [***] Third Party Core IP, Third Party Product IP or Useful Third Party Product IP (as applicable) [***]. If a Party [***] Third Party Core IP, Third Party Product IP or Useful Third Party Product IP [***], then such Party will promptly notify the other Party. Promptly following any such notice, with respect to Third Party Core IP and Third Party Product IP, unless the Parties [***], the Parties will [***] in accordance with the principles set forth in this Section 6.11. Notwithstanding anything in this Agreement to the contrary, during negotiations and if the Parties fail to secure rights under any Third Party Core IP and Third Party Product IP on mutually agreed terms within [***] of the [***], then unless otherwise agreed by the Parties, [***].

6.11.8. **Resolution by a Third Party Expert**. If the Parties cannot agree (a) whether certain Third Party Patent Rights constitute (i) Additional Ionis Core IP under Section 6.11.2, (ii) Third Party Core IP under Section 6.11.3 or (iii) Third Party Product IP under Section 6.11.4, then in each case ((i) - (iii)), the Party proposing to acquire rights to such Third Party Patent Rights or Know-How for use under this Agreement will send written notice thereof to the other Party or (b) as to any allocation of payments contemplated by Section 6.11.9(a), then a Party may send written notice to the other Party, and in each case ((a) and (b)), the Parties will engage an agreed upon independent Third Party expert who shall be an intellectual property lawyer with expertise in the patenting of Oligonucleotides and who has appropriate professional credentials in the relevant jurisdiction to determine the question of whether or not such Third Party intellectual property is Additional Ionis Core IP, Third Party Core IP or Third Party Product IP, as applicable (including whether such intellectual property is Necessary) or as to such allocation (as applicable). The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether or not such Third Party intellectual property is Additional Ionis Core IP, Third Party Core IP or Third Party Product IP, as applicable, or as to such allocation (as applicable) such that, in each case, the terms of Section 6.11.2, Section 6.11.3, Section 6.11.4 or Section 6.11.5 will apply. The costs of any Third Party expert engaged under this Section 6.11.8 will be paid by [***].

6.11.9. **Allocation of Certain Costs and Recoveries.**

(a) **Allocation for Multiple Programs or Products**. As part of the agreement by the Parties on the financial terms of a license or other Agreement with a Third Party that would be applicable to each Party's practice of any (i) Third Party Core IP, (ii) Third Party Product IP, (iii) Additional Ionis Core IP, (iv) Useful Third Party Product IP or (v) Third Party Acquisition IP, in each case, to Research, Develop, Manufacture and Commercialize Products under this Agreement, the Parties shall discuss (A) [***] that will apply thereto, (B) [***], (C) whether the applicable Third Party intellectual property is or would be used or practiced in connection with (1) [***] or (2) [***] and (D) in each case [***]. Taking into account such considerations, the Parties will discuss in good faith through the CSC [***] of the amounts payable in respect of such Third Party Core IP, Third Party Product IP, Additional Ionis Core IP, Third Party Acquisition IP or [***] Third Party Product IP between [***], with respect to which such intellectual property is used or practiced. Notwithstanding anything in this Agreement to the contrary, neither Party will [***] Third Party Core IP, Third Party Product IP, Additional Ionis Core IP, Third Party Acquisition IP or Useful Third Party Product IP, as applicable, in a manner that (I) [***] or (II) [***].

(b) **Costs and Damages under Third Party Claims**. Notwithstanding any determination of the Third Party expert under Section 6.11.8, if a Third Party that Controls any Patent Right or Know-How is awarded a judgment from a court of competent jurisdiction arising from its claim against Biogen asserting that rights to such Patent Rights or Know-How (as applicable) are necessary for Biogen to Develop, Manufacture or Commercialize a Product, then:

(i) if such Third Party Patent Rights or Know-How are Third Party Core IP or Third Party Product IP then (A) Biogen may offset against [***] (1) [***]% of [***], and (2) [***]% of the [***], in each case ((1) and (2)) subject to Section 6.9.2(g) and (B) if Biogen is granted a license under such Third Party Patent Rights in connection with such Third Party claim, then the [***];

(ii) if such Third Party Patent Rights constitute Additional Ionis Core IP, then Biogen will be (A) entitled to [***] and (B) subject to the floor for Additional Ionis Core IP set forth in Section 6.9.2(g), permitted to offset against any [***] (1) [***]% of [***] and (2) [***]% of any amounts paid by Biogen to such Third Party to satisfy any actual damages or fees awarded by such court against Biogen; and

(iii) If such Third Party Patent Rights constitute Useful Third Party Product IP, then subject to Section 6.9.2(g), Biogen may [***] as follows:

(A) if the Parties agreed in writing not to acquire rights under any such Third Party Patent Rights that constitute Useful Third Party Product IP, then [***]% of (1) its [***] and (2) the sum of (i) [***] and (ii) [***]; and

(B) in all other cases, (1) [***]% the [***] and (2) if [***], then the [***] in accordance with Section 6.11.5.

6.12. Payments.

6.12.1. 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 for such Product 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, 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 taken 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 [***] 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 [***] report estimating the total Net Sales of, and royalties payable to Ionis for Products projected for such Calendar Quarter.

6.12.2. **Mode of Payment**. All payments under this Agreement will be (a) payable in full in United States 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) except as set forth in Section 6.13 or Section 12.5.1, 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 as utilized by Biogen, in accordance with GAAP, fairly applied and as employed on a consistent basis throughout Biogen's operations.

6.12.3. **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.

6.13. **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 [***]. Such inspection right will not be exercised more than once with respect to records covering any specific period of time, unless a prior audit indicated a discrepancy, in which case such records may be re-audited one time. 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 undisputed discrepancy revealed by said inspection within [***] days of receiving the Audit Report, with interest calculated in accordance with Section 6.15. 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.

6.14. Taxes.

6.14.1. 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.

6.14.2. Withholding Tax.

(a) 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 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, interest or penalties 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.

6.14.3. 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 determine if any taxes are applicable to payments under this Agreement and 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 6.14.

6.14.4. The provisions of this Section 6.14 are to be read in conjunction with the provisions of Section 12.4 below.

6.15. 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***" promptly following the Effective Date. 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 Neurology 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, each Target Sanction Plan in accordance with Section 1.2.3(d)(iv), (iii) making recommendations with respect to intellectual property considerations to be taken into account in each Development Candidate Identification Plan under Section 1.8.2(a), including any Biogen Background Technology to be included in any Development Candidate Identification Plan (subject to Biogen's agreement in its sole discretion with respect thereto), (iv) the preparation of recommendations with respect to intellectual property considerations in connection with proposed Development Candidates and Related Program Compounds for consideration under Section 1.8.3(d)(i), (v) assessing and making recommendations to the Neurology JDC 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 Neurology 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 as set forth under Section 1.8.7, 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 Research 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 Core Research Program and the Neurological Disease Research Program, promptly following the Effective 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 Neurology 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 Neurology Plans or solely by a Third Party performing activities under the Neurology 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 Biogen for potential designation as a Development Candidate. If the JPC (or independent patent counsel engaged pursuant to Section 7.1.3(f)) determines that any Collaborator IP would be infringed or misappropriated (as applicable) by the Development, Manufacture or Commercialization of such Development Candidate or Compound, then [***]; *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 a [***] 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 6.11, if Collaborator IP (other than Additional Ionis Core IP) arises from activities performed by a Third Party under the applicable Neurology Plan, then any payment obligations arising under the applicable Collaborator License based on the Development or Commercialization of a Product will be shared the Parties 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 that [***] approved prior to execution thereof and (ii) in the case where [***] enters into such Collaborator License, [***] will be solely 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 4.1.5 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, 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 Biogen 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 7.2.5(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 7.2.5(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 7.2.5(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 7.2.5(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. Prosecution of Multi-Indication Product-Specific Patents; Biogen Supremacy to Enforce and Extend. With respect to Product-Specific Patents related to Multi-Indication Products, the Parties will endeavor to prosecute such Patent Rights to claim inventions related to Neurological Diseases separately from inventions related to Non-Neurological Indications. If there is an Ionis Product-Specific Patent that Covers both (a) a Multi-Indication Product licensed to Biogen under Section 4.1.1 and (b) a Multi-Indication Product of Ionis (each such Ionis Product-Specific Patent, a "***Multi-Indication Product-Specific Patent***"), then so long as Biogen is Developing and Commercializing such Multi-Indication Product pursuant to its license under Section 4.1.1, upon the grant of such license, Biogen will have the sole and exclusive right, but not the obligation, to institute and control any (i) Proceeding related to the infringement of such Multi-Indication Product-Specific Patent, (ii) Prosecution and Maintenance of such Multi-Indication Product-Specific Patent and (iii) patent term extension related to such Multi-Indication Product-Specific Patent.

7.2.5. 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 7.2.5, 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 7.2.5, 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 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 7.2.5(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 7.2.5(c), then Ionis will have no obligation to notify Biogen if Ionis intends to abandon such Biogen-Prosecuted Patent.

(d) Notwithstanding Section 7.2.5(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 6.9.2(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 7.2.5(c) above to file or prosecute the Conflicting Patent Right.

(e) If, during the Agreement Term, Ionis intends not to file or 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 7.2.5(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 7.2.5(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, titles and interest 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 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 such Party will promptly notify the other Party in writing. If Biogen also enforces any Patent Rights Controlled by Biogen (including any Ionis Product-Specific Patents 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, 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 such Section 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) agreement entered into by Ionis with a Third Party following the Effective Date in accordance with Section 6.11.2(a), Section 6.11.3(c), Section 6.11.4(d) or Section 6.11.6(a) (each, a "***New Third Party License***"), (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 Execution Date and the Effective 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, except as required pursuant to the HSR Act and as contemplated by the Stock Purchase Agreement; 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 Execution Date and the Effective Date that:

8.2.1. Ionis Controls the Licensed Technology listed on SCHEDULE 8.2.5(a) and SCHEDULE 8.2.5(b) and it has the full right, power and authority to grant all rights and licenses (or sublicenses, as the case may be) it purports to grant to Biogen under this Agreement;

8.2.2. 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 that would be required in order for Biogen to further Develop, Manufacture and Commercialize a potential Product, to the extent such potential Product practices the inventions claimed in the Ionis Core Technology Patents in the same manner as Ionis practices such inventions with respect to the products in the Ionis Product Pipeline.

8.2.3. The Licensed Technology constitutes all of the Patent Rights and Know-How Controlled by Ionis 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 (or contemplated) hereunder with respect to potential Products, to the extent such potential Products practice the inventions claimed in the Ionis Core Technology Patents in the same manner as Ionis practices such inventions with respect to the products in the Ionis Product Pipeline.

8.2.4. Neither Ionis nor its Affiliates owns or Controls any Patent Rights or Know-How covering formulation or delivery technology that would be useful or necessary in order for Biogen to further Develop or Commercialize a potential Compound contemplated under the Collaboration Programs, to the extent such potential Compound practices the inventions claimed in the Ionis Core Technology Patents in the same manner as Ionis practices such inventions with respect to the products in the Ionis Product Pipeline.

8.2.5. SCHEDULE 8.2.5(a) and SCHEDULE 8.2.5(b) each set forth true, correct and complete lists of all (a) Ionis Core Technology Patents and (b) Ionis Manufacturing and Analytical Patents a, 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 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.

8.2.6. 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 Core Technology Patents, the Ionis Manufacturing and Analytical Patents, Ionis Manufacturing and Analytical Know-How or Ionis Know-How 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 Core Technology Patents, the Ionis Manufacturing and Analytical Patents, Ionis Manufacturing and Analytical Know-How or Ionis Know-How, in any case, that would impact activities under this Agreement.

8.2.7. That (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.

8.2.8. Other than as set forth on SCHEDULE 8.2.8, no Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent is currently involved in any interference, reissue, re-examination, cancellation or opposition proceeding and neither Ionis, nor any of its Affiliates, has received any written notice from any Person or has knowledge of such actual or threatened proceeding.

8.2.9. Ionis has set forth on SCHEDULE 6.11.1 a true, correct and complete lists of the agreements with Third Party licensors or sellers pursuant to which Ionis has licensed or acquired the Know-How and Patent Rights Controlled by Ionis as of the Effective Date that is necessary or useful to conduct the research, Development, Manufacture or Commercialization of potential Products to the extent that such potential Products practice the inventions claimed in the Ionis Core Technology Patents in the same manner as Ionis practices such inventions with respect to the products in the Ionis Product Pipeline. 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.

8.2.10. SCHEDULE 8.2.10 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 with respect to any Products, to the extent such potential Products practice the inventions claimed in the Ionis Core Technology Patents in the same manner as Ionis practices such inventions with respect to the products in the Ionis Product Pipeline.

8.2.11. To the best of Ionis' knowledge, there are no issued patents owned by a Third Party that (a) are not Controlled by Ionis and (b) are necessary to practice an invention claimed within a Patent Right included in the Ionis Core Technology Patents in connection with any Product, to the extent such potential Product practices the inventions claimed in the Ionis Core Technology Patents in the same manner as Ionis practices such inventions with respect to the products in the Ionis Product Pipeline.

8.2.12. There are no Ionis Product-Specific Patents that Cover High Interest Targets, Compounds or Products, as such High Interest Targets, Compounds or Products exist as of the Execution Date or Effective Date.

8.2.13. SCHEDULE 8.2.13 represents a complete and accurate list of all (a) antisense products that Ionis, an Ionis Affiliate or a Third Party collaboration partner of Ionis are developing in Clinical Studies or commercializing, or are subject of registration for marketing authorization and (b) Development Candidates under any of the Ionis/Biogen Additional Agreements, and in each case ((a) and (b)), includes the chemical features incorporated into any such products.

8.3. **Effective Date Covenants of Ionis**. During the period between the Execution Date and the Effective Date:

8.3.1. Ionis will not, and will cause its Affiliates not to assign, transfer, convey or otherwise encumber its rights, title or interest in or to any Patent Rights or Know-How (including by granting any option or covenant not to sue with respect thereto) that would constitute Ionis Core Technology Patents, Ionis Manufacturing and Analytical Know-How or Ionis Know-How but for such assignment, transfer, conveyance or encumbrance in a manner that would adversely affect Biogen's rights under this Agreement.

8.3.2. Ionis will not, and will cause its Affiliates not to enter into an agreement, written or oral, with a Third Party granting such Third Party any rights to exploit the Ionis Core Technology Patents, Ionis Manufacturing and Analytical Know-How or Ionis Know-How in a manner that would adversely affect Biogen's rights and obligations under this Agreement.

8.3.3. Ionis will not, and will cause its Affiliates not to enter into an agreement, written or oral, with a Third Party granting such Third Party any rights with respect to the discovery, research, development, manufacture or commercialization of any product in the Field in any country or jurisdiction that includes an Oligonucleotide that is designed to bind to the RNA that encodes a Neurology Target, in a manner that would adversely affect Biogen's rights under this Agreement.

8.3.4. Ionis will not, and will cause its Affiliates not to encumber any Neurology Target under an agreement, written or oral, with a Third Party that would prevent Ionis from granting Biogen the license under Section 4.1.1 of this Agreement with respect to any Neurology Target or any Strategy directed thereto.

8.3.5. Ionis will not, and will cause its Affiliates not to amend, modify, terminate or waive any rights under any Ionis In-License Agreement in a manner that would adversely affect Biogen's rights and obligations under this Agreement without Biogen's prior written consent.

8.3.6. Ionis will not, and will cause its Affiliates not to, commit any acts or permit the occurrence of any omissions that would cause or result in the termination of any Ionis In-License Agreement in its entirety or with respect to any rights under such agreement for which such termination would adversely affect Biogen's rights and obligations under this Agreement. Ionis will notify Biogen in writing within one Business Day after any such termination of any Ionis In-License Agreement.

8.3.7. Ionis will promptly notify Biogen of any updates to each of SCHEDULE 6.11.1, SCHEDULE 8.2.5(a), SCHEDULE 8.2.5(b) and SCHEDULE 8.2.10, and shall provide Biogen with an updated schedule, as applicable, as soon as reasonably practicable.

8.4. **Additional Ionis Covenants**. From and after the Execution Date through the expiration or earlier termination of this Agreement, Ionis hereby covenants to Biogen that, except as expressly permitted under this Agreement:

8.4.1. On an Annual basis, and on agreement of the Parties from time-to-time, Ionis will amend SCHEDULE 8.2.5(a), SCHEDULE 8.2.5(b), SCHEDULE 8.2.5(c) (which schedule shall set forth a true, complete and correct list of all Ionis Product-Specific Patents, if any) and SCHEDULE 8.2.10 and submit such amended Schedules (if any) to Biogen at the next meeting of the JPC to reflect any pre-existing or new Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents, Ionis Product-Specific Patents or Third Party Obligations are not properly identified on such Schedule.

8.4.2. Ionis will maintain and not breach any Ionis In-License Agreements and any agreements with Third Parties entered into after the Execution Date 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 a Development Candidate under this Agreement;

8.4.3. 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;

8.4.4. 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;

8.4.5. 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;

8.4.6. 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;

8.4.7. All employees and contractors of Ionis performing Development activities hereunder on behalf of Ionis (including for any Affiliate) 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, prior to performing any such Development activities; and

8.4.8. If 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 the applicable Option and the license granted to Biogen under this Agreement with respect to such Product is in effect at the relevant time when Ionis gains such Control, then Ionis will make such technology available to Biogen on commercially reasonable terms.

8.5. **Additional Biogen Covenants**. From and after the Execution Date through the expiration or earlier termination of this Agreement, Biogen hereby covenants to Ionis that, except as expressly permitted under this Agreement all employees and contractors (other than academic or non-profit institutions) of Biogen performing Development activities hereunder on behalf of Biogen (including for any Affiliate) will be obligated to assign all rights, title and interests in and to any inventions developed by them, whether or not patentable, to Biogen or such Affiliate, respectively, as the sole owner thereof, prior to performing any such Development activities.

8.6. **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 ANY 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 or the exercise of its rights under the Biogen Background Technology,

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, conditioned or delayed), (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, *provided that* such self-insurance is at levels consistent with levels customarily maintained against similar risks by companies similarly situated to Biogen operating 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 UNDER THIS AGREEMENT, (C) A PARTY'S BREACH OF ARTICLE 2, 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), 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. IN ADDITION, THIS SECTION 9.5 SHALL NOT ACT TO LIMIT OR OTHERWISE EXCLUDE BIOGEN'S LIABILITY FOR DAMAGES THAT ARE ATTRIBUTABLE TO (I) LOST PROFITS OR (II) LOST ROYALTIES, IN EACH CASE ((I) AND (II)), ARISING FROM A BREACH OF SECTION 10.6.4(a) BY BIOGEN OR ITS AFFILIATES.

ARTICLE 10.
TERM; TERMINATION

10.1. **Effectiveness**. This Agreement will take effect automatically without further action of either Party upon the Effective Date; *provided*, *however*, that ARTICLE 8, ARTICLE 9, this Section 10.1, Section 10.3.1, ARTICLE 11 and ARTICLE 12, will each become binding and effective as of the Execution Date.

10.2. **Agreement Term; Expiration**. Subject to Section 10.1, 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:

10.2.1. 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 (except Discontinued Products) in such country;

10.2.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to all Products (except Discontinued Products) in all countries pursuant to Section 10.2.1;

10.2.3. where, following the expiration of the Research Term, there are no Collaboration Programs directed to Collaboration Targets and no High Interest Targets to which Biogen has any remaining rights under this Agreement (for example, because (a) with respect to a High Interest Target, Biogen failed to exercise its right to designate a High Interest Target as a Collaboration Target by the deadline set forth in Section 1.7(d), (b) with respect to a Collaboration Target, a Target Technical Failure with respect to a Collaboration Target occurred and the Carryover Period for such Collaboration Target expired without Biogen's election to bring a Carryover Development Candidate under the Agreement pursuant to Section 1.8.2(g) or (c) with respect to a Collaboration Program, Biogen failed to designate a Development Candidate by the Development Candidate Designation Deadline as set forth in Section 1.8.3(d), failed to cure a failure to Initiate IND-Enabling Toxicology Studies as set forth in Section 1.8.4(b), failed to cure a failure to exercise the Option by the Option Deadline as set forth in Section 3.1.2(e) or failed to cure a failure to pay the License Access Fee as set forth in Section 6.6).

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.2 is the "***Agreement Term***."

10.3. Termination of the Agreement.

10.3.1. Termination Prior to the Effective Date.

(a) Termination Due to Material Adverse Effect. This Agreement will terminate in its entirety if a Material Adverse Effect has occurred and Biogen provides notice of termination to Ionis prior to the Effective Date that such Material Adverse Effect has occurred. In such event, neither Party shall have any further obligations under this Agreement, except for such Party's obligations of non-disclosure pursuant to ARTICLE 11, which shall survive for the period set forth therein.

(b) Termination for Failure to Close before the Termination Date. If the Effective Date has not occurred within 180 days after the Execution Date (the "***Termination Date***"), then this Agreement may be terminated by either Party upon written notice to the other. In such event, neither Party shall have any further obligations under this Agreement, except for such Party's obligations of non-disclosure pursuant to ARTICLE 11, which shall survive for the period set forth therein. Notwithstanding the foregoing, a Party's right to terminate this Agreement under this Section 10.3.1(b) shall not be available to any Party that knowingly fails (whether by act or omission) to fulfill any obligation under this Agreement or the Stock Purchase Agreement, which failure causes or results in the failure to consummate the transactions contemplated hereby prior to the Termination Date.

10.3.2. **Biogen's Termination for Convenience**. At any time following the Effective Date and payment by Biogen of the up-front fee under Section 6.1, subject to Section 10.6.1 below, Biogen may terminate this Agreement in its entirety or on a Collaboration Program-by-Collaboration Program basis, at any time by providing 90 days written notice to Ionis of such termination.

10.3.3. **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 12.5.3, 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.

10.3.4. **Termination Due to Failure to Obtain HSR Clearance With Respect to an Option**.

(a) If the Parties make an HSR Filing with respect to a proposed Collaboration Program under Section 3.1.3 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 the applicable proposed 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 proposed 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 3.1.3(b). Notwithstanding the foregoing, this Section 10.3.4 will not apply if an HSR Filing is not required to fully perform this Agreement with respect to a proposed Collaboration Program.

(b) If Biogen has paid the up-front fee under Section 6.1, and if this Agreement is terminated with respect to a Collaboration Program in accordance with Section 10.3.4(a), then, until [***] as follows:

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

(ii) If (A) Ionis, (B) its Affiliates or (C) the licensee under the Subsequent Deal, in each case of (A) through (C), [***].

(iii) Nothing in this Section 10.3.4(b) obligates Ionis to (A) [***] or (B) [***]. For clarity, Ionis' rights to (1) [***] or (2) [***] of this Agreement.

10.3.5. Biogen's Right to Terminate for Material Breach by Ionis.

(a) If Biogen believes that Ionis is in material breach of this Agreement (including if Biogen believes that Ionis is in material breach of its obligations under ARTICLE 1 or Section 5.1 with respect to a particular Strategy directed to a High Interest Target or Collaboration Program (as applicable)), then Biogen may deliver notice of such material breach to Ionis. Within [***] days of such notice, Ionis and Biogen will meet to discuss and resolve the matter in good faith, and, if such breach is curable, attempt to devise a mutually agreeable plan to cure such breach (including to resolve any outstanding issues related to Ionis' use of Commercially Reasonable Efforts under ARTICLE 1 or Section 5.1). If the breach is curable, then Ionis will have [***] days to cure such breach following such meeting (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). Notwithstanding the foregoing, if such breach is curable but is not reasonably curable within [***] days and if Ionis is making a *bona fide* effort to cure such breach and implement such mutually agreed cure plan (if any), then the cure period will be extended for a time period to be agreed by the Parties in order to permit Ionis a reasonable period of time to cure such breach (but in no event will such time period be more than an additional [***] days). If Ionis fails to cure such material breach by the end of such [***] day or [***] day period (as such [***] day period may be extended up to [***] additional days pursuant to the preceding sentence), as applicable, or if the material breach is not subject to cure, then, subject to Section 10.3.7, Biogen in its sole discretion may elect to (as applicable):

(i) with respect to a material breach of Ionis' obligations under ARTICLE 1 or Section 5.1, if such material breach involves one or more Strategies or Collaboration Programs (as applicable) prior to the License Effective Date with respect to such Strategies or Collaboration Programs, trigger the alternative remedy provisions of Section 10.4 below as such provisions relate to such Strategies or Collaboration Programs in lieu of terminating this Agreement for such Strategies or Collaboration Programs by providing written notice to Ionis;

(ii) with respect to any material breach, terminate this Agreement with respect to the applicable Strategies directed to those High Interest Targets or Collaboration Programs that are affected by such breach by providing written notice to Ionis; or

(iii) with respect to any material breach of Ionis' obligations with respect to one or more Collaboration Programs after the License Effective Date with respect to such Collaboration Programs, trigger the alternative remedy provisions of Section 10.6.5.

(b) If Biogen makes an election under Section 10.3.5(a)(i) to trigger the alternative remedy provisions of Section 10.4 below with respect to one or more Strategies directed to those High Interest Targets or Collaboration Programs (as applicable) prior to the License Effective Date for such Strategies or Collaboration Programs in lieu of terminating this Agreement for such Strategies or Collaboration Programs, then such election shall be Biogen's sole and exclusive remedy for Ionis' breach of its obligations under ARTICLE 1 or Section 5.1, as applicable, with respect to such Strategies or Collaboration Programs.

(c) Without limiting the foregoing, breach by a Party of ARTICLE 2 of this Agreement constitutes a material breach of this Agreement with respect to those Strategies and Collaboration Programs affected by such breach.

10.3.6. Ionis' Right to Terminate for Material Breach by Biogen.

(a) On a Collaboration Program-by-Collaboration Program basis, if Ionis believes that Biogen is (i) in material breach of a payment obligation under ARTICLE 6 with respect to a Product that is the subject of such Collaboration Program, (ii) in material breach of one or more material provisions of this Agreement with respect to a Product that is the subject of such Collaboration Program where such material breaches have occurred multiple times over the course of at least a [***]-month period (where such material breach is not a single continuous event) and demonstrate a pattern of failing to timely comply with Biogen's obligations under this Agreement or (iii) in material breach of its obligations under Section 5.1 or Section 5.2.1 with respect to such Collaboration Program, then Ionis may deliver notice of such material breach with respect to such Collaboration Program to Biogen. Within [***] days of such notice, Ionis and Biogen will meet to discuss and resolve the matter in good faith, and, if such breach is curable, attempt to devise a mutually agreeable plan to cure such breach (including to resolve any outstanding issues related to Biogen's failure to fulfill its obligations under Section 5.1 or Section 5.2.1). If the breach is curable, then Biogen will have [***] days to cure such breach following such meeting (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). Notwithstanding the foregoing, if such breach is curable but is not reasonably curable within [***] days and if Biogen is making a *bona fide* effort to cure such breach and implement such mutually agreed cure plan (if any), then the cure period will be extended for a time period to be agreed by the Parties in order to permit Biogen a reasonable period of time to cure such breach (but in no event will such time period be more than an additional [***] days). If Biogen fails to cure such material breach by the end of such [***] day or [***] day period (as such [***] day period may be extended up to [***] additional days pursuant to the preceding sentence), as applicable, or if the material breach is not subject to cure, then, subject to Section 10.3.7, Ionis in its sole discretion may elect to terminate this Agreement with respect to the applicable Strategies directed to those High Interest Targets or the Collaboration Programs that are affected by such material breach by providing written notice thereof to Biogen.

10.3.7. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 10.3.5 or Section 10.3.6 disputes in good faith the existence, materiality or failure to cure of any such breach that is not a breach of an undisputed payment obligation, 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 10.3.5 or Section 10.3.6, or trigger the alternative remedy provisions of Section 10.4, 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. Without limiting the foregoing, it is understood that the alternative remedy provisions of Section 10.4 or Section 10.6.5 shall not be applicable, and Biogen may not exercise such provisions, with respect to any breach involving the failure to make a payment when due.

10.3.8. 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.

10.3.9. Termination for Patent Challenge. Either Party may terminate this Agreement if the other Party (a) 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 (excluding any dispute over inventorship, which disputes will be resolved in accordance with Section 7.1.3(g)) within (i) the Licensed Patents (if Biogen is the challenging Party) or (ii) the Biogen Program Technology or Biogen Product-Specific Patents (if Ionis is the challenging Party) or (b) 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 Patent Rights and, in each case ((a) or (b)), within [***] days' written notice from such Party, the challenging Party fails to rescind any and all of such actions, *provided however* that, nothing in this clause prevents the challenging Party from taking any of the actions referred to in this clause and *provided further* that the notifying Party will not have the right to terminate under this Section 10.3.9 if the challenging Party:

(a) takes any such action as described in clause (a) or (b) 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 the notifying Party asserting infringement of such Patent Rights; or

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

(c) licenses a product for which the notifying Party has an existing challenge, whether in a court or administrative proceeding, against such Patent Rights.

10.4. **Alternative Remedies to Termination Available to Biogen Prior to License Effective Date**. If, prior to the License Effective Date with respect to a particular Collaboration Program, with respect to a particular Strategy directed to a High Interest Target or Collaboration Program (as applicable), Biogen elects to exercise the alternative remedy provisions of this Section 10.4 in lieu of terminating this Agreement for such Strategies or Collaboration Program by providing written notice of such election to Ionis in accordance with Section 10.3.5(a)(i), the effectiveness of which notice shall remain subject to Section 10.3.7, as applicable, then, solely with respect to the Strategy or 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 as of the effective date of Biogen's notice to Ionis electing the alternative remedy provisions of this Section 10.4:

(a) Ionis will have no further right or obligation to Develop any Product under the applicable Strategy or Collaboration Program,

(b) Biogen may elect that some or all of the Biogen Reduced Participation and Information Obligations will apply (in each case, solely with respect to the applicable Strategy or Collaboration Programs that is the subject of Ionis' material breach);

(c) Biogen will be deemed for all purposes of this Agreement to have exercised the Option for the applicable Collaboration Program;

(d) Biogen will have and Ionis grants, the exclusive license granted to Biogen under Section 4.1.1 for the applicable Collaboration Program;

(e) Ionis shall within [***] days following the effective date of Biogen's notice to Ionis electing the alternative remedy provisions of this Section 10.4, deliver to one of Biogen or Biogen's designated Affiliates or Third Party contractor (at Biogen's election), all Ionis Manufacturing and Analytical Know-How and Ionis Know-How in Ionis' Control that is necessary to Develop and Manufacture the applicable Products, solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf for the conduct of the applicable Strategy or Collaboration Program. In addition, Ionis will provide to Biogen, and its Affiliates and Third Party contractors all Know-How, assistance, assignments of relevant Third Party agreements, to the extent freely assignable and only if such agreements are specific to the Manufacture and supply of Products under such assumed Collaboration Program(s) and other support reasonably requested by Biogen to enable Biogen to assume responsibility for and perform the Development and Manufacture of the applicable Products in an efficient and orderly manner. If any such relevant Third Party agreements are not freely assignable or are not specific to the Manufacture and supply of Products under such assumed Collaboration Program(s), then Ionis will, and cause its Affiliates to, obtain for Biogen substantially all of the practical benefit and burden under such Third Party agreements, including by (i) entering into appropriate and reasonable alternative arrangements on terms agreeable to each of Ionis and Biogen (or such Affiliate) and (ii) subject to the consent and control of Biogen, enforcing, at Biogen's cost and expense and for the account of Biogen, any and all rights of Ionis (or such Affiliate) against the other party thereto arising out of the breach or cancellation thereof by such other party or otherwise; and

(f) The financial provisions of ARTICLE 6 as they apply to such Strategy or Collaboration Program will be modified as follows:

(i) *[***] Payments*. Biogen will [***];

(ii) *Annual License Access Fee*. Biogen will [***];

(iii) *Option Fee*. Any Option Fee payable for the applicable Strategy or Collaboration Program will [***]; and

(iv) The milestone provisions of Section 6.7 and the royalty provisions of Section 6.9 will [***] with respect to such Collaboration Program.

10.5. **Target-Based Termination**. Following the Effective Date, this Agreement shall only terminate with respect to a Collaboration Target upon the later of the earlier of (a) the date this Agreement is terminated in its entirety by a Party in accordance with this ARTICLE 10 or expires in accordance with Section 10.2.3, or (b) the date of termination of the last Collaboration Program and, if the Research Term is ongoing, termination of the last Strategy directed to such Collaboration Target for which activities are being performed. Thereafter, such Collaboration Target shall be a "***Terminated Target***" unless such Collaboration Target is also defined as a "High Interest Target" or a "Collaboration Target" under the Neurology II Agreement, in which case such target will not be a Terminated Target hereunder until the date on which the Collaboration Program for such gene target terminates under the Neurology II Agreement. Notwithstanding anything in this Agreement to the contrary, an Ionis Neurology Target or a High Interest Target that was never designated as a Collaboration Target will not be a Terminated Target and a Collaboration Target will not be a Terminated Target if this Agreement expires (and is not terminated) in accordance with Section 10.2.1 or Section 10.2.2 with respect to such Collaboration Target.

10.6. **Consequences of Expiration or Termination of the Agreement**.

10.6.1. **In General**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 on or following the Effective Date at any time and for any reason, the following terms will apply to any Product that is the subject of a Collaboration Program to which such expiration or termination applies:

(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 for Products that are the subject of 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) **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.

(c) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 1.7 (End of Research Term), Section 1.8.2(f) (End of Development Candidate Identification Term), Section 2.1.1(e) (Failure to Designate a High Interest Target as a Collaboration Target), Section 3.1.2 (Option and Option Deadline) (but only with respect to each Party's transfer obligations thereunder), Section 4.1.3 (Effect of Termination on Sublicenses), Section 4.2.2 (Grant Back to Ionis), Section 4.3.3 (Enabling Licenses to Biogen), Section 4.3.4 (Enabling License to Ionis), Section 4.4 (Licenses to Ionis for Biogen Results), Section 4.5 (Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis), Section 4.8.2 (Technology Transfer after Collaboration Program Designation) (but only to the extent necessary to satisfy the requirements of Section 10.6.4(d)(vi)), Section 6.10 (Payments to Biogen for a Discontinued Product), Section 6.12.3 (Records Retention), Section 6.13 (Audits), Section 7.1.1 (Ionis Technology and Biogen Technology), Section 7.1.2 (Agreement Technology), Section 7.4.2 (Discontinued Product), Section 7.7.2 (Ionis' Obligations), Section 8.6 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.3.4(b) (Termination Due to Failure to Obtain HSR Clearance), Section 10.3.8 (Termination for Insolvency), Section 10.5 (Target-Based Termination), Section 10.6 (Consequences of Expiration or Termination of the Agreement) (except Section 10.6.5 (Remedies Available to Biogen for Ionis' Material Breach After 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 10.6.4(d)(ix) (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 7.2.5 (Other Matters Pertaining to Prosecution and Maintenance of Patents), 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).

10.6.2. **Natural Expiration**. If this Agreement expires in accordance with Section 10.2.1 or Section 10.2.2 after the License Effective Date for a Collaboration Program, then upon expiration of the Reduced Royalty Period for a Product that is the subject of such Collaboration Program in all countries in which such Product is being or has been sold, Ionis will and hereby does grant to Biogen an irrevocable, perpetual, non-exclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Ionis Know-How to Manufacture, Develop and Commercialize the applicable Product, the applicable Collaboration Target shall not become a Terminated Target and such Product shall not become a Discontinued Product.

10.6.3. **Termination Prior to License Effective Date**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 following the Effective Date but before the License Effective Date for a particular Collaboration Program, then, in addition to the terms set forth in Section 10.6.1, the following terms will apply to each Product and Compound, for each Collaboration Program that is directed to a Terminated Target if Biogen has not exercised the Option for any Collaboration Program directed to the applicable Terminated Target:

(a) Solely in the event that this Agreement is terminated by a Party in its entirety, Biogen's right to designate High Interest Targets as Collaboration Targets under this Agreement will expire, the High Interest Target List will be dissolved, and Ionis will be free to Develop and Commercialize the applicable Product, (and any other applicable Compounds) targeting all such Terminated Targets (and any other Neurology Targets) on its own or with a Third Party.

(b) In the event that this Agreement is terminated by a Party in its entirety, Biogen's Options under Section 3.1 will expire and Ionis will be free to Develop and Commercialize all Product(s) (and any other applicable Compounds or Oligonucleotides) on its own or with a Third Party.

(c) In the event that this Agreement is terminated with respect to all Collaboration Programs directed to a Terminated Target, Biogen's Options under Section 3.1 will expire with respect to all Collaboration Programs directed to such Terminated Target and Ionis will be free to Develop and Commercialize Product(s) targeting such Terminated Targets (and any other applicable Compounds or Oligonucleotides designed to bind to the RNA that encodes such Terminated Targets), on its own or with a Third Party.

(d) In the event that this Agreement expires or is terminated by a Party in its entirety, then neither Party will have any further obligations under Section 2.1 of this Agreement.

(e) In the event that this Agreement is terminated with respect to a Collaboration Target, then neither Party will have any further obligations under Section 2.1 of this Agreement with respect to such Terminated Target.

(f) To the extent requested by Ionis, Biogen will promptly (i) assign to Ionis any manufacturing agreements with a CMO to which Biogen is a party, solely to the extent such manufacturing agreements relate to any Compound or Product directed to a Terminated Target 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 for Discontinued Products directed to the Terminated Target 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 the Biogen FTE Cost in transferring such data, results and information.

(g) Except as explicitly set forth in Section 10.6.1, Biogen will have no further rights and Ionis will have no further obligations with respect to each Terminated Target.

(h) If Biogen terminates this Agreement for convenience with respect to all Strategies directed to, and all Collaboration Programs for, a Collaboration Target, then solely with respect to such Terminated Target:

(i) Biogen will, and does hereby, grant to Ionis an exclusive sublicensable, worldwide, license or sublicense, as the case may be, to Biogen Technology Controlled by Biogen as of the date of such reversion that Covers the applicable Discontinued Product(s) targeting any such Terminated Target solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Product(s) targeting any such Terminated Target in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*).

(ii) Biogen will, and does hereby, grant to Ionis a non-exclusive sublicensable, worldwide, license or sublicense, as the case may be, to Biogen Background Technology Controlled by Biogen as of the date of such reversion that Covers the applicable Discontinued Product(s) targeting any such Terminated Target in the form that such Discontinued Product(s) exist as of the date of such reversion (other than Permitted Changes in Form with respect to such 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) targeting any such Terminated Target in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*).

(iii) Ionis will reimburse Biogen for any amounts owed by Biogen to Third Parties as a result of the grant of any such license to Ionis under, or Ionis' practice of, any Biogen Background Technology; *provided that* Ionis has been notified of the terms of such payment obligations to any such Third Party, and, if Ionis notifies Biogen that it does not wish to be granted a license under any Patent Rights or Know-How that are subject to such payment obligations included in the Biogen Background Technology, then such Patent Rights or Know-How (as applicable) will be excluded from the Biogen Background Technology licensed to Ionis hereunder, and Ionis will have no obligation to reimburse Biogen for any such payments.

(iv) If Ionis or its Affiliates or Sublicensee sells any such Discontinued Product(s) targeting any such Terminated Target and that is Covered by any Patent Rights within the Biogen Background Technology, then on a country-by-country basis Ionis will pay to Biogen a royalty equal to [***]. For the purpose of the foregoing royalty calculation, "net sales" will be calculated in accordance with the definition of "Net Sales" as set forth in APPENDIX 1, applied *mutatis mutandis* to such calculation. The provisions of Sections 6.12, 6.13, 6.14 and 6.15 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 10.6.3(h)(iv). If the Parties are unable to agree as to the appropriate royalty percentage to be paid by Ionis to Biogen under this Section 10.6.3(h)(iv) within a period of [***] days after the effective date of termination, then either Party may refer the matter to Expert Resolution under Section 12.1.4.

(v) Within [***] days following the date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's rights, title and interests in and to all Regulatory Materials, including any IND and orphan drug designation that relate to the applicable Discontinued Product(s) that target such Terminated Targets, *provided that*, (A) 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 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 (other than any Gene-Editing Product, messenger RNA or, solely to the extent agreed in writing by the Parties, Duplex Product) as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include such an Oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis and (B) for clarity, such assignment of Biogen's rights, title and interests 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 (A) of the preceding sentence, then 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.

(vi) With respect to Discontinued Products targeting Terminated Targets, 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 Product API, Clinical Supplies and Finished Drug Product, and any intermediates, impurity markers and reference standards relating to such Discontinued Product in Biogen's possession at the time of such termination, at a price equal to [***]% of either (i) [***] or (ii) [***], in each case ((i) and (ii)), as reflected in Biogen's books and records.

10.6.4. **Termination after License Effective Date**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 following the Effective Date and after the License Effective Date for a particular Collaboration Program, then, in addition to the terms set forth in Section 10.6.1, the following terms will apply to any Collaboration Program that is the subject of such termination, including all Products that are the subject thereof.

(a) The applicable licenses granted by Ionis to Biogen under this Agreement will terminate with respect to such terminated Collaboration Program. Biogen, its Affiliates and Sublicensees will cease selling the applicable Products that are the subject of such Collaboration Program, unless Ionis elects to have Biogen continue to sell the applicable Products as part of the Transition Services to the extent provided in Section 10.6.6.

(b) If such termination applies to all Collaboration Programs directed to a Collaboration Target and has the effect of making such target a Terminated Target, then neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the applicable Terminated Target.

(c) If such termination applies to all Collaboration Programs directed to a Collaboration Target and has the effect of making such target a Terminated Target, then except as explicitly set forth in Section 10.6.1, Biogen will have no further rights and Ionis will have no further obligations with respect to the applicable Terminated Target.

(d) If (i) Biogen terminates the Agreement under Section 10.3.2 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement under Section 10.3.6 (Ionis' Right to Terminate for Material Breach by Biogen), and such termination applies to all Collaboration Programs directed to a Collaboration Target and has the effect of making such target a Terminated Target, then the following additional terms will also apply solely with respect to Collaboration Program(s) directed to such Terminated Targets, including all Products that are the subject of such Collaboration Program(s):

(i) Biogen will, and does hereby, grant to Ionis an exclusive sublicensable, worldwide, license or sublicense, as the case may be, to 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) targeting such Terminated Target in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*).

(ii) Biogen will, and does hereby, grant to Ionis a non-exclusive sublicensable, worldwide, license or sublicense, as the case may be, to Biogen Background Technology Controlled by Biogen as of the date of such reversion that Covers the applicable Discontinued Product(s) targeting any such Terminated Target in the form that such Discontinued Product(s) exist as of the date of such reversion (other than Permitted Changes in Form with respect to such 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) targeting such Terminated Target in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*).

(iii) Ionis will reimburse Biogen for any amounts owed by Biogen to Third Parties as a result of the grant of any such license to Ionis under, or Ionis' practice of, any Biogen Background Technology; *provided that* Ionis has been notified of the terms of such payment obligations to any such Third Party, and, if Ionis notifies Biogen that it does not wish to be granted a license under any Patent Rights or Know-How that are subject to such payment obligations included in the Biogen Background Technology, then such Patent Rights or Know-How (as applicable) will be excluded from the Biogen Background Technology licensed to Ionis hereunder, and Ionis will have no obligation to reimburse Biogen for any such payments.

(iv) If Ionis or its Affiliates or Sublicensee sells any such Discontinued Product(s) targeting any such Terminated Target and that is Covered by any Patent Rights within the Biogen Background Technology, then on a country-by-country basis Ionis will pay to Biogen a royalty equal to [***]. For the purpose of the foregoing royalty calculation, "net sales" will be calculated in accordance with the definition of "Net Sales" as set forth in APPENDIX 1, applied *mutatis mutandis* to such calculation. The provisions of Sections 6.12, 6.13, 6.14 and 6.15 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 10.6.4(d)(iv). If the Parties are unable to agree as to the appropriate royalty percentage to be paid by Ionis to Biogen under this Section 10.6.4(d)(iv) within a period of [***] days after the effective date of termination, then either Party may refer the matter to Expert Resolution under Section 12.1.4.

(v) 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) targeting such Terminated Target previously assigned by Ionis to Biogen under this Agreement;

(vi) Within [***] days following the effective date of the termination Biogen will transfer to Ionis solely for use with respect to the Development and Commercialization of the applicable Discontinued Product(s) targeting such Terminated Target, 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 10.6.4(d)(i), except as otherwise provided in Section 10.6.4(d)(vii) below;

(vii) Within [***] days following the effective date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's rights, title and interests in and to all Regulatory Materials, including any NDA, IND and orphan drug designation that relate to the applicable Discontinued Product(s) targeting such Terminated Target, *provided that*, (A) 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 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 (other than any Gene-Editing Product, messenger RNA or , solely to the extent agreed in writing by the Parties, Duplex Product) as an active pharmaceutical ingredient, *provided*, *further* that, for such products that do not include such an Oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (B) for clarity, such assignment of Biogen's rights, title and interests 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 (A) of the preceding sentence, then 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;

(viii) Biogen will, and does hereby, exclusively license to Ionis any trademarks that are specific to a Discontinued Product(s) targeting a Terminated Target solely for use with such Discontinued Product(s); *provided*, *however*, 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;

(ix) Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents arising from the Collaboration Programs directed to the applicable Terminated Target, including all Products that are the subject thereof, 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*, 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

(x) Ionis will have the obligation to pay royalties to Biogen under Section 6.10 with respect to the applicable Discontinued Product(s). Such payments will be governed by the financial provisions in Section 6.12, and the definition of Net Sales will apply to sales of Discontinued Product(s) by Ionis, in each case *mutatis mutandis*.

(e) With respect to Discontinued Products targeting Terminated Targets, 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 Product API, Clinical Supplies and Finished Drug Product, and any intermediates, impurity markers and reference standards relating to such Discontinued Product in Biogen's possession at the time of such termination, at a price equal to [***]% of either (i) [***] or (ii) [***], in each case ((i) and (ii)), as reflected in Biogen's books and records.

(f) To the extent requested by Ionis, Biogen will promptly assign to Ionis any manufacturing agreements solely to the extent related to Terminated Targets and identified by Ionis to which Biogen is a party.

10.6.5. Remedies Available to Biogen for Ionis' Material Breach after License Effective Date.

(a) **Termination of Committees and Information Sharing**. If, after the License Effective Date with respect to a particular Collaboration Program, Ionis materially breaches this Agreement and fails to cure such breach within the time periods set forth under Section 10.3.5(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) Elect that some or all of the Biogen Reduced Participation and Information Obligations will apply (in each case, solely with respect to the applicable Collaboration Programs that are the subject of the Ionis Breach Event);

(ii) Terminate Ionis' participation in any ongoing research and development programs under the applicable Collaboration Program and Biogen's funding obligations associated therewith; and

(iii) If Ionis has not completed the activities for which it is responsible under the applicable Collaboration Program, then Biogen may, but will not be obligated to, assume all responsibility for all such activities that would have otherwise been Ionis' responsibility under this Agreement.

Ionis will cooperate with the foregoing and provide to Biogen or one or more of its Affiliates or Third Party contractors all Know-How, assistance, assignments of relevant Third Party agreements, to the extent freely assignable and only if such agreements are specific to the Manufacture and supply of Products under such assumed Collaboration Program(s), and other support reasonably requested to assist Biogen in assuming complete responsibility for the Development and Manufacture of the applicable Products that are the subject of such Collaboration Program in an efficient and orderly manner. If any such relevant Third Party agreements are not freely assignable or are not specific to the Manufacture and supply of Products under such assumed Collaboration Program(s), then Ionis will, and cause its Affiliates to, obtain for Biogen substantially all of the practical benefit and burden under such Third Party agreements, including by (i) entering into appropriate and reasonable alternative arrangements on terms agreeable to each of Ionis and Biogen (or such Affiliate) and (ii) subject to the consent and control of Biogen, enforcing, at Biogen's cost and expense and for the account of Biogen, any and all rights of Ionis (or such Affiliate) against the other party thereto arising out of the breach or cancellation thereof by such other party or otherwise.

(b) License Access Fee. If Ionis is performing activities under Section 5.2.2 with respect to a Collaboration Program following the applicable License Effective Date, and in connection with Ionis' performance of such activities, there is any delay in the Initiation of a Pivotal Clinical Trial beyond the Fee Commencement Date with respect to the Collaboration Programs as a result of an Ionis Breach Event, then Biogen will [***] solely to the extent caused by such delay.

(c) Biogen's Right of Setoff. If there is an [***] 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 Ionis Breach Event [***] (the "***Setoff Amount***"). If Biogen exercises its setoff right under this Section 10.6.5(c), 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 10.6.5(C), 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 10.6.5(C), 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 10.6.5(C) 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 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 6.15 (Interest), 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: (1) appoint a member of the Advisory Panel to the extent required in Section 2 of SCHEDULE 10.6.5(C); (2) meet with the Advisory Panel as required in Section 3 of SCHEDULE 10.6.5(C); or (3) 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 10.6.5(c) and SCHEDULE 10.6.5(C) with respect to any and all Setoff Disputes.

10.6.6. Transition Services.

(a) In the case where (i) Biogen terminates the Agreement under Section 10.3.2 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement under Section 10.3.6 (Ionis' Right to Terminate for Material Breach by Biogen) with respect to one or more Products, the terms of this Section 10.6.6 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 Collaboration Target. As such, Ionis may request Biogen perform transition services as listed on SCHEDULE 10.6.6 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 Terminated Target, transition the responsibilities under all Approvals and ongoing Clinical Studies for the applicable Products to Ionis or its designee and (iii) following termination of the applicable Terminated Target, 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 10.6.6(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 10.6.6(b), 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 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 10.6.6, 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 10.6.6 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) that 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 or the Neurology II 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. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement or the Neurology II 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), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing a 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.

11.3. **Residual Knowledge**. Notwithstanding any provision of this Agreement to the contrary, at any time during the Agreement Term or thereafter a Party or any Affiliate of such Party may use for its research purposes all information in non-tangible form resulting from access to or work related to a Strategy, High Interest Target, Ionis Neurology Target, Collaboration Target or Product or under this Agreement prior to the effective date of termination of this Agreement, including ideas, concepts, Know-How or techniques contained therein, in each case, that may be retained by persons who have had access thereto prior to the effective date of termination of this Agreement in their unaided human memory.

11.4. Press Release; Publications; Disclosure of Agreement.

11.4.1. Public Announcements. On or promptly after the Execution 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.

11.4.2. Use of Name. Except as set forth in Section 11.4.10, 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.

11.4.3. 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.

11.4.4. Prior to License Effective Date. Prior to the License Effective Date for a particular Collaboration Program, all Compounds and any Products that are the subject of such Collaboration Program are the sole property of Ionis and, subject to the provisions of this Section 11.4.4, Ionis will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Products to the public, which disclosures 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 or Development activities under this Agreement with respect to such Collaboration Program, (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, (c) Ionis will in good faith consider any changes that are timely recommended by Biogen and (d) to the extent such communication discloses data or results arising from a Collaboration Program or Development activities, (i) if Biogen informs Ionis that such communication contains Biogen Confidential Information, then Ionis will delete such Biogen Confidential Information from such communication and (ii) if Biogen informs Ionis that such communication would disclose inventions made by either Party in the course of a Collaboration Program or Development activities under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such communication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by Biogen, then Ionis in either case ((i) or (ii)) will (A) delay such proposed publication for up to [***] days from the date Biogen informed Ionis of its objection to such communication, to permit the timely preparation and first filing of patent application(s) on the information involved or (B) remove the identified disclosures prior to the publication of such communication.

11.4.5. **After License Effective Date**. After the License Effective Date for a particular Collaboration Program, all Compounds and Products that are the subject of such Collaboration Program are the sole property of Biogen and, subject to the provisions of this Section 11.4.5, Biogen will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding any Product that is the subject of such Collaboration Program 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 discloses data or results arising from a Collaboration Program or Development activities, (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 such communication and (c) (i) if Ionis informs Biogen that such communication contains Ionis Confidential Information, then Biogen will delete such Ionis Confidential Information from such communication and (ii) if Ionis informs Biogen that such communication would disclose inventions made by either Party in the course of a Collaboration Program or Development activities under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such communication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by Ionis, then Biogen in either case ((i) or (ii)) will (A) delay such proposed publication for up to [***] days from the date Ionis informed Biogen of its objection to such communication, to permit the timely preparation and first filing of patent application(s) on the information involved or (B) remove the identified disclosures prior to the publication of such communication.

11.4.6. **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 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 CSC members. During the advance review period described in Sections 11.4.4 or 11.4.5, such "C" level executives or CSC 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. If the Parties cannot agree at the CSC, then no such joint press release, presentation or public disclosure may be made.

11.4.7. **Scientific or Clinical Presentations for Products**. Regarding any proposed scientific publications or public presentations related to summaries of data or results arising from Collaboration Programs, 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 reasonable efforts to control public scientific disclosures of such data or results to prevent any potential adverse effect of any premature public disclosure of such data or 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 data or results as required on the clinical trial registry of each respective Party, as applicable. 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 a Collaboration Program or the Development activities 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 Initiated after the License Effective Date for a particular Collaboration Program of which the applicable Product is subject, Biogen shall determine authorship or attribution with respect to any proposed publications regarding the results of such Clinical Study 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*.

11.4.8. **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.

11.4.9. **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.

11.4.10. **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 Product) 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, Research & Development of Biogen and the Chief Operating 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 CSC 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 CSC 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 10.6.5(c) and SCHEDULE 10.6.5(c).

12.1.4. **Expert Resolution**. In the event that a matter is referred to expert resolution under this Section 12.1.4 ("***Expert Resolution***") pursuant to Section 1.8.2(e), Section 1.8.3(d)(iv), Section 3.1.2(f), Section 5.2.1, Section 10.6.3(h)(iv), Section 10.6.4(d)(iv), pursuant to subclause (b) of the definition of Biogen Background Technology in APPENDIX 1, or under APPENDIX 3, the matter will be resolved by an independent qualified Third Party expert acceptable to both Parties for final resolution of the dispute. The expert will use the information, materials and data provided to her or him by either Party to promptly resolve the dispute. The decision of the expert will be binding upon both Parties. The Parties will equally share the costs of the expert. If the Parties cannot agree on the expert within [***] days following either Party's request to nominate such expert under this Section 12.1.4, then each Party will nominate an independent expert (who will not be a current or former employee of a Party or any of their Affiliates or have any personal or financial interest in a Party or any of their Affiliates), and promptly thereafter, such two independent experts will agree on the Third Party expert to resolve the dispute in accordance with this Section 12.1.4. In the event of any expert proceeding under this Section 12.1.4, any deadline or activities that rely on the resolution of the dispute will be tolled during the pendency of such proceeding. Except to the extent necessary to confirm or enforce an award or as may be required by Law, neither Party nor any of the experts may disclose the existence, content or results of any proceeding under this Section 12.1.4 without the prior written consent of both Parties.

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). Except for the reimbursements, offsets and credits explicitly set forth in Section 1.8.1(d)(ii), Section 1.10, Section 6.6.3, Section 6.9.2(g), Section 6.11.2, Section 6.11.3, Section 6.11.4, Section 6.11.5, Section 6.11.6, Section 6.11.9(b), Section 10.6.5(c) and Section 12.5.1(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**.

12.4.1. 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 interest 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*, if Biogen transfers or assigns this Agreement to [***] described in this Agreement, then Biogen (or such Affiliate), will [***] 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.

12.4.2. The [***].

12.4.3. 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 [***], Ionis will provide Biogen with Ionis' Annual tax returns (federal and state) and, in years in which Ionis utilizes [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.5. Change of Control.

12.5.1. Research Activities. If, at any time during the Research Term, Ionis undergoes a Change of Control, then Ionis will notify Biogen within [***] of the public announcement of such Change of Control and the following shall apply:

(a) Within [***] days after the effective date of such Change of Control, Biogen will [***]. If such Change of Control is between Ionis and a Biogen Competitor, then [***].

(b) At any time after such Change of Control and prior to the applicable Change of Control Trigger Date for such Change of Control, if Biogen reasonably and in good faith determines that Ionis and such Third Party acquirer will not be [***] under each Neurology Plan (in which determination Biogen may take into account [***]), then, at any time prior to the applicable Change of Control Trigger Date Biogen may elect (as part of its written notice to Ionis of such belief), on a Strategy-by-Strategy or Collaboration Program-by-Collaboration Program basis with respect to the Strategy or Collaboration Program to which the failure relates or for this Agreement in its entirety, to (i) assume final decision-making ability with respect to the Neurology Plans and any activities conducted thereunder, and solely make all decisions that this Agreement would otherwise require or permit the Neurology JRC, the applicable Neurology JDC, the JPC, the CSC 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, and (ii) assume responsibility for any or all target validation activities, drug discovery activities or Ionis-Conducted IND-Enabling Toxicology Studies for the applicable existing or new Strategies or Collaboration Programs directed to existing or new High Interest Targets or Collaboration Targets. If Biogen elects to take over activities in accordance with subclause (ii) of this Section 12.5.1(b), then by providing timely written notice to Ionis no later than [***] days following such election, Biogen may request that Ionis performs a technology transfer under Section 12.5.1(d) solely to facilitate the transition of the activities for which Biogen elects to assume responsibility. If Biogen elects to trigger one or more of the remedies set forth in subclause (ii) of this Section 12.5.1(b), then (A) [***], and (B) [***], and the remainder of this Agreement shall remain in force and un-amended by Biogen's exercise of such remedies. For the purposes of this Section 12.5, the "***Change of Control Trigger Date***" means [***] the effective date of such Change of Control transaction occurred. By way of example only, if the effective date of a Change of Control transaction occurred July 31, 2021, then the Change of Control Trigger Date would be [***].

(c) Biogen will provide written notice to Ionis when Biogen commences target validation activities under this Agreement for a new Strategy directed to a High Interest Target and when Biogen completes activities under a particular Target Sanction Plan (or earlier ceases target validation activities for a particular Strategy). In addition, Biogen will provide written notice to Ionis when Biogen commences Development Candidate generation activities for a Collaboration Program under a Development Candidate Identification Plan (or earlier ceases Development Candidate generation activities for a Collaboration Program).

(d) If Biogen timely requests a technology transfer pursuant to Section 12.5.1(b), then the following shall apply:

(i) Biogen shall have the right, during regular business hours over a period of [***] months following the date of such request, to [***] Biogen representatives [***] target validation activities and drug discovery activities under this Agreement [***]. During regular business hours over such [***]-month period, Ionis will provide [***];

(ii) Ionis shall within [***] days following the effective date of Biogen's notice electing to exercise its step-in rights under Section 12.5.1(b)(ii) and requesting a technology transfer with respect to such exercise, deliver to one of Biogen or Biogen's designated Affiliates or Third Party contractor (at Biogen's election), all Ionis Manufacturing and Analytical Know-How and Ionis Know-How in Ionis' Control that is necessary (A) to conduct those activities for which Biogen has exercised its step-in rights under Section 12.5.1(b)(ii) and (B) to Manufacture and supply research grade ASOs sufficient to support such activities, in each case ((A) and (B)), solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf to conduct the activities assumed by Biogen under Section 12.5.1(b). In addition, Ionis will provide to Biogen, and its designated Affiliates and Third Party contractors all Know-How, assistance, assignments of relevant Third Party agreements, to the extent freely assignable and only if such agreements are specific to the Manufacture and supply of Products under such assumed Collaboration Program(s), and other support reasonably requested by Biogen to enable Biogen to assume responsibility for and perform such activities in an efficient and orderly manner. If any such relevant Third Party agreements are not freely assignable or are not specific to the Manufacture and supply of Products under such assumed Collaboration Program(s), then Ionis will, and cause its Affiliates to, obtain for Biogen substantially all of the practical benefit and burden under such Third Party agreements, including by (i) entering into appropriate and reasonable alternative arrangements on terms agreeable to each of Ionis and Biogen (or such Affiliate) and (ii) subject to the consent and control of Biogen, enforcing, at [***] cost and expense and for the account of Biogen, any and all rights of Ionis (or such Affiliate) against the other party thereto arising out of the breach or cancellation thereof by such other party or otherwise; and

(iii) where Biogen exercises its step in right under Section 12.5.1(b), then in conducting target validation activities, drug discovery activities or Ionis-Conducted IND-Enabling Toxicology Studies for the applicable Strategies or Collaboration Programs following such exercise, Biogen must separate such activities from its or its Affiliates' other development activities relating to any other product or program outside of this Agreement or any other Ionis/Biogen Additional Agreement (such other development activities, "***Biogen Other Activities***"). To that end, and subject to the licenses granted under Section 4.3, Biogen will (A) establish separate teams to conduct such activities for which it has exercised the step in right, and such Biogen Other Activities and (B) prevent any Know-How that is Confidential Information relating to the High Interest Target or Collaboration Program for which the step in right was exercised from being disclosed to, or used by, individuals performing such Biogen Other Activities.

(e) At any time after such Change of Control and prior to the applicable Change of Control Trigger Date for such Change of Control, upon written notice to Ionis, Biogen may, in lieu of electing to exercise its remedies under Section 12.5.1(b) and Section 12.5.1(d), either:

(i) elect that the Research Term shall continue and the Ionis Activities under any Neurology Plan shall wind-down, in which case the following shall apply:

(1) except to the extent that Biogen requests the earlier termination of any of the following activities ((1) through (4)), (1) Ionis shall complete all target validation activities under Target Sanction Plans that were agreed to prior to Biogen's written notice under this Section 12.5.1(e)(i), (2) Ionis shall complete all ongoing Ionis Activities under the Core Research Plan (but for clarity, no new work will be initiated under the Core Research Plan), (3) for each Target Sanction Plan that results in achievement of Target Sanction, (I) Biogen shall pay the Target Designation Milestone Payment, (II) the Parties shall prepare a Development Candidate Identification Plan and (III) Ionis will carry out its obligations under such plan, all in accordance with Section 1.8.2, and (4) Ionis will continue to perform its obligations under each ongoing Development Candidate Identification Plan until the end of the applicable Development Candidate Identification Term and under each ongoing Toxicology Strategy until completion of all Ionis Activities thereunder;

(2) the Research Term will end upon the earlier of Biogen's early termination of, or Ionis' completion of, all of the Ionis Activities under clauses (1), (2) and (3) of Section 12.5.1(e)(i)(1) above;

(3) within [***] days following the Refund Date, Ionis shall pay to Biogen an amount equal to [***]; and

(4) for each Collaboration Program for which a Development Candidate is identified as provided herein, Biogen may, upon written notice to Ionis, to be delivered within [***] days after Biogen designates a Development Candidate for the applicable Collaboration Program, elect to either (1) exercise the applicable Option for such Collaboration Program by notifying Ionis in writing of Biogen's election to license such Collaboration Program, or (2) establish a Toxicology Strategy for such Collaboration Program pursuant to Section 1.8.3(c), in which case Ionis and Biogen will continue to exercise their rights and perform their respective obligations with respect to the applicable Collaboration Program under the terms of this Agreement, including all applicable payment obligations under ARTICLE 6, and in each case ((1) and (2)), the following modifications shall apply to the Agreement: (I) at Biogen's election, the Neurology JRC, the applicable Neurology JDC, the JPC, the CSC or any other subcommittees or working groups established pursuant to this Agreement shall each disband with respect to each Collaboration Program with respect to which Biogen exercised the Option, on the License Effective Date, and Biogen will assume final decision-making ability with respect to such Collaboration Programs and any activities conducted thereunder and Biogen will solely make all decisions with respect to such activities and Collaboration Programs for which the Neurology JRC, the applicable Neurology JDC, the JPC, the CSC or any other subcommittees or working groups, or the Parties collectively, would otherwise be permitted or required to make under this Agreement; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis; and (II) Biogen may exclude Ionis from all discussions with Regulatory Authorities regarding the applicable Products that are the subject of such Collaboration Programs, except to the extent Ionis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law; or

(ii) allow the Change of Control Trigger Date to lapse without providing any such notice of election under this Section 12.5.1, in which case Ionis and Biogen will continue to exercise their rights and perform their respective obligations under the terms of this Agreement.

(f) For the purposes of calculating Ionis' payment to Biogen under Section 12.5.1(e)(i)(3) above, the "***Refund Date***" shall be (i) the date that [***], (ii) if [***], or (iii) if [***], the earlier of (A) the date that [***] and (B) the date that [***]; the "***Dividend***" shall be the number equal to [***]; the "***Divisor***" shall be [***]; and the "***Pro Rata Portion***" shall be calculated by [***]. By way of illustration, if [***].

(g) For clarity, the occurrence of a Change of Control is not a breach of this Agreement.

(h) For clarity, where Biogen elects to trigger one or more of the remedies set forth in Section 12.5.1, then Biogen shall remain subject to [***], and the remainder of this Agreement shall remain in force and unamended by Biogen's exercise of such remedies, subject to Biogen's right to [***].

12.5.2. **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 Competitive Product or 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 12.5.3(a) will not apply to any such Pre-Existing Competitive Product or Pre-Existing Competitive Program; *provided* that the conditions of Section 12.5.2(a) and Section 12.5.2(c) are satisfied.

12.5.3. 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 12.5.3(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 12.5.3(a)(i) through 12.5.3(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 12.5.3(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 12.5.3(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.

12.6.1. 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 Operating Officer E-mail: bmonia@ionisph.com
with a copy to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel E-mail: legalnotices@ionisph.com

If to Biogen, addressed to:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 Attention: Vice President Corporate Development E-mail: john.mcdonald@biogen.com
with a copy to:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 Attention: Chief Legal Officer E-mail: legaldepartment@biogen.com
with a copy to:	Ropes & Gray LLP Prudential Tower 800 Boylston Street Boston, MA 02199-3600 Attention: Susan Galli, Esq. Email: susan.galli@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 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 interest 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), is a comprehensive and integrated statement of the agreement between the Parties with respect to the subject matter hereof. 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) the word "or" is used in the inclusive sense (and/or), (e) 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, (f) words in the singular or plural form include the plural and singular form, respectively, (g) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (h) unless otherwise specified, "$" is in reference to United States dollars and (i) 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 GAAP (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 and good laboratory and clinical practices and cGMP 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 Execution Date.

BIOGEN MA INC.

By: /s/Michel Vounatsos

Name: Michel Vounatsos

Title: Chief Executive Officer

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

IONIS PHARMACEUTICALS, INC.

By: /s/Stanley T. Crooke

Name: Stanley T. Crooke

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:

"***[***]% Obligation***" has the meaning set forth in Section 1.8.1.

"***AAA***" has the meaning set forth in SCHEDULE 12.1.2 .

"***AAA Rules***" has the meaning set forth in SCHEDULE 10.6.5(**c**).

"***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 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 European 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 of written notice of acceptance by the applicable Regulatory Authority of such MAA for filing in such country, and (d) in Japan, receipt 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 12.5.3(a).

"***Acquired Competitive Program***" has the meaning set forth in Section 12.5.3(a).

"***Acquisition Costs***" has the meaning set forth in Section 6.11.6(a).

"***Acquisition Transaction***" has the meaning set forth in Section 6.11.6(a).

"***Action***" has the meaning set forth in Section 12.2.2.

"***Active Target***" means a High Interest Target, or Collaboration Target, as applicable, with respect to which, at the time in question, one or more of the following is true:

(a) if the Research Term (as it may be extended pursuant to Section 1.2.1(a)) has not yet expired:

(i) a [***] is [***], or a [***] under Section 1.2.3(d)(ii) or Section 1.4;

(ii no more than [***] days have passed since [***], as applicable (if any);

(iii) a [***];

(iv) no more than [***] days have passed since [***] (if any);

(v) no more than [***] days have passed since [***] (if any); or

(vi) actual target validation activities are ongoing under a Target Sanction Plan for such target; or

(b) during the Agreement Term and whether or not the Research Term has expired,

(i) a [***];

(ii) a [***];

(iii) a [***];

(iv) the [***] (if any) has not yet expired;

(v) there is [***] has not yet expired;

(vi) there is an [***];

(vii) Biogen has elected to [***] and (A) [***], or (B) [***]; or

(viii) Biogen has elected to [***], or [***].

"***Additional Ionis Core IP***" has the meaning set forth in Section 6.11.2(a).

"***Advisory Panel***" has the meaning in SCHEDULE 10.6.5(**c**) of this Agreement.

"***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 (i) 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 (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 hereto.

"***Agreement Term***" has the meaning set forth in Section 10.2.

"***Alliance Manager***" has the meaning set forth in Section 1.14.9.

"***ALS***" means the disease amyotrophic lateral sclerosis.

"***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 a compound comprising one or two Oligonucleotides (including any analog, variant, mimic, or mimetic thereof) that modulates expression or splicing of a gene target via the binding, partially or wholly, of an Oligonucleotide of such compound to the RNA of such gene target, excluding any [***] Products.

"***[***]***" has the meaning set forth in Section 6.5.1.

"***[***] Adjustment Period***" has the meaning set forth in Section 6.5.3.

"***Associated Product***" has the meaning set forth in Section 12.5.3(c).

"***Associated Program***" has the meaning set forth in Section 12.5.3(c).

"***Audit Report***" has the meaning set forth in Section 6.13.

"***Bankruptcy Code***" has the meaning set forth in Section 10.3.8(b).

"***Biogen***" has the meaning set forth in the Preamble of this Agreement.

"***Biogen Activities***" means, (a) under any Neurology Plan, any and all research, pre-clinical 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 Neurology Plan it approves, and (b) any research, pre-clinical or clinical activities with respect to which Biogen exercises its step-in rights under Section 1.8.1(d)(ii), Section 1.10 or Section 12.5.1(b).

"***Biogen-Approved Costs***" has the meaning set forth in Section 1.13.3.

"***Biogen Background Technology***" means, with respect to a given Development Candidate, Related Program Compound or Discontinued Product, as applicable, (a) Patent Rights (other than Biogen Program Patents) and Know-How that are Controlled by Biogen or its Affiliates that the Parties agree to include in the applicable Development Candidate Identification Plan (over which Ionis may not exercise its final decision making authority) or (b) Patent Rights (other than Biogen Program Patents) that are Controlled by Biogen or its Affiliates as of the date that the license is granted under Sections 1.8.3(d)(iii), 3.1.2(e), 10.6.3(h)(i), or 10.6.4(d)(i), as applicable, that the Parties agree (or, if the Parties are unable to agree, then as determined by Expert Resolution in accordance with Section 12.1.4) Cover such Development Candidate, Related Program Compound or Discontinued Product, as applicable, as such Development Candidate, Related Program Compound or Discontinued Product exists as of such effective date of the applicable license; *provided that* no inventions Covered by such Patent Rights were incorporated by Ionis into such Development Candidate, Related Program Compound or Discontinued Product, as applicable, without Biogen's written consent or is not otherwise reflected in the applicable Development Candidate Identification Plan.

"***Biogen Competitor***" means a Third Party that (a) [***] or (b) Biogen is at such time, or has been in the past, [***].

"***Biogen Excluded Targets***" has the meaning set forth in Section 1.8.5(b).

"***Biogen 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 6.9.1.

"***Biogen In-License Agreements***" has the meaning set forth in Section 6.11.1(b).

"***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 [***] Royalty***" has the meaning set forth in Section 6.9.1.

"***Biogen Manufacturing Program Patent***" has the meaning set forth in Section 4.8.2(d).

"***Biogen Other Activities***" has the meaning set forth in Section 12.5.1(d)(iii).

"***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 7.2.5(c).

"***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 to [***], other than (i) reports required by Section 5.4.2, Section 6.12.1 and Section 10.6.4 (if applicable) (ii) upon Ionis' reasonable request, information to the extent required to confirm Biogen's compliance with its obligations under Section 5.2 and (iii) as reasonably required to permit Ionis to perform its obligations under this Agreement. Notwithstanding the foregoing, Biogen's disclosure obligations under Section 6.5 shall continue in full force and effect, *except* [***]. 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 6.9.2(c).

"***Biogen Results***" has the meaning set forth in Section 4.8.2(d).

"***Biogen Sales Model***" has the meaning set forth in Section 6.5.1.

"***Biogen [***] Royalty***" has the meaning set forth in Section 6.9.1.

"***Biogen Step-In***" has the meaning set forth in Section 1.10.2."***Biogen Technology***" means the Biogen Program Technology, Jointly-Owned Program Technology, Biogen Product-Specific Patents and any trademarks described in Section 4.1.6, 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 the Non-Breaching Party believes 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 [***].

"***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 2018, the Effective Date) and ending on December 31.

"***Carryover Development Candidate***" has the meaning set forth in Section 1.8.2(g).

"***Carryover Period***" has the meaning set forth in Section 1.8.2(g).

"***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 such Party's outstanding securities, (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 its 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.

"***Change of Control Trigger Date***" has the meaning set forth in Section 12.5.1(b).

"***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, Pivotal Clinical 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***" means the conduct of the Neurology Plans in accordance with this Agreement.

"***Collaboration Divestiture Period***" has the meaning set forth in Section 12.5.3(a)(ii).

"***Collaboration Program***" has the meaning set forth in Section 1.3.1.

"***Collaboration Program Designation Date***" has the meaning set forth in Section 1.3.1.

"***Collaboration Program Final Deadline***" has the meaning set forth in Section 1.3.3.

"***Collaboration Target***" means a gene target with respect to which the Parties are pursing one or more Collaboration Programs.

"***Collaborator IP***" has the meaning set forth in Section 7.1.3(c).

"***Collaborator License***" has the meaning set forth in Section 7.1.3(c).

"***Combination Product***" means any single product in finished form containing as active ingredients both a Product and one or more other pharmaceutically active compounds or substances, whether co-formulated or co-packaged (i.e., within a single box or sales unit or otherwise sold for a single price).

"***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 (i) perform any Biogen Activities in a Neurology Plan and (ii) the "*General Activities*" described in SCHEDULE 5.2.1, and Commercially Reasonable Efforts as it applies to Ionis' performance hereunder includes use of Commercially Reasonable Efforts to adhere to the activities and timelines for which Ionis is responsible and that are set forth in each Neurology Plan.

"***Competing Collaboration Acquirer***" has the meaning set forth in Section 12.5.2.

"***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 Oligonucleotide 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 Target-by-Collaboration Target basis, any ASO that is designed to bind to the RNA that encodes the applicable Collaboration Target, where such ASO is discovered by Ionis (or by Biogen in the event Biogen assumes responsibility for drug discovery activities as permitted under this Agreement) prior to or during a Development Candidate Identification Term for any Collaboration Program for such Collaboration Target, including each Development Candidate under any 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 7.2.5(d).

"***Contracting Party***" has the meaning set forth in Section 1.8.7.

"***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***") (in the case of any agreement between Ionis and a Third Party, other than costs for Additional Ionis Core IP, Third Party Core IP, Third Party Product IP and Third Party Acquisition IP that are allocated to Ionis pursuant to Section 6.11), 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 applicable Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party acquirer of a Party that becomes an Affiliate of a Party after the Effective Date, no intellectual property of such Third Party acquirer will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Core Research Plan***" has the meaning set forth in Section 1.2.

"***Core Research Program***" has the meaning set forth in Section 1.2.

"***Cost Estimate***" has the meaning set forth in Section 5.2.2.

"***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.

"***CRO***" has the meaning set forth in Section 1.8.3(c).

"***CSC***" has the meaning set forth in Section 1.14.1.

"***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 such 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 such Product to seek Approval for additional indications for such Product.

"***Development Candidate***" means a Compound that is reasonably determined by Ionis' RMC in accordance with Ionis' standard procedures for designating development candidates, and that is subsequently designated by the Neurology JRC (or [***] through the exercise of its final decision-making authority) in each case in accordance with Section 1.8.3(a) and Section 1.8.3(d) as ready to start IND-Enabling Toxicology Studies; *provided, however*, that with respect to any Primarily Neuro Multi-Indication Target, such Compound will be reasonably selected by Biogen (giving good faith consideration to the input of Ionis' representatives on the Neurology JRC) as a Development Candidate from the body of work Ionis used to determine the applicable Compound Ionis believes is ready to start IND-Enabling Toxicology Studies.

"***Development Candidate Data Package***" means, with respect to a given [***], the data package [***]; provided such package contains [***]. The Development Candidate Data Package shall include (a) all Development Candidates that Ionis is designating as [***] Development Candidates and (b) (i) a summary of the patent status relating to such Development Candidate and a list of the Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents, in each case, that Cover such Development Candidate and that have not previously been disclosed to Biogen and (ii) a summary of any [***]. 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 Deficiency Notice***" has the meaning set forth in Section 1.8.3(a).

"***Development Candidate Decision Period***" has the meaning set forth in Section 1.8.3(d)(ii).

"***Development Candidate Designation Deadline***" has the meaning set forth in Section 1.8.3(d)(iii).

"***Development Candidate Generation Period***" means, on a Collaboration Program-by-Collaboration Program basis, the period of [***] months commencing on the date that Biogen pays the Target Designation Milestone Payment for such Collaboration Program, or such longer period as the Neurology JRC may mutually agree to account for the use of a novel Strategy pursuant to Section 1.8.1(e); *provided that* if, prior to the expiration of the applicable Development Candidate Identification Term for a Collaboration Program, the Parties agree through the Neurology JRC that a Technical Failure has occurred with respect to such Collaboration Program, then the Development Candidate Identification Term for such Collaboration Program shall end and such Collaboration Program will not be included in the calculation of the [***]% Obligation under Section 1.8.1. For clarity, if the Parties mutually agree through the Neurology JRC to extend the Development Candidate Generation Period for any Collaboration Program, then such longer period shall be used in determining when such Collaboration Program is taken into account in the calculation of whether or not Ionis is meeting the [***]% Obligation at the First Measurement Date or any Subsequent Measurement Date.

"***Development Candidate Identification Plan***" has the meaning set forth in Section 1.8.2(a).

"***Development Candidate Identification Term***" has the meaning set forth in Section 1.8.2(d).

"***Development Candidate Outside Date***" has the meaning set forth in Section 3.1.2(a).

"***Diagnostic Option***" has the meaning set forth in Section 3.2.1.

"***Differentiated Compound***" means any ASO that is designed to bind to the RNA that encodes a Collaboration Target discovered by or on behalf of Ionis and meeting the criteria for a Development Candidate after the expiration of every Development Candidate Identification Term for any Collaboration Program directed to such Collaboration Target and, if applicable, the Carryover Period for such Collaboration Target, but prior to the expiration of the [***] for a Product under any Collaboration Program directed to such Collaboration Target.

"***Differentiated Compound Notice***" has the meaning set forth in Section 2.2.1.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means a Product directed to a Terminated Target.

"***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.

"***Dividend***" has the meaning set forth in Section 12.5.1(f).

"***Divisor***" has the meaning set forth in Section 12.5.1(f).

"***DMPK Agreement***" means the DMPK Research, Development, Option and License Agreement between the Parties dated June 27, 2012, as amended or restated from time to time.

"***DOJ***" has the meaning set forth in Section 3.1.3(a).

"***Draft Report***" means, with respect to an IND-Enabling Toxicology Study, an integrated, audited draft report containing the pharmacology, toxicology, bioanalytical and pharmacokinetic data generated from such IND-Enabling Toxicology Study.

[***]

"***Effective Date***" means the date upon which the Closing Date (as defined under the Stock Purchase Agreement) occurs.

"***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.

"***Equal Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Estimated Target Sanction Date***" has the meaning set forth in Section 1.8.5(b).

"***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.

"***Exclusivity Release Date***" has the meaning set forth in Section 2.1.1(d)(i).

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

"***Executives***" has the meaning set forth in Section 12.1.1."***Expert Resolution***" has the meaning set forth in Section 12.1.4.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***Fee Commencement Date***" has the meaning set forth in Section 6.6.

"***Fee End Date***" has the meaning set forth in Section 6.6.

"***Field***" means, except as may be limited under Section 4.1.5, 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 such Product has been obtained in such country.

"***First Measurement Date***" has the meaning set forth in Section 1.8.1(a).

"***FTC***" has the meaning set forth in Section 3.1.3(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 1.13.3.

"***FTE Rate***" means $[***] for the Calendar Year 2018. The FTE Rate will be increased each Calendar Year thereafter by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.9.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Ionis as determined using the methodology set forth in SCHEDULE 4.9.2(c) fairly applied and as employed on a consistent basis throughout Ionis' operations.

"***GAAP***" means generally accepted accounting principles in the United States, consistently applied.

"***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 (the "***Reference Product***"), one or more product(s) sold by a Third Party that is not a licensee or Sublicensee of Biogen pursuant to a license, sublicense or subcontract pursuant to which Biogen receives a royalty, profit share or other consideration directly as a result of the sales of such product where such product(s) (a) have the same active pharmaceutical ingredient as such Reference Product, are approved in reliance, in whole or in part, on a prior Regulatory Approval of the Reference Product, and are determined by a Regulatory Authority to be substitutable for the Reference Product or (b) are approved by the Regulatory Authority as a substitutable generic or substitutable biosimilar for such Reference Product or otherwise are approved in a manner that relies on or incorporates data submitted by Biogen or its Affiliates in connection with the regulatory filings for such Reference Product through an ANDA or 505(b)(2) pathway, or any enabling legislation thereof, or any equivalent process where bioequivalence to such Reference Product has been asserted.

"***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 1.2.3(a). 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 Acceptance Notice***" has the meaning set forth in Section 1.2.3(b)(i).

"***High Interest Target Designation Period***" has the meaning set forth in Section 1.2.3(b)(ii).

"***High Interest Target List***" has the meaning set forth in Section 1.2.3(a).

"***HIT Request Date***" has the meaning set forth in Section 1.2.3(b)(i).

"***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.

"***Inactive Target***" means a High Interest Target or Collaboration Target, as applicable, that is not an Active Target, including any Terminated Target.

"***Incremental Tax Cost***" has the meaning set forth in Section 12.4.2.

"***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 Delay Condition***" has the meaning set forth in Section 1.8.4(b).

"***IND-Enabling Toxicology Data Package***" means, with respect to an IND-Enabling Toxicology Study for a Development Candidate conducted by Ionis, all data, results and information related to such IND-Enabling Toxicology Study in the possession of Ionis and its contractors to the extent generated during such IND-Enabling Toxicology Study and not already included within the Draft Report provided to Biogen.

"***IND-Enabling Toxicology Deficiency Notice***" has the meaning set forth in Section 3.1.1.

"***IND-Enabling Toxicology Strategy Date***" has the meaning set forth in Section 1.8.4(b).

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND.

"***IND-Enabling Toxicology Study Completion Date***" means, on a Development Candidate-by-Development Candidate basis with respect to the conduct of the IND-Enabling Toxicology Studies for such Development Candidate under a Collaboration Program, (a) if Biogen is the Party conducting such IND-Enabling Toxicology Studies, [***] days following the date on which all activities under such IND-Enabling Toxicology Studies have been completed, and the Draft Report is available to Biogen with respect to such IND-Enabling Toxicology Study, and (b) if Ionis is the Party conducting such IND-Enabling Toxicology Studies, the [***] date of (i) the date on which all activities under such IND-Enabling Toxicology Studies have been completed and the complete IND-Enabling Toxicology Data Package from the IND-Enabling Toxicology Studies for such Development Candidate is made available to Biogen in accordance with Section 3.1.1 and (ii) the date on which Biogen receives any information described in the IND-Enabling Toxicology Study Deficiency Notice (if Biogen sends such notice to Ionis), including the resolution of any dispute regarding omissions or deficiencies with respect to such IND-Enabling Toxicology Data Package in accordance with Section 3.1.1.

"***IND-Enabling Toxicology Trigger Date***" has the meaning set forth in Section 3.1.2(a).

"***[***] Milestone***" has the meaning set forth in Section 6.3.

"***[***] Milestone Payment***" has the meaning set forth in Section 6.3.

"***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 Product Plan***" or "***IPP***" has the meaning set forth in Section 5.2.5.

"***Ionis***" has the meaning set forth in the Preamble of this Agreement.

"***Ionis Activities***" means the activities for which Ionis is designated as responsible under any Neurology Plan.

"***Ionis Activities Data***" has the meaning set forth in Section 5.2.3(a).

"***Ionis Attribution Language***" has the meaning set forth in Section 11.4.10(a).

"***Ionis/Biogen Additional Agreements***" means the (a) Spinraza Agreement, (b) DMPK Agreement, (c) the Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated December 10, 2012, (d) the Neurology II Agreement and (e) the Research Collaboration, Option and License Agreement between the Parties dated December 19, 2017, in each case, as amended or restated from time to time.

"***Ionis Breach Event***" has the meaning set forth in Section 10.6.5(a).

"***Ionis Collaboration Program Designation Date***" has the meaning set forth in Section 1.4.2.

"***Ionis-Conducted IND-Enabling Toxicology Study***" has the meaning set forth in Section 1.8.4(c).

"***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 8.2.5(a) attached hereto.

"***Ionis In-License Agreements***" has the meaning set forth in Section 6.11.1(a).

"***Ionis IND-Enabling Toxicology Costs***" has the meaning set forth in Section 1.8.4(d).

"***Ionis IND Study Diligence Obligation***" has the meaning set forth in Section 1.8.4(c).

"***Ionis Internal ASO Safety Database***" has the meaning set forth in Section 5.4.2(a).

"***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 they related to ASOs as of the Execution Date is set forth on SCHEDULE 8.2.5(b) attached hereto. Ionis Manufacturing and Analytical Patents do not include the Ionis Product-Specific Patents or the Ionis Core Technology Patents.

"***Ionis Multi-Indication Compound***" has the meaning set forth in APPENDIX 3.

"***Ionis Neurology Target***" means a Neurology Target that (a) is not (i) a High Interest Target for which target validation activities are planned under the then-current Neurological Disease Research Plan or (ii) a Collaboration Target and (b) has a Neurological Disease as its primary disease association.

"***Ionis Product Pipeline***" means the products and the Strategies listed on SCHEDULE 8.2.13.

"***Ionis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Ionis or its Affiliates on the Execution Date or at any time during the Agreement Term. A list of Ionis Product-Specific Patents Covering Products in existence as of the Execution Date is set forth on SCHEDULE 8.2.5(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 4.8.2(d).

"***Ionis Strategy***" has the meanings set forth in Section 1.3.3 and Section 1.4.4.

"***Ionis Target Sanction Diligence Obligation***" has the meaning set forth in Section 1.2.3(d)(v).

"***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.

"***Key Criteria***" means, with respect to a Collaboration Program, the applicable criteria set forth in [***], and such other criteria set forth in [***] that are designated as "Key Criteria" by mutual agreement of the Parties.

"***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, and in each case that are unpatented.

"***[***] Asset***" has the meaning set forth in Section 6.5.1.

"***Lead Party***" has the meaning set forth in Section 7.4.1.

"***License Access Fee***" has the meaning set forth in Section 6.6.

"***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 Option Fee for such Collaboration Program; *provided that* Biogen provides such notice and payment by the Option Deadline for such Collaboration Program or within the cure period set forth under Section 3.1.2(e).

"***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. For clarity, Licensed Patents that are jointly-owned by Ionis and Biogen will count toward the calculation of the Full Royalty Period in a particular country if the use or sale of a Product by an unauthorized Third Party in such country would infringe a Valid Claim of such Licensed Patent.

"***Licensed Technology***" means, on a Collaboration Program-by-Collaboration Program basis, any and all Licensed Patents and Licensed Know-How, 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 Alnylam Pharmaceuticals, Inc. under the Second Amended and Restated Collaboration and License Agreement between Alnylam Pharmaceuticals, Inc. and Ionis dated January 8, 2015, as amended.

"***Limited Availability Neurology Target***" has the meanings set forth in Section 1.3.3 and Section 1.4.4.

"***Loss of Market Exclusivity***" means, on a Product-by-Product and country-by-country basis, (a) one or more Generic Products for which such Product is the Reference Product are being marketed in such country; and (b) Net Sales of such Product in such country in any Calendar Quarter following the initial sale of the first such Generic Product(s) in such country decreases to less than [***]% of the average Net Sales of such Product in such country during the [***] preceding the initial sale of such Generic Product(s).

"***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 Finished Drug Product.

"***Manufacturing Process Development Terms***" means Section 4.1.3(b), Section 4.3.1(a), Section 4.3.2, Section 4.4, Section 4.5, Section 4.7.2 and Section 4.8.2(d) of this Agreement.

"***Marketing Approval***" means, for the purposes of determining the milestone payments due under Section 6.7, the first to occur of (a) NDA Approval, (b) MAA Approval, or (c) JNDA Approval.

"***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 Ionis, taken as a whole, (b) that when taken as a whole, has or would reasonably be expected to have a material adverse effect on (i) the Licensed Technology taken as a whole, (ii) the practice of the Licensed Technology taken as a whole and as contemplated by this Agreement or (iii) the Development, Manufacture or Commercialization of Compounds or Products for Neurology Targets as contemplated by this Agreement, or (c) that materially impairs the ability of Ionis to perform its obligations pursuant to the transactions contemplated by this Agreement or the Stock Purchase Agreement.

"***Milestone Event***" means any of the Target Designation Milestone, the IND Initiation Milestone or any Post-Option Development Milestone Event, as the case may be.

"***Minimum Third Party Payments***" means [***].

"***[***]***" means a disease that has, as its [***].

"***Multi-Indication Product***" means a product for a Non-Neurological Indication associated with a Multi-Indication Target.

"***Multi-Indication Product-Specific Patent***" has the meaning set forth in Section 7.2.4.

"***Multi-Indication Target***" has the meaning set forth in Section 1.2.3(c).

"***Multi-Indication Target Notice***" has the meaning set forth in Section 1.2.3(c).

"***Necessary***" means, with respect to any Patent Right, any Patent Right of a Third Party that (a) [***] and (b) [***] (i) [***] or (ii) if prior to [***], in each case ((i) and (ii)), [***].

"***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.

"***Net Sales***" shall mean, with respect to a Product, the gross amount billed or invoiced in a country by Biogen, its Affiliates or Sublicensees for the sale or other disposition of such Product in such country to Third Parties (including distributors, wholesalers and end-users), less the following deductions:

(a) sales returns and allowances actually paid, granted or accrued on such Product, including trade, quantity, prompt pay and cash discounts and any other adjustments, including those granted on account of price adjustments or billing errors;

(b) credits or allowances given or made for rejection, recall, return or wastage replacement of, and for uncollectible amounts on, such Product or for rebates or retroactive price reductions (including Medicare, Medicaid, copay assistance, managed care and similar types of rebates and chargebacks);

(c) taxes, duties or other governmental charges levied on or measured by the billing amount for such Product, as adjusted for rebates and refunds, including without limitation pharmaceutical excise taxes (such as those imposed on a Product by the United States Patient Protection and Affordable Care Act of 2010 and other comparable Laws), but which shall not include any tax, duty, or other charge imposed on or measured by net income (however denominated) or any franchise taxes, branch profits taxes, or similar tax; and

(d) charges for freight, customs and insurance directly related to the distribution of such Product and wholesaler and distributor administration fees.

in each case (clauses (a) through (d)) to the extent such deductions: (i) are reasonable and customary, (ii) are included in the gross invoiced sales price for such Product or otherwise directly paid, allowed, accrued, or incurred by Biogen, its Affiliates or Sublicensees with respect to the sale of such Product (iii) are applicable and in accordance with standard allocation procedures, (iv) have not already been deducted or excluded, (v) are incurred in the ordinary course of business in type and amount consistent with good industry practice, and (vi) except with respect to the uncollectible amounts and pharmaceutical excise taxes described in clauses (b) and (c) above, are determined in accordance with, and as recorded in revenues under, GAAP. Net Sales shall not be imputed to transfers of such Product without consideration or for nominal consideration for use in any clinical trial, or for any *bona fide* charitable, compassionate use or indigent patient program purpose where such Product is sold at or below cost of goods sold or as a sample. In the case of any transfer of any Product between or among Biogen and its Affiliates or Sublicensees for resale, Net Sales shall be determined based on the sales made by such Affiliate or Sublicensee to a Third Party. Sales by any distributor will not be included as sales by a Sublicensee for the purposes of calculation of Net Sales, *provided that* the sale of Product by Biogen or its Affiliate or Sublicensee to such distributor is on an arms' length basis, and Biogen pays Ionis a royalty on the sale of such Product to such distributor.

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.

Notwithstanding the foregoing, in the event a Product is sold as a component of a Combination Product in any country in any Calendar Year, Net Sales shall be calculated by [***]. In the event that no separate sales of the Product or any Other Components included in a Combination Product are made by Biogen, its Affiliates or licensees in a country during a Calendar Year in which such Combination Product is sold in such country, the average Net Sales in the above described equation shall be replaced with [***].

"***Neurological Disease Research Plan***" has the meaning set forth in Section 1.2.

"***Neurological Disease Research Program***" has the meaning set forth in Section 1.2.

"***Neurology II Agreement***" has the meaning set forth in the Recitals of this Agreement.

"***Neurology JDC***" has the meaning set forth in Section 1.14.5.

"***Neurology JRC***" has the meaning set forth in Section 1.14.3.

"***Neurology Plan***" means any of the following plans: (a) the Core Research Plan, (b) the Neurological Disease Research Plan, including, for clarity, any final Target Sanction Plan, (c) any Development Candidate Identification Plans, (d) the Toxicology Strategy or (e) any Integrated Product Plans.

"***Neurology Target***" means any gene target that is a "High Interest Target" or "Collaboration Target" under the Neurology II Agreement and any other gene target that (a) as of the Execution Date, (i) is not encumbered by Ionis under an agreement with a Third Party such that Ionis could not grant Biogen the license under Section 4.1.1 of this Agreement with respect to such gene target, and (ii) has not yet achieved Target Sanction status, and (b) as of the Execution Date, the Effective Date or during the Research Term, the expression or activity of the gene in neurons is demonstrated to have an association to any one or more of the following (each of (A) through (I) below, a "***Neurological Disease***"):

(A) [***];

(B) [***];

(C) [***];

(D) [***];

(E) [***];

(F) [***];

(G) [***];

(H) [***]; and

(I) [***].

For purposes of clarity, a gene target that has as its primary disease association an association to [***] will not be considered a Neurology Target.

"***[***]***" means (a) [***] or (b) [***].

"***[***] Compound***" has the meaning set forth in Section 1.8.3(e).

"***[***] Development Candidate***" has the meaning set forth in Section 1.8.3(e).

"***New Third Party License***" has the meaning set forth in Section 7.9.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***NPV***" has the meaning set forth in APPENDIX 3.

"***Non-Neurological Indications***" means therapeutic uses that are not designed to treat any Neurological Disease.

"***[***]***" means diseases that have, as their [***].

"***Oligonucleotide***" means a synthetic compound that comprises or consists of at least 5 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 3.1.2(a).

"***Option Deadline***" has the meaning set forth in Section 3.1.2(a).

"***Option Fee***" has the meaning set forth in Section 6.4.

"***Option Period***" means, with respect to a Collaboration Program, the period beginning on the date a Strategy directed to a Neurology Target is designated as a Collaboration Program hereunder and ending on the License Effective Date or the expiration or earlier termination of the Option with respect to such Collaboration Program.

"***Other Activities***" has the meaning set forth in Section 1.13.3.

"***Other Components***" means any other pharmaceutically active compounds or substances referred to in the definition of a Combination Product, other than a Product.

"***Panel Decision***" has the meaning set forth in Section 10.6.5(c).

"***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 Change in Form***" means (a) with respect to any Development Candidate, Related Program Compound or Product, [***] and (b) with respect to any Product, [***].

"***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 ASOs (or supply ASOs to end users) solely to conduct pre-clinical research, or (ii) enable such Third Party to manufacture or formulate ASOs, 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 non-commercial 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.

"***Phase 1 Readout***" has the meaning set forth in Section 6.6.1.

"***Phase 1 Trial***" means, with respect to a Product, a first clinical study in human beings of such Product, as further defined in 21 C.F.R. 312.21(a) or the corresponding regulation in jurisdictions other than the United States.

"***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 Pivotal Clinical 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 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.

"***Pivotal Clinical Trial***" means (a) a Phase 3 Trial, or (b) a human clinical trial of a Product that satisfies the requirements of 21 C.F.R. § 312.21(c) and is a registration trial designed to establish statistically significant efficacy and safety of such Product for the purpose of enabling the preparation and submission of application for an NDA, MAA, JNDA or similar application for marketing approval to the competent Regulatory Authorities in a given country, as evidenced by (i) an agreement with or statement from the FDA on a Special Protocol Assessment or equivalent in another country or (ii) other guidance or minutes issued by the FDA, for such registration trial or equivalent in another country, or (iii) Biogen's public statements, with respect to each, where the results of such clinical trial are intended (if supportive) to be used to establish both safety and efficacy of such Product in patients that are the subject of such trial and serve as the basis for obtaining initial or supplemental Regulatory Approval in the United States of such Product. For clarity, any compassionate use dosing with respect to a Product shall not be considered the Initiation of a Pivotal Clinical Trial with respect to such Product.

"***Post-Option Development Milestone Event***" has the meaning set forth in Section 6.7.

"***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 12.5.2.

"***Pre-Existing Competitive Program***" has the meaning set forth in Section 12.5.2.

"***Precipitous Ionis Turnover***" has the meaning set forth in Section 1.10.

"***Primarily Neuro Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Primarily Other Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.8 attached hereto.

"***Prioritized Biogen Research Program***" means, with respect to an Ionis Neurology Target, Biogen has either (a) [***] or (b) [***], in each case ((a) and (b)), with respect to [***].

"***Priority Review Voucher***" means a voucher or right granted by the FDA or other Regulatory Authority that allows for priority review of a potential product that is issued or granted to a sponsor of a neglected disease or rare disease product application when a product to treat a neglected disease or rare disease is approved by such Regulatory Authority.

"***Pro Rata Portion***" has the meaning set forth in Section 12.5.1(f).

"***Procedures***" has the meaning set forth in SCHEDULE 12.1.2 .

"***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, with respect to a Product, 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 such Product, (b) methods of using such Product as a prophylactic or therapeutic or (c) the specific method of manufacture of such Product (unless in the case of (c), such Patent Rights also claim any other product or services of Ionis); *provided however*, Patent Rights Controlled by Ionis or any of its Affiliates that (i) include claims that are directed to subject matter applicable to ASOs or products 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.

"***Product Specific Payments***" means, with respect to any Patent Rights or Know-How, any payments (including royalties, up front payments, milestone payments, sublicensing income or revenue, fees and annual access payments) due to Third Parties in consideration of such Patent Rights or Know-How that are directly triggered as a result of the Research, Development, Manufacture or Commercialization of one or more Products in accordance with this Agreement. Product Specific Payments exclude Acquisition Costs.

"***Program Determination***" has the meaning set forth in Section 6.5.2.

"***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.

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

"***Qualifications***" has the meaning set forth in SCHEDULE 10.6.5(**c**).

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Reduced Royalty Period***" means, on a country-by-country and Product-by-Product basis, the period commencing upon the expiration of the Full Royalty Period for such Product in such country and ending when the Royalty Quotient for such Product is [***]% or less for [***] consecutive years.

"***Refund Date***" has the meaning set forth in Section 12.5.1(f).

"***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 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.

"***Related Know-How***" means, with respect to any Additional Ionis Core IP, Third Party Product IP or Third Party Acquisition IP, any Know-How that is related to such Additional Ionis Core IP, Third Party Product IP or Third Party Acquisition IP, as applicable, solely to the extent that payments due under the applicable agreement are in consideration of the acquisition of rights or other access to such Additional Ionis Core IP, Third Party Product IP or Third Party Acquisition IP, as applicable, together with such Know-How.

"***Related Program Compounds***" has the meaning set forth in Section 1.8.3(a).

"***Research***" means conducting the research activities with ASOs or Compounds as set forth in the Neurology Plans, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "***Researching***" means to engage in Research.

"***Research Term***" has the meaning set forth in Section 1.2.1.

"***Research Term Extension Date***" has the meaning set forth in Section 1.8.1(d)(i).

"***Results***" has the meaning set forth in Section 4.8.2(d).

"***Reverse Royalties***" has the meaning set forth in Section 6.10.1.

"***RMC***" means Ionis' Research Management Committee, or any successor committee.

"***Royalty Quotient***" has the meaning set forth in Section 6.9.2(c).

"***Separate IND-Enabling Toxicology Notice***" has the meaning set forth in Section 3.1.2(b)(ii).

"***Setoff Amount***" has the meaning set forth in Section 10.6.5(c).

"***Setoff Dispute***" has the meaning set forth in Section 10.6.5(c).

"***Setoff Dispute Notice***" has the meaning set forth in Section 10.6.5(c).

"***[***] Asset***" has the meaning set forth in Section 6.5.1.

"***Specific Performance Milestone Event***" has the meaning set forth in Section 5.2.1.

"***Special Protocol Assessment***" means the procedures adopted by the United States Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research for evaluating issues related to the adequacy of certain proposed studies associated with the development of products in human drug applications as defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379g(1)) for products covered by the Prescription Drug User Fee Act of 1992, as further described in section 119(a) of the Food and Drug Administration Modernization Act.

"***Spinraza Agreement***" means the Development, Option and License Agreement between the Parties dated January 3, 2012, as amended or restated from time to time.

"***Step-In Party***" has the meaning set forth in Section 7.4.1.

"***Stock Purchase Agreement***" means the Stock Purchase Agreement of even date herewith between Ionis and Biogen (or Biogen's Affiliate).

"***Strategy***" means, with respect to [***].

"***Strategy Acceptance Notice***" has the meaning set forth in Section 1.2.3(d)(ii)(B).

"***Strategy Acceptance Period***" has the meaning set forth in Section 1.2.3(d)(ii)(B).

"***Strategy Initiation Date***" has the meaning set forth in Section 1.2.3(d)(ii)(C).

"***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 10.3.4(b)(i).

"***Subsequent Measurement Date***" has the meaning set forth in Section 1.8.1(b).

"***Superior Patent Right***" has the meaning set forth in Section 7.2.5(d).

"***Target Designation Milestone***" has the meaning set forth in Section 6.2.

"***Target Designation Milestone Payment***" has the meaning set forth in Section 6.2.

"***Target Related Biogen Program Claim***" has the meaning set forth in Section 4.3.4.

"***Target Related Ionis Program Claim***" has the meaning set forth in Section 4.3.3.

"***Target Sanction***" means when the therapeutic potential of a Strategy directed to a Neurology Target has been demonstrated in pre-clinical disease models and such Strategy directed to such Neurology Target has received approval by Ionis' RMC to justify expending resources to identify a human development candidate, all in accordance with Ionis' standard processes.

"***Target Sanction Data Package***" means, with respect to a Strategy directed to a Neurology Target, the data package Ionis presented to Ionis' RMC to obtain approval to justify expending resources to identify a human Development Candidate, all in accordance with Ionis' standard processes; *provided* such package contains the same level of detail as the data packages Ionis currently presents to Ionis' RMC to approve Ionis' own internal gene targets and is consistent with and contains the results from all the activities under the applicable Target Sanction Plan.

"***Target Sanction Plan***" has the meaning set forth in Section 1.2.

"***Target Technical Failure***" has the meaning set forth in Section 1.8.2(f).

"***Target Technical Failure Date***" has the meaning set forth in Section 1.8.2(f).

"***Technical Failure***" has the meaning set forth in Section 1.8.2(d).

"***Terminated Target***" has the meaning set forth in Section 10.5.

"***Termination Date***" has the meaning set forth in Section 10.3.1(b).

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Acquisition IP***" has the meaning set forth in Section 6.11.6(a).

"***Third Party Core IP***" has the meaning set forth in Section 6.11.3(a).

"***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.

"***Third Party Product IP***" has the meaning set forth in Section 6.11.4(a).

"***Toxicology Strategy***" has the meaning set forth in Section 1.8.3(c).

"***Transition Services***" has the meaning set forth in Section 10.6.6(b).

"***Trial Court***" has the meaning set forth in Section 10.6.5(c).

"***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.

"***Useful Third Party Product IP***" has the meaning set forth in Section 6.11.5(a).

"***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

Multi-Indication Target Process

Neurology Targets with Broader Therapeutic Benefit.

(a) If, pursuant to Section 1.2.3(e), the CSC is unable to agree upon whether a Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target, the Parties will engage a Third Party expert under Section 12.1.4 to make such determination. Such Third Party expert will first determine the net present value ("***NPV***") of a therapeutic targeting such Multi-Indication Target and allocate such NPV between the markets for Neurological Disease indications and for Non-Neurological Indications, where such NPV calculations and allocations will take into consideration, and risk-adjust for, the relevant market sizes, competitive landscapes, scientific rationale for each market and any other factors deemed relevant by such Third Party expert. Based on such NPV calculations and allocations, Multi-Indication Targets will be classified as either "***Primarily Neuro Multi-Indication Targets***"; "***Equal Multi-Indication Targets***" or "***Primarily Other Multi-Indication Targets***", where (1) a Multi-Indication Target with [***]% or more of its NPV allocated to the market for Neurological Disease indications will be a Primarily Neuro Multi-Indication Target, (2) a Multi-Indication Target with less than [***]% but more than [***]% of its NPV allocated to the market for Neurological Disease indications will be an Equal Multi-Indication Target, and (3) a Multi-Indication Target with [***]% or less of its NPV allocated to the market for Neurological Disease indications will be Primarily Other Multi-Indication Target.

(b) **Primarily Neuro Multi-Indication Targets**. If a Multi-Indication Target is classified as a Primarily Neuro Multi-Indication Target, then within [***] days of such classification, Biogen will send Ionis a written notice either (i) electing to negotiate in good faith with Ionis a development plan and [***] (i.e., [***]) for the Non-Neurological Indications if Developed and Commercialized under this Agreement, which plan and provisions will be recommended to the CSC for approval; (ii) granting Ionis and its Affiliates the right to work on their own or with a Third Party to discover, develop and commercialize an Oligonucleotide directed to such Multi-Indication Target for primarily Non-Neurological Indications (an "***Ionis Multi-Indication Compound***"); or (iii) precluding Ionis and its Affiliates from working on their own or with a Third Party to discover, develop or commercialize an Ionis Multi-Indication Compound. If under this clause (b) Ionis or any of its Affiliates or licensees Commercializes a product incorporating an Ionis Multi-Indication Compound, and Biogen has paid the applicable Option Fee for the applicable Collaboration Program, then until the earlier of (i) the [***] anniversary of the date of First Commercial Sale of such product or (ii) the date Biogen, its Affiliates and Sublicensees stop Commercializing the Product related to such Multi-Indication Target, Ionis will pay to Biogen a royalty of [***]% of Annual worldwide Net Sales of such product sold by Ionis, its Affiliates or Sublicensees. The definition of Net Sales in APPENDIX 1 and the other provisions contained in Sections 6.12, 6.13, 6.14, and 6.15 governing payment of royalties from Biogen to Ionis will govern the payment of such royalty from Ionis to Biogen under this clause (b), *mutatis mutandis*. If within [***] days of Biogen making an election under clause (1) of this clause (b) to pursue the Non-Neurological Indication, the CSC has not agreed on a development plan and enhanced economic provisions to be paid by Biogen for the Non-Neurological Indication, then (I) Ionis and its Affiliates will not work on their own or with a Third Party to discover, develop and commercialize in the Field an Ionis Multi-Indication Compound unless otherwise permitted under this Agreement and (II) Biogen and its Affiliates will not work on their own or with a Third Party to discover, develop or commercialize Compounds related to such Multi-Indication Target for Non-Neurological Indications.

(c) **Equal Multi-Indication Targets**. If a Multi-Indication Target is classified as an Equal Multi-Indication Target, neither Party nor its respective Affiliates, licensees or Sublicensees may develop or commercialize a product targeting such Multi-Indication Target for any indication unless and until Ionis and Biogen have agreed on (i) a development plan and enhanced economic provisions to be paid by Biogen (i.e., multi-indication filing and approval milestone payments, but not additional license fees) for the Non-Neurological Indications, and (ii) the restrictions under which Ionis or Biogen (as applicable) would develop or commercialize a product targeting such Multi-Indication Target (which terms may include the requirements set forth under clause (d) below).

(d) **Primarily Other Multi-Indication Targets**. If a Multi-Indication Target is classified as a Primarily Other Multi-Indication Target, then (A) Biogen may continue to Develop and Commercialize Products for Neurological Disease indications pursuant to the terms of this Agreement, and (B) within [***] days of such classification, Biogen will send Ionis a written notice either (iv) electing to negotiate in good faith with Ionis and agree on a development plan and [***] (i.e., [***]) for the Non-Neurological Indications if Developed and Commercialized under this Agreement, which plan and provisions will be recommended to the CSC for approval; or (5) granting Ionis and its Affiliates the right to work on their own or with a Third Party to discover, develop and commercialize an Ionis Multi-Indication Compound so long as such Ionis Multi-Indication Compound (i) [***], *provided*, in addition to the foregoing provisions, if the Development Candidate targeting such Multi-Indication Target being Developed or Commercialized by Biogen, its Affiliates or Sublicensees under this Agreement is [***], Ionis cannot develop or commercialize such Ionis Multi-Indication Compound for [***].

(e) If within [***] days of Biogen making an election under clause (b)(1) of this APPENDIX 3 to pursue the Non-Neurological Indication, the CSC has not agreed on a development plan and [***] (i.e., [***]) for the Non-Neurological Indications, then Ionis and its Affiliates will have the right to work on their own or with a Third Party to discover, develop and commercialize an Ionis Multi-Indication Compound so long as such Ionis Multi-Indication Compound [***].

SCHEDULE 1.8.3(c)

Development Candidate Toxicology Strategy

Components of IND-Enabling Toxicology Strategy

[***]

SCHEDULE 1.8.4(a)

List of Approved CROs

[***]

SCHEDULE 1.14.1

Collaboration Steering Committee Governance

CSC Representatives

Ionis

- Lynne Parshall – Senior Strategic Advisor
- Brett Monia – Chief Operating Officer
- Frank Bennett – SVP, Research
- Richard Geary – SVP, Development

Biogen

- Michael Ehlers, EVP Research & Development
- John McDonald, VP, Business Development
- Gilmore O'Neill, SVP, Late Stage Development
- Anabella Villalobos, SVP, Biotherapeutic and Medicinal Sciences

SCHEDULE 1.14.3

Neurology JRC Governance

(a) The Neurology JRC will determine the Neurology JRC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The Neurology JRC will codify these operating procedures in the written minutes of the first meeting.

(b) The Neurology JRC may hold meetings in person or by audio or video conference as determined by the Neurology JRC; 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 JRC 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 JRC meetings, including any subject matter expert(s) with valuable knowledge of High Interest Targets or Collaboration Targets (as applicable) or the diseases associated with such targets.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JRC meetings occur, Neurology JRC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.14.3, Section 7.1.3 and Section 12.1, as applicable.

(d) The Neurology JRC members from the same Party will collectively have one vote. The Neurology JRC 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 JRC meeting.

(e) The Neurology JRC 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 JRC dissolves.

SCHEDULE 1.14.5

Neurology JDC Governance

(a) The Neurology JDC will determine its operating procedures, including frequency of meetings (at least quarterly, subject to Section 1.14.8(a) and unless there is no update with respect to the applicable Collaboration Program), location of meetings, and responsibilities for agendas and minutes. The Neurology JDC will codify these operating procedures in the written minutes of its first meeting.

(b) The Neurology JDC may hold meetings in person or by audio or video conference as determined by the Neurology JDC; 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 JDC 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 JDC meetings, including any subject matter expert(s) with valuable knowledge of the applicable or Collaboration Target or the diseases associated with such target.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JDC meetings occur, Neurology JDC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.14.5, Section 7.1.3 and Section 12.1, as applicable.

(d) Neurology JDC members from the same Party will collectively have one vote. The Neurology JDC 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 JDC meeting.

(e) The Neurology JDC 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 JDC dissolves.

SCHEDULE 1.14.9

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;

(c) Organizing CSC, Neurology JRC and Neurology JDC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the CSC, Neurology JRC and Neurology JDC 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 CSC, Neurology JRC and Neurology JDC;

(f) Ensuring compliance in maintaining the Ionis Internal ASO Safety Database as outlined in Section 5.4;

(g) Ensuring proper approval of publications prior to submission as required in Section 11.4;

(h) Determining an appropriate format for summaries of resource and FTE utilization, and ensuring such summarized are timely provided to the Neurology JRC as outlined in Section 1.11.

SCHEDULE 4.3.1(a)

Drug Substance Process and Formulation Development Activities

[***]

SCHEDULE 4.9.2(c)

Ionis' Fully Absorbed Cost of Goods Methodology

Cost Estimate of API Cost per Kilogram

(000's)

All of the following shall be consistent with GAAP.

[***]

SCHEDULE 5.2.1

Biogen's Development and Commercialization Activities

[***]

SCHEDULE 5.2.5

Integrated Product Plan Content

[***]

SCHEDULE 6.9.2(e)

Royalty Calculation Examples

[***]

SCHEDULE 6.9.2(f)

Allocation of Net Sales

[***]

SCHEDULE 6.11.1

Certain Ionis In-License Agreements

[***]

SCHEDULE 8.2.5(a)

Ionis Core Technology Patents

[***]

SCHEDULE 8.2.5(b)

Ionis Manufacturing and Analytical Patents

[***]

SCHEDULE 8.2.5(c)

Ionis Product-Specific Patents

[***]

SCHEDULE 8.2.8

Opposition Proceedings

[***]

SCHEDULE 8.2.10

Prior Agreements

[***]

SCHEDULE 8.2.13

Ionis Product Pipeline

Drug	Indication	Partner
IONIS-GCGR$_{Rx}$	Diabetes	
IONIS-FXI$_{Rx}$	Clotting Disorders	
Volanesorsen	FCS	
IONIS-DGAT2$_{Rx}$	NASH	
AKCEA-APO(a)-L$_{Rx}$	CVD	
AKCEA-ANGPTL3-L$_{Rx}$	Rare Hyperlipidemias	
IONIS-GHR-L$_{Rx}$	Acromegaly	
IONIS-AGT-L$_{Rx}$	Treatment-Resistant Hypertension	
AKCEA-APOCIII-L$_{Rx}$	CVD	
IONIS-HBV$_{Rx}$	Hepatitis B Virus	
IONIS-HTT$_{Rx}$	Huntington's Disease	
IONIS-HBV-L$_{Rx}$	Hepatitis B Virus	
IONIS-SOD-1$_{Rx}$	ALS	Biogen
IONIS-MAPT$_{RX}$	Neurodegenerative	Biogen
IONIS-STAT3-2.5$_{Rx}$	Cancer	
IONIS-AR-2.5$_{Rx}$	Cancer	
IONIS-KRAS-2.5$_{Rx}$	Lung/Pancreatic Cancer/CRC	
IONIS-FB-L$_{Rx}$	AMD	
Inotersen	Amyloidosis	
IONIS-PKK$_{Rx}$	Hereditary Angioedema	
IONIS-PKK-L$_{Rx}$	Hereditary Angioedema	
IONIS-TMPRSS6-L$_{Rx}$	Beta-Thalassemia	
SPINRAZA®	Spinal Muscular Atrophy	Biogen
KYNAMRO®	HoFH	
Volanesorsen	FPL	
AKCEA-ANGPTL3-L$_{Rx}$	NAFLD/Metabolic Complications	
IONIS-FXI-L$_{Rx}$	Clotting Disorder	
IONIS-RHO-2.5$_{Rx}$	Autosomal Dominant Retinitis Pigmentosa	
IONIS-ENaC-2.5$_{Rx}$	Cystic Fibrosis	
IONIS-TTR-L$_{Rx}$	ATTR	
IONIS-C9$_{Rx}$	ALS	Biogen
IONIS-EZH2-2.5$_{Rx}$	Cancer	
IONIS-IRF4-2.5$_{Rx}$	Cancer	
IONIS-AZ4-2.5-L$_{Rx}$	CVD	
IONIS-AZ5-2.5$_{Rx}$	Kidney Disease	
IONIS-JBI1-2.5$_{Rx}$	GI Autoimmune Disease	
IONIS-JBI2-2.5$_{Rx}$	GI Autoimmune Disease	
IONIS-BIIB6$_{Rx}$	Neurodegenerative Diseases	Biogen
IONIS-BIIB7$_{Rx}$	Neurodegenerative Diseases	Biogen
IONIS-BIIB8$_{Rx}$	Neurodegenerative Diseases	Biogen

[***]

SCHEDULE 10.6.5(c)

Advisory Panel Regarding Setoff Disputes

[***].

SCHEDULE 10.6.6

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.

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).

EXECUTION VERSION

Exhibit 10.2

STOCK PURCHASE AGREEMENT

THIS STOCK PURCHASE AGREEMENT (***"Agreement"***) is entered into as of April 19, 2018 (the ***"Execution Date"***), by and between **BIOGEN MA INC.**, a Massachusetts corporation (***"Biogen"***), and **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation (***"Ionis"***).

RECITALS

A. Ionis has agreed to sell, and Biogen has agreed to purchase, shares of Ionis' common stock (the ***"Common Stock"***) subject to and in accordance with the terms and provisions hereof.

B. The capitalized terms used herein and not otherwise defined have the meanings given to them in Appendix 1.

AGREEMENT

For good and valuable consideration, the Parties agree as follows:

SECTION 1. SALE AND PURCHASE OF STOCK

1.1 Purchase of Stock. Subject to the terms and conditions of this Agreement, at the Closing, Ionis will issue and sell to Biogen, and Biogen will purchase from Ionis,11,501,153 shares of Common Stock (the ***"Shares"***) for an aggregate purchase price of US$625 million (representing a price per share equal to 125% of the daily volume-weighted average per share price of the Common Stock on the Nasdaq Global Select Market over the 10 trading day period ending on and including the last trading day prior to the Execution Date) (the ***"Purchase Price"***).

1.2 Payment. At the Closing, Biogen will pay the Purchase Price by wire transfer of immediately available funds in accordance with wire instructions provided by Ionis to Biogen at least three Business Days prior to the Closing, and Ionis will deliver the Shares in book-entry form to Biogen.

1.3 Closing.

(a) The closing of the transactions contemplated by this Section 1 (the ***"Closing"***) will be held at the offices of Ionis within three Business Days after the conditions to closing set forth in Section 7 are satisfied or waived (other than those conditions that by their nature are to be satisfied or waived at the Closing) or at such other place, time and/or date as may be jointly designated by Biogen and Ionis (the ***"Closing Date"***).

(b) Closing Deliverables.

(i) At the Closing, Ionis shall deliver to Biogen:

(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 Biogen and duly executed on behalf of Ionis by an authorized officer of Ionis, certifying that the conditions to Closing set forth in Section 7.2 of this Agreement have been fulfilled; and

(3) a certificate of the secretary of Ionis dated as of the Closing Date certifying that attached thereto is a true and complete copy of all resolutions adopted by the board of directors of Ionis authorizing the execution, delivery and performance of this Agreement and the Collaboration Agreement and the transactions contemplated respectively therein 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, Biogen will deliver to Ionis:

(1) a duly-executed Cross-Receipt;

(2) a certificate in form and substance reasonably satisfactory to Ionis and duly executed on behalf of Biogen by an authorized officer of Biogen, certifying that the conditions to Closing set forth in Section 7.1 of this Agreement have been fulfilled; and

(3) a certificate of the secretary of Biogen dated as of the Closing Date certifying that attached thereto is a true and complete copy of all resolutions adopted by the board of directors of Biogen authorizing the execution, delivery and performance of this Agreement and the Collaboration Agreement and the transactions contemplated respectively therein 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.

SECTION 2. REPRESENTATIONS AND WARRANTIES OF IONIS

Except as otherwise specifically contemplated by this Agreement, Ionis hereby represents and warrants to Biogen that:

2.1 Private Placement. Neither Ionis 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 Biogen in Section 3, the Shares will be issued and sold to Biogen 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. Ionis 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 Organization and Qualification. Ionis is duly incorporated, validly existing and in good standing under the laws of the State of Delaware, with full corporate power and authority to conduct its business as currently conducted. Ionis 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 Ionis.

2.3 Authorization; Enforcement. Ionis 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 hereof. The execution, delivery and performance of this Agreement by Ionis and the consummation by it of the transactions contemplated hereby (including the issuance of the Shares) have been duly authorized by Ionis' Board of Directors (the ***"Board"***) and no further consent or authorization of Ionis, the Board, or its stockholders is required. This Agreement has been duly executed by Ionis and constitutes a legal, valid and binding obligation of Ionis enforceable against Ionis 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 and except as enforceability may be subject to general principles of equity and except as rights to indemnity and contribution may be limited by state or federal securities laws or public policy underlying such laws.

2.4 Issuance of Shares. The Shares are duly authorized and, 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 stockholders of Ionis.

2.5 SEC Documents, Financial Statements.

(a) The Common Stock is registered pursuant to Section 12(b) or 12(g) of the Exchange Act. Ionis has delivered or made available (by filing on the SEC's electronic data gathering and retrieval system (EDGAR)) to Biogen complete copies of its most recent Annual Report on Form 10-K, its most recent Quarterly Report on Form 10-Q, and any current report on for 8-K, in each case filed with the SEC after January 1, 2018 and 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 federal, state and local laws, rules and regulations 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.

(b) The financial statements, together with the related notes and schedules, of Ionis 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 Ionis 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).

(c) The Common Stock is listed on Nasdaq, and Ionis has taken no action designed to, or which to its knowledge is likely to have the effect of, terminating the registration of the Common Stock under the Exchange Act or delisting the Common Stock from Nasdaq. As of the date of this Agreement, Ionis 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. Ionis maintains internal control over financial reporting as defined in Rule 13a-15(f) under the Exchange Act. Ionis 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 Ionis 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 Ionis (or each former principal executive officer of Ionis and each former principal financial officer of Ionis, as applicable) 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 Ionis with the SEC.

2.7 Capitalization and Voting Rights

(a) The authorized capital of Ionis as of December 31, 2017 is accurately set forth in the SEC Documents. All of the issued and outstanding shares of Common Stock (A) have been duly authorized and validly issued, (B) are fully paid and non-assessable and (C) were issued in compliance with all applicable federal and state securities laws and not in violation of any preemptive rights.

(b) All of the authorized shares of Common Stock are entitled to one (1) vote per share.

(c) Except as described or referred to in the SEC Documents, as of December 31, 2017, there are not: (i) any outstanding equity securities, options, warrants, rights (including conversion or preemptive rights) or other agreements pursuant to which Ionis is or may become obligated to issue, sell or repurchase any shares of its capital stock or any other securities of Ionis or (ii) any restrictions on the transfer of capital stock of Ionis other than pursuant to state and federal securities laws or as set forth in this Agreement.

(d) Ionis is not a party to or subject to any agreement or understanding relating to the voting of shares of capital stock of Ionis or the giving of written consents by a stockholder or director of Ionis.

2.8 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by Ionis and the consummation by Ionis 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 Ionis' Certificate of Incorporation or Bylaws, (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 Ionis is a party, or (iii) result in a violation of any law, rule, regulation, order, judgment or decree (including United States federal and state securities laws and regulations and regulations of any self-regulatory organizations) applicable to Ionis, 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 Ionis or result in a liability for Biogen.

(b) Ionis 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 or self regulatory agency in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms hereof, or to issue and sell the Shares in accordance with the terms hereof other than such as have been made or obtained, and except for (i) any post-closing filings required to be made under federal or state securities laws, (ii) any required filings or notifications regarding the issuance or listing of additional shares with Nasdaq, and (iii) any consent required under the HSR Act.

2.9 Litigation. Other than as set forth in the SEC Documents filed prior to the date of this Agreement, there is no action, suit, proceeding or investigation pending (of which Ionis has received notice or otherwise has knowledge) or, to Ionis' knowledge, threatened, against Ionis or which Ionis intends to initiate, except where such action, suit, proceeding or investigation, as the case may be, would not reasonably be expected to have a Material Adverse Effect.

2.10 Licenses and Other Rights; Compliance with Laws. Ionis 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. To Ionis' knowledge, Ionis 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. Ionis is and has been in compliance with all laws applicable to its business, properties and assets, and to the products and services sold by it, 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) The Intellectual Property that is owned by Ionis or its subsidiaries is owned free from any liens or restrictions, and all of Ionis' material Intellectual Property Licenses are in full force and effect in accordance with their terms, are free of any liens or restrictions, and neither Ionis, nor to Ionis' knowledge, any other party thereto, is in material breach of any such material Intellectual Property License, and no event has occurred that with notice or lapse of time or both would constitute such a breach or default thereunder or would result in the termination thereof or would cause or permit the acceleration or other change of any right or obligation of the loss of any benefit thereunder by Ionis or its subsidiaries except (i) for such failures to be in full force and effect, such liens or restrictions, and such material breaches that would not reasonably be expected to have a Material Adverse Effect, or (ii) as set forth in any such Intellectual Property License. Except as set forth in the SEC Documents, there is no legal claim or demand of any person pertaining to, or any proceeding which is pending (of which Ionis has received notice or otherwise has knowledge) or, to the knowledge of Ionis, threatened, (i) challenging the right of Ionis in respect of any Intellectual Property of Ionis, or (ii) that claims that any default exists under any Intellectual Property License, except, in the case of (i) and (ii) above, where any such claim, demand or proceeding has not had and would not reasonably be expected to have a Material Adverse Effect.

(b) Except as set forth in the SEC Documents: (i) Ionis or one of its subsidiaries owns, free and clear of any lien or encumbrance, or has a valid license to, or has 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 Ionis' business, except where any of the foregoing would not reasonably be likely to have a Material Adverse Effect (such Proprietary Rights owned by or licensed to Ionis collectively, the "***Ionis Rights***"); and (ii) Ionis and its subsidiaries have taken reasonable measures to protect the Ionis 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 Absence of Certain Changes.

(a) Except as disclosed in the SEC Documents filed prior to the Execution Date, since December 31, 2017, no change or event has occurred, except where such change or event has not and would not reasonably be expected to have a Material Adverse Effect on Ionis.

(b) Except as set forth in the SEC Documents filed prior to the Execution Date, since December 31, 2017, Ionis 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 capital stock, or (ii) sold, exchanged or otherwise disposed of any of its material assets or rights.

(c) Since December 31, 2017, Ionis 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.

2.13 Not an Investment Company. Ionis is not, and solely after receipt of the Purchase Price, will not be, an "investment company" as defined in the Investment Company Act of 1940, as amended.

2.14 No Integration. Ionis 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) which 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.

SECTION 3. REPRESENTATIONS AND WARRANTIES OF BIOGEN

Except as otherwise specifically contemplated by this Agreement, Biogen hereby represents and warrants to Ionis that:

3.1 Authorization; Enforcement. Biogen has the requisite corporate power and authority to enter into this Agreement and to consummate the transactions contemplated hereby. Biogen has taken all necessary corporate 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 Biogen enforceable against Biogen in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting creditors' and contracting parties' rights generally and except as enforceability may be subject to general principles of equity and except as rights to indemnity and contribution may be limited by state or federal securities laws or public policy underlying such laws.

3.2 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by Biogen and the consummation by Biogen 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 Biogen's Certificate of Incorporation or Bylaws, (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 Biogen is a party, or (iii) result in a violation of any law, rule, regulation, order, judgment or decree (including United States federal and state securities laws and regulations and regulations of any self-regulatory organizations) applicable to Biogen, 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 Biogen or result in a liability for Ionis.

(b) Biogen 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 or self regulatory agency in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms hereof, or to purchase the Shares in accordance with the terms hereof other than such as have been made or obtained except for any consent required under the HSR Act.

3.3 Investment Purpose. Biogen 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. Biogen 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 and to the extent permitted by Section 6.1 and Section 6.2.

3.4 Reliance on Exemptions. Biogen understands that Ionis 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 Ionis is relying upon the truth and accuracy of, and Biogen's compliance with, the representations, warranties, agreements, acknowledgments and understandings of Biogen set forth herein in order to determine the availability of such exemptions and the eligibility of Biogen to acquire the Shares.

3.5 Accredited Investor; Access to Information. Biogen 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. Biogen has been furnished with materials relating to the offer and sale of the Shares, that have been requested by Biogen, including, without limitation, Ionis' SEC Documents, and Biogen has had the opportunity to review the SEC Documents. Biogen has been afforded the opportunity to ask questions of Ionis. Neither such inquiries nor any other investigation conducted by or on behalf of Biogen or its representatives or counsel will modify, amend or affect Biogen's right to rely on the truth, accuracy and completeness of the SEC Documents and Ionis' representations and warranties contained in this Agreement. Biogen has, with respect to all matters relating to this Agreement and the offer and sale of the Shares, not relied upon counsel.

3.6 Governmental Review. Biogen understands that no United States federal or state agency or any other government or governmental agency has passed upon or made any recommendation or endorsement of the Shares or an investment therein.

SECTION 4. STANDSTILL AGREEMENT.

4.1 Prior to the earlier of (i) the expiration of the Research Term under the Collaboration Agreement, and (ii) the date on which Biogen and its Affiliates collectively hold less than 2% of Ionis' outstanding Common Stock on an issued and outstanding basis without giving effect to any convertible securities (the "***Standstill Period***"), Biogen and its Affiliates will not, directly or indirectly, except as expressly approved or invited by Ionis:

(a) effect or seek, offer or propose (whether publicly or otherwise) to effect, or cause or participate in or in any way advise, assist or encourage any other person to effect or seek, offer or propose (whether publicly or otherwise) to effect or participate in, (i) any acquisition of any securities (or beneficial ownership thereof) or material assets of Ionis, (ii) any tender or exchange offer, merger, or other business combination involving Ionis, (iii) any recapitalization, restructuring, liquidation, dissolution or other extraordinary transaction with respect to Ionis, or (iv) any "*solicitation*" of "*proxies*" (as such terms are used in the proxy rules of the SEC) or consents to vote any voting securities of Ionis;

(b) form, join or in any way participate in a "*group*" (as defined under the Exchange Act) with respect to any securities of Ionis;

(c) otherwise act, alone or in concert with others, to seek to control or influence the management, Board of Directors or policies of Ionis;

(d) take any action that would reasonably be expected to require Ionis to make a public announcement regarding any of the types of matters set forth in clause (a) above; or

(e) enter into any discussions or arrangements with any person with respect to any of the foregoing.

4.2 Biogen also agrees during the Standstill Period not to request Ionis (or its representatives), directly or indirectly, to amend or waive any provision of this Section 4, other than by means of a *bona fide* confidential communication to the Ionis Chairman of the Board or Chief Executive Officer. Biogen represents and warrants that, as of the Execution Date, neither Biogen nor any of its Affiliates owns, of record or beneficially, any voting securities of Ionis, or any securities convertible into or exercisable for any voting securities of Ionis.

4.3 Notwithstanding the provisions set forth in Sections 4.1 and 4.2 (the "***Standstill Provisions***"), Biogen shall immediately, and without any other action by Ionis, be released from its obligations under the Standstill Provisions if: (a) Ionis executes a definitive agreement with a third party providing for an acquisition (by way of merger, tender offer or otherwise), of more than 50% of Ionis' outstanding Common Stock or all or substantially all of Ionis' assets, then (in any of such cases), (b) a third party commences a tender offer seeking to acquire beneficial ownership of more than 50% of Ionis' outstanding Common Stock (or publicly announces an intention to acquire by way of merger, tender or otherwise more than 50% of Ionis' outstanding Common Stock), (c) a third party undertakes (or publicly announced an intent to undertake) a proxy contest to replace a majority of Ionis' board of directors, (d) Ionis waives any standstill or similar provision in any other agreement between Ionis and a third party or (e) the Collaboration Agreement is terminated. None of (x) the ownership nor purchase by an employee benefit plan of Biogen or Biogen's Affiliates in any diversified index, mutual or pension fund managed by an independent advisor, which fund in-turn holds, directly or indirectly, securities of Ionis, (y) transfers or resales of the Shares by Biogen to any other person in compliance with Section 6 or (z) the mere voting of the Shares in accordance with Section 5, will be deemed to be a breach of Biogen's standstill obligations under this Section 4.

SECTION 5. VOTING AGREEMENT

5.1 Voting Agreement.

(a) If the Proxyholder instructs Biogen in writing to vote in favor of, or against, any matter, action, ratification or other event for which approval of the holders of Ionis' stock is sought (either by vote or written consent) or upon which such holders are otherwise entitled to vote, including but not limited to the election of directors, *but excluding* any Extraordinary Matter (collectively, an ***"Ionis Stockholder Matter"***), then Biogen will (i) after receiving proper notice of any meeting of stockholders of Ionis related to such Ionis Stockholder Matter (or, if no notice is required or such notice is properly waived, after notice from the Proxyholder is given), be present, in person or by proxy, as a holder of Shares at all such meetings and be counted for the purposes of determining the presence of a quorum at such meetings and (ii) vote (in person, by proxy or by action by written consent, as applicable) all Shares as to which Biogen has beneficial ownership or as to which Biogen otherwise exercises voting or dispositive authority in the manner directed by the Proxyholder.

(b) Extraordinary Matters. Biogen may vote or execute a written consent with respect to, any or all of the voting securities of Ionis as to which they are entitled to vote or execute a written consent, as it may determine in its sole discretion, with respect to the following matters, if presented to Ionis's stockholders for approval (each such matter being an "***Extraordinary Matter***"):

(i) any transaction which would result in a Change of Control of Ionis;

(ii) any issuance of Common Stock that represents more than 20% of the then outstanding Ionis Common Stock;

(iii) the entry into any licensing, partnering, partnership, collaboration, research and development, joint venture or other commercial agreement;

(iv) the payment of any dividends to any class of stockholders of Ionis; and

(v) any liquidation or dissolution of Ionis.

(c) Appointment of Proxy. To secure Biogen's obligations to vote the Shares in accordance with this Agreement and to comply with the other terms hereof, Biogen hereby appoints the Proxyholder, or his designees, as Biogen's true and lawful proxy and attorney, with the power to act alone and with full power of substitution, to vote or act by written consent with respect to all of Biogen's Shares in accordance with the provisions set forth in this Agreement, and to execute all appropriate instruments consistent with this Agreement on behalf of Biogen. The proxy and power granted by Biogen pursuant to this Section 5 are coupled with an interest and are given to secure the performance of Biogen's duties under this Agreement. Each such proxy and power will be irrevocable until the agreements contained in this Section 5 expire in accordance with Section 5.1(e). The proxy and power will survive the merger, consolidation, conversion or reorganization of Biogen or any other entity holding any Shares (other than any Shares sold by Biogen in compliance with Section 6). For the avoidance of doubt, the proxy granted by this Section 5 shall not apply to any Extraordinary Matter.

(d) No Revocation. The voting agreements contained in this Section 5 are coupled with an interest and may not be revoked prior to their expiration in accordance with Section 5.1(e).

(e) Expiration. The agreements contained in this Section 5 will expire (i) in part, solely with respect to any Shares sold by Biogen in an arm's length sale to a non-Affiliate in compliance with this Agreement upon the execution of the sale of such Shares, and (ii) as a whole on the earlier of (1) April 19, 2023, (2) the date on which Biogen and its Affiliates collectively hold less than 2% of Ionis' outstanding Common Stock on an issued and outstanding basis without giving effect to any convertible securities and (3) the date the Collaboration Agreement is terminated. For the avoidance of doubt, the agreements contained in this Section 5 shall not limit Biogen's ability to transfer or resell any Shares, provided that such transfers or resales are done in accordance with Section 6.

SECTION 6. TRANSFER, RESALE, LEGENDS.

6.1 Transfer or Resale. Biogen 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, Biogen 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, including pursuant to the registration rights set forth in Section 6.5 and Appendix 2; (ii) Biogen has delivered to Ionis 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; 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.

6.2 Agreement to Hold Shares. Biogen 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 March 31, 2019 (the ***"Initial Holding Period"***). Biogen further agrees that from April 1, 2019 through March 31, 2020, inclusive, (the ***"Partial Holding Period"*** and together with the Initial Holding Period, the ***"Holding Periods"***), Biogen will hold and will not sell at least 5,750,577 of the Shares purchased at the Closing (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). In addition, after the expiration of both Holding Periods, in any single trading day Biogen will not sell an amount of Shares that exceeds 10% of the average daily trading volume of Ionis' Common Stock over the five trading day period ending on the trading day immediately prior to such trading date. Notwithstanding the foregoing, this Section 6.2 will not preclude Biogen from selling the Shares to a Third Party pursuant to a tender offer made by such Third Party.

6.3 Legends. Biogen understands the Shares will bear a restrictive legend in substantially the following form (and a stop-transfer order may be placed against transfer of the Shares):

THE SHARES EVIDENCED HEREBY ARE SUBJECT TO AN AGREEMENT TO VOTE THESE SHARES IN THE MANNER SET FORTH IN THE STOCK PURCHASE AGREEMENT DATED APRIL 19, 2018 BETWEEN IONIS PHARMACEUTICALS, INC. AND BIOGEN MA INC.

THE SALE, PLEDGE, HYPOTHECATION OR TRANSFER OF THESE SECURITIES IS SUBJECT TO THE TERMS AND CONDITIONS OF A STOCK PURCHASE AGREEMENT DATED APRIL 19, 2018 BETWEEN IONIS PHARMACEUTICALS, INC. AND BIOGEN MA INC.

Biogen may request that Ionis remove, and Ionis agrees to authorize and instruct (including by causing any required legal opinion to be provided) the removal of any legend from the Shares within two (2) Business Days of any such request, at any time following the Holding Period; *provided*, *however*, each party will be responsible for any fees it incurs in connection with such request and removal.

6.4 10b5-1 Plan. If requested by Biogen, Ionis will approve and adopt, without unreasonable delay or condition, any written plan by Biogen for trading the Shares that is designed in accordance with Rule 10b5-1(c) of the Exchange Act, as long as such plan does not violate this Agreement and applicable securities laws.

6.5 Registration Rights. Ionis hereby provides Biogen with the registration rights set forth on **Appendix 2** attached hereto, which is hereby incorporated in and made a part of this Agreement as if set forth in full herein.

SECTION 7. CONDITIONS TO CLOSING

7.1 Conditions to Obligations of Ionis. Ionis' obligation to complete the purchase and sale of the Shares and deliver the Shares to Biogen is subject to the fulfillment or waiver of the following conditions at or prior to the Closing:

(a) Receipt of Funds. Ionis 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 Biogen 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 the Company 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 court, arbitrator, governmental body, agency or official.

(e) No Governmental Prohibition; HSR Clearance. The sale of the Shares by Ionis will not be prohibited by any applicable law or governmental order or regulation. Any applicable waiting periods under the HSR Act will have expired or terminated.

(f) Collaboration Agreement. Biogen shall have duly executed and delivered the Collaboration Agreement to Ionis, and subject to execution by Biogen, such agreement shall be in full force and effect.

(g) Letter Agreement. Biogen shall have duly executed and delivered the Letter Agreement to Ionis, and subject to execution by Biogen, such agreement shall be in full force and effect.

(h) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(ii) shall have been delivered by Biogen to Ionis.

7.2 Conditions to Biogen's Obligations at the Closing. Biogen's obligation to complete the purchase and sale of the Shares is subject to the fulfillment or waiver of the following conditions at or before the Closing:

(a) Representations and Warranties. The representations and warranties made by Ionis in Section 2 will be true and correct 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 as of such other date.

(b) Covenants. All covenants and agreements contained in this Agreement to be performed or complied with by Ionis on or prior to the Closing Date shall have been performed or complied with in all material respects.

(c) Transfer Agent Instructions. Ionis will have delivered to its transfer agent irrevocable written instructions to issue the Shares to Biogen in a form and substance acceptable to such transfer agent.

(d) Nasdaq Qualification. The Shares will be duly authorized for listing by Nasdaq, subject to official notice of issuance.

(e) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or delay the Closing, will have been instituted or be pending before any court, arbitrator, governmental body, agency or official.

(f) Collaboration Agreement. Ionis shall have duly executed and delivered the Collaboration Agreement to Biogen, and subject to execution by Ionis, such agreement shall be in full force and effect.

(g) Letter Agreement. Ionis shall have duly executed and delivered the Letter Agreement to Biogen, and subject to execution by Ionis, such agreement shall be in full force and effect.

(h) No Governmental Prohibition. The sale of the Shares by Ionis, and the purchase of the Shares by Biogen will not be prohibited by any applicable law or governmental order or regulation. Any applicable waiting periods under the HSR Act will have expired or terminated.

(i) Closing Deliverables. All closing deliverables as required under Section 1.3(b)(i) shall have been delivered by Ionis to Biogen.

SECTION 8. TERMINATION.

8.1 Ability to Terminate. This Agreement may be terminated at any time prior to the Closing by:

(a) mutual written consent of Ionis and Biogen;

(b) Ionis, upon written notice to Biogen, so long as Ionis 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 7.1, as applicable, could not be satisfied by the Termination Date, (i) upon a breach of any covenant or agreement on the part of Biogen set forth in this Agreement, or (ii) if any representation or warranty of Biogen shall have been or become untrue, in each case such that any of the conditions set forth in Section 7.1 could not be satisfied by the Termination Date;

(c) Biogen, upon written notice to Ionis, so long as Biogen 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 7.2, as applicable, could not be satisfied by the Termination Date, upon a breach of any covenant or agreement on the part of Ionis set forth in this Agreement, or if any representation or warranty of Ionis shall have been or become untrue, in each case such that any of the conditions set forth in Section 7.2 could not be satisfied by the Termination Date;

(d) either Ionis or Biogen, if the Closing has not occurred within 180 days after the Execution Date (the "**Termination Date**"), upon written notice to the other. In such event, neither party shall have any further obligations under this Agreement. Notwithstanding the foregoing, the right to terminate this Agreement under this Section 8.1(d) shall not be available to any party that knowingly fails (whether by act or omission) to fulfill any obligation under this Agreement or the Collaboration Agreement, which failure causes or results in the failure to consummate the transactions contemplated hereby prior to the Termination Date.

8.2 Effect of Termination. In the event of the termination of this Agreement pursuant to Section 8.1 hereof, (a) this Agreement (except for this Section 8.2, Section 9 and Section 1.6 of Appendix B, 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) 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 8.2 shall relieve any party from liability for fraud or any intentional or willful breach of this Agreement.

SECTION 9. GOVERNING LAW; MISCELLANEOUS.

9.1 **Governing Law; Jurisdiction.** This Agreement will be governed by and interpreted in accordance with the laws of the State of Delaware without regard to the principles of conflict of laws.

9.2 HSR Clearance; Market Listing; Assistance and Cooperation.

(a) Subject to the terms and conditions of this Agreement and Section 3.1.3 (HSR Compliance) of the Collaboration Agreement, in connection with the acquisition of the Shares, each of Biogen and Ionis will (i) make all required filings and submissions under the HSR Act as determined by Biogen in consultation with Ionis, as promptly as practicable, but in no event later than 10 Business Days after the date of this Agreement, and (ii) use commercially reasonable efforts to obtain as promptly as practicable the termination or expiration of any waiting period under the HSR Act (**"HSR Clearance**"); provided that the obligations in clause (ii) shall not require Biogen or any of its Affiliates to (x) 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 (y) 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 (x).

(b) Each of Biogen and Ionis shall use commercially reasonable efforts to provide or cause to be provided promptly all assistance and cooperation to allow Biogen and Ionis to prepare and submit any filings or submissions under the HSR Act, including providing to Biogen and Ionis, as applicable, any information that it may require for the purpose of any filing, notification, application or request for further information made in respect of any such filing.

(c) Each of Biogen and Ionis shall, in connection with the Agreement contemplated hereby, with respect to actions taken on or after the date of this Agreement, without limitation: (1) promptly notify the other of, and if in writing, furnish the other with copies of (or, in the case of oral communications, advise the other of) any communications from or with any Governmental Authority, including the Federal Trade Commission and the United States Department of Justice, with respect to the Agreement, (2) permit the other to review and discuss in advance, and consider in good faith the view of the other in connection with, any proposed written or oral communication with any Governmental Authority, (3) not participate in any substantive meeting or have any substantive communication with any Governmental Authority unless it has given the other party a reasonable opportunity to consult with it in advance and, to the extent permitted by such Governmental Authority, gives the other the opportunity to attend and participate therein, (4) furnish the other party's outside legal counsel with copies of all filings and communications between it and any such Governmental Authority with respect to the Agreement; *provided* that neither party will be required to provide the other party with its Board of Directors or internal committee materials; and such material may be redacted as necessary (I) to comply with contractual arrangements, (II) to address good faith legal privilege or confidentiality concerns and (III) to comply with applicable law, (5) furnish the other party's outside legal counsel with such necessary information and reasonable assistance as the other party's outside legal counsel may reasonably request in connection with its preparation of necessary submissions of information to any such Governmental Authority, and (6) use commercially reasonable efforts to respond as soon as practicable to requests for information by any Governmental Authority.

(d) From the Execution Date through the Closing Date, Ionis shall use commercially reasonable efforts to (a) maintain the listing and trading of the Common Stock on Nasdaq and (b) effect the listing of the Shares on Nasdaq.

9.3 Counterparts; Signatures by Facsimile. This Agreement may be executed in two counterparts, both of which are considered one and the same agreement and will become effective when the counterparts have been signed by each party and delivered to the other party hereto. This Agreement, once executed by a party, may be delivered to the other party hereto by electronic PDF or facsimile transmission of a copy of this Agreement bearing the signature of the party so delivering this Agreement.

9.4 Headings. The headings of this Agreement are for convenience of reference only, are not part of this Agreement and do not affect its interpretation.

9.5 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.

9.6 Entire Agreement; Amendments. This Agreement (including any schedules and exhibits hereto) constitutes 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 9.6 will be binding upon Biogen and Ionis.

9.7 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 or facsimile 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 Ionis, addressed to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer Fax: 760-918-3592
with a copy to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Email: legalnotices@ionisph.com
If to Biogen, addressed to:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 Attention: Vice President Corporate Development E-mail: john.mcdonald@biogen.com
with a copy to:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 Attention: Chief Legal Officer E-mail: legaldepartment@biogen.com
with a copy to:	Ropes & Gray LLP Prudential Tower 800 Boylston Street Boston, MA 02199-360 Attention: Susan Galli Zachary Blume Email: Susan.Galli@ropesgray.com Zachary.Blume@ropesgray.com Fax: 617-951-7050

9.8 Successors and Assigns. This Agreement is binding upon and inures to the benefit of the parties and their successors and assigns. Ionis will not assign this Agreement or any rights or obligations hereunder without the prior written consent of Biogen, and Biogen will not assign this Agreement or any rights or obligations hereunder without the prior written consent of Ionis; *provided*, *however*, that Biogen may assign this Agreement together with all of the Shares it then owns (subject to Section 4 and Section 5) to any wholly-owned subsidiary and any such assignee may assign the Agreement together with all of the Shares it then owns (subject to Section 4 and Section 5) to Biogen or any other subsidiary wholly-owned by Biogen, in any such case, without such consent provided that the assignee agrees to assume Biogen's obligations under Section 4 and Section 5 of this Agreement.

9.9 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.

9.10 Further Assurances; Survival. 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. The provisions of this Agreement will survive termination.

9.11 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.

9.12 Equitable Relief. Ionis 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 Biogen. Ionis therefore agrees that Biogen is entitled to seek temporary and permanent injunctive relief or specific performance in any such case. Biogen 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 Ionis. Biogen therefore agrees that Ionis is entitled to seek temporary and permanent injunctive relief or specific performance in any such case.

9.13 Expenses. Ionis and Biogen are each liable for, and will pay, their own expenses incurred in connection with the negotiation, preparation, execution and delivery of this Agreement, including, without limitation, attorneys' and consultants' fees and expenses.

In Witness Whereof, Biogen and Ionis have caused this Agreement to be duly executed as of the date first above written.

Biogen MA Inc.

By: /s/ Michel Vounatsos

Its:

Ionis Pharmaceuticals, Inc.

By: /s/ Stanley T. Crooke, M.D., Ph.D.

Its:

APPENDIX 1

DEFINED TERMS

"***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 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 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 (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"Business Day" means a day Monday through Friday on which banks are generally open for business in the State of California.

"Change of Control" means with respect to a party, any (i) direct or indirect acquisition of all or substantially all of the assets of such party, (ii) direct or indirect acquisition by a person, or group of persons acting in concert, of 50% or more of the voting equity interests of a party, (iii) tender offer or exchange offer that results in any person, or group of persons acting in concert, beneficially owning 50% or more of the voting equity interests of a party, or (iv) merger, consolidation, other business combination or similar transaction involving a party, pursuant to which any person owns all or substantially all of the consolidated assets, net revenues or net income of a party, taken as a whole, or which results in the holders of the voting equity interests of a party immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold 50% or more of the combined voting power of the surviving, purchasing or continuing entity immediately after such merger, consolidation, other business combination or similar transaction, in all cases where such transaction is to be entered into with any person other than the other party to this Agreement or its Affiliates.

"***Collaboration Agreement***" means that certain New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement, dated the Execution Date, between Biogen and Ionis.

"Exchange Act" means the Securities Exchange Act of 1934, as amended, and the rules and regulations of the SEC thereunder.

"GAAP" means generally accepted accounting principles in the United States of America as applied by Ionis.

"***Governmental Authority***" means any Federal, state, provincial, local, municipal, foreign or other governmental or quasi-governmental authority, including without limitation 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.

"***HSR Act***" means Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended.

"***Intellectual Property***" shall mean 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.

"***Letter Agreement***" means that certain letter agreement, dated the Execution Date, between Biogen and Ionis.

"***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 Ionis or Biogen, as the case may be, taken as a whole, (b) that when taken as a whole, has or would reasonably be expected to have a material adverse effect on (i) the Licensed Technology taken as a whole, (ii) the practice of the Licensed Technology taken as a whole and as contemplated by the Collaboration Agreement or (iii) the Development, Manufacture or Commercialization of Compounds or Products for Neurology Targets as contemplated by the Collaboration Agreement, or (c) that materially impairs the ability of Ionis or Biogen to perform its obligations pursuant to the transactions contemplated by this Agreement or the Collaboration Agreement. The capitalized terms used in this definition and not otherwise defined in this Agreement have the meanings given to them in the Collaboration Agreement.

"Nasdaq" means The Nasdaq Global Select Market.

"Proxyholder" means Ionis Pharmaceuticals, Inc. and its Chief Executive Officer and/or Chief Operating Officer, in their capacities as such officers of Ionis Pharmaceuticals, Inc.

"SEC" means the United States Securities and Exchange Commission or any successor entity.

"Securities Act" means the Securities Act of 1933, as amended, and the rules and regulations of the SEC thereunder.

APPENDIX 2

REGISTRATION RIGHTS GRANTED BY IONIS TO BIOGEN

1.1 PIGGYBACK REGISTRATIONS. Ionis will notify Biogen in writing at least 15 days prior to the filing of any registration statement under the Securities Act for purposes of a public offering of securities of Ionis (including, but not limited to, registration statements relating to secondary offerings of securities of Ionis, but excluding Special Registration Statements) and will afford Biogen an opportunity to include in such registration statement all or part of the Shares held by Biogen. If Biogen wishes to include in any such registration statement all or any part of the Shares held by Biogen, it will, within 15 days after the above-described notice from Ionis, so notify Ionis in writing. Such notice will state the intended method of disposition of the Shares by Biogen. If Biogen decides not to include all of its Shares in any registration statement thereafter filed by Ionis, Biogen will nevertheless continue to have the right to include any Shares in any subsequent registration statement or registration statements as may be filed by Ionis with respect to offerings of its securities, all upon the terms and conditions set forth herein. ***"Special Registration Statement"*** means (i) a registration statement relating to any employee benefit plan, including but not limited to any employee equity plan or employee stock purchase plan or (ii) with respect to any corporate reorganization or transaction under Rule 145 of the Securities Act, any registration statements related to the issuance or resale of securities issued in such a transaction or (iii) a registration related to stock issued upon conversion of debt securities.

(a) Underwriting. If the registration statement of which Ionis gives notice under this Section 1.1 is for an underwritten offering, Ionis will so advise Biogen. In such event, the right of Biogen to include Shares in a registration pursuant to this Section 1.1 will be conditioned upon Biogen's participation in such underwriting and the inclusion of Biogen's Shares in the underwriting to the extent provided herein. If Biogen proposes to distribute its Shares through such underwriting, it will enter into an underwriting agreement in customary form with the underwriter or underwriters selected for such underwriting by Ionis. Notwithstanding any other provision of this Agreement, if the underwriter determines in good faith that marketing factors require a limitation of the number of shares to be underwritten, the number of shares that may be included in the underwriting will be allocated first to Ionis, and then any remaining shares will be allocated among Biogen and any other third parties who have a contractual right to participate in such underwriting (and have elected to so participate) on a *pro rata* basis based on the total number of shares of Common Stock held by Biogen and such third parties. If Biogen disapproves of the terms of any such underwriting, Biogen may elect to withdraw therefrom by written notice to Ionis and the underwriter, delivered at least ten (10) business days prior to the effective date of the registration statement. Any Shares excluded or withdrawn from such underwriting will be excluded and withdrawn from the registration.

(b) Right to Terminate Registration. Ionis will have the right to terminate or withdraw any registration initiated by it under this Section 1.1 whether or not Biogen has elected to include securities in such registration.

1.2 FORM S-3 REGISTRATION. Biogen may send Ionis a written request (a ***"Biogen S-3 Registration Request"***) or requests that Ionis effect a registration on Form S-3 (or any successor to Form S-3) or any similar short-form registration statement and any related qualification or compliance with respect to all or a part of the Shares owned by Biogen, and in such case Ionis will as soon as practicable, effect such registration and all such qualifications and compliances as may be so requested and as would permit or facilitate the sale and distribution of all or such portion of Biogen's Shares as are specified in such request; *provided, however*, that Ionis will not be obligated to effect any such registration, qualification or compliance pursuant to this Section 1.2:

(a) if Form S-3 is not available for such offering by Biogen;

(b) if Biogen, together with the holders of any other securities of Ionis entitled to inclusion in such registration, propose to sell Shares and such other securities (if any) at an aggregate price to the public of less than $50,000,000;

(c) if within thirty (30) days of receipt of a written request from Biogen pursuant to this Section 1.2, Ionis gives notice to Biogen of Ionis' intention to make a public offering within ninety (90) days, other than pursuant to a Special Registration Statement; *provided*, that such right to delay a request will be exercised by Ionis not more than once in any twelve month period;

(d) if Ionis furnishes Biogen a certificate signed by the Chairman of the Board of Directors of Ionis stating that in the good faith judgment of Ionis' Board of Directors, it would be seriously detrimental to Ionis and its stockholders for such Form S-3 registration to be effected at such time, in which event Ionis will have the right to defer the filing of the Form S-3 registration statement for a period of not more than ninety (90) days after receipt of Biogen's request under this Section 1.2; *provided*, that such right to delay a request will be exercised by Ionis not more than once in any twelve month period;

(e) if Ionis has, within the twelve month period preceding the date of such request, already effected one registration on Form S-3 for Biogen pursuant to this Section 1.2, or

(f) in any particular jurisdiction in which Ionis would be required to qualify to do business or to execute a general consent to service of process in effecting such registration, qualification or compliance.

(g) Subject to the foregoing, Ionis will file a Form S-3 registration statement covering the Shares requested by Biogen for registration as soon as practicable after receipt of Biogen's requests.

1.3 Expenses of Registration. Biogen will bear Registration Expenses with respect to the Shares incurred in connection with any registration, qualification or compliance pursuant to Section 1.1 on a pro rata basis based upon the number of Shares registered over the total number of shares of Ionis' common stock (including Shares) registered under the applicable registration. All Registration Expenses with respect to the Shares incurred in connection with any registration, qualification or compliance pursuant to Section 1.2 herein will be borne by Biogen. Biogen will also be responsible for any underwriter discounts or other fees in connection with the Shares, and the cost of its own counsel, advisors and employees who facilitate any registration or offering of Shares under this Agreement. ***"Registration Expenses"*** will mean all reasonable, documented expenses incurred by the Ionis in complying with Sections 1.1 or 1.2, including, without limitation, all registration and filing fees, printing expenses, fees and disbursements of Ionis' counsel, blue sky fees, and the expense of any audits, comfort letters or consents incident to or required by any such registration, and the fully-burdened full time equivalent rate of Ionis' employees who conduct activities related to any registration or offering of Shares under this Agreement·

1.4 Obligations of Ionis. Whenever required to effect the registration of any Shares, Ionis will, as expeditiously as reasonably possible:

(a) prepare and file with the SEC a registration statement with respect to such Shares and use all commercially reasonable efforts to cause such registration statement to become effective, and, upon Biogen's request, keep such registration statement effective for up to 30 days or, if earlier, until Biogen has completed the distribution related thereto; *provided*, *however*, that at any time, upon written notice to Biogen and for a period not to exceed 60 days thereafter (the "***Suspension Period***"), Ionis may delay the filing or effectiveness of any registration statement or suspend the use of any registration statement (and Biogen hereby agrees not to offer or sell any Shares pursuant to such registration statement during the Suspension Period) if Ionis reasonably believes that there is or may be in existence material nonpublic information or events involving Ionis, the failure of which to be disclosed in the prospectus included in the registration statement could result in a Violation (as defined below). If Ionis will exercise its right to delay the filing or effectiveness or suspend the use of a registration hereunder, the applicable time period during which the registration statement is to remain effective will be extended by a period of time equal to the duration of the Suspension Period. Ionis may extend the Suspension Period for an additional consecutive sixty (60) days with Biogen's consent, which consent will not be unreasonably withheld. If so directed by Ionis, Biogen will (i) not offer to sell any Shares pursuant to the registration statement during the period in which the delay or suspension is in effect after receiving notice of such delay or suspension; and (ii) use its commercially reasonable efforts to deliver to Ionis (at Ionis' expense) all copies, other than permanent file copies then in Biogen's possession, of the prospectus relating to such Shares current at the time of receipt of such notice. Notwithstanding the foregoing, Ionis will not be required to file, cause to become effective or maintain the effectiveness of any registration statement other than a registration statement on Form S-3 that contemplates a distribution of securities on a delayed or continuous basis pursuant to Rule 415 under the Securities Act.

(b) Prepare and file with the SEC such amendments and supplements to such registration statement and the prospectus used in connection with such registration statement as may be necessary to comply with the provisions of the Securities Act with respect to the disposition of all securities covered by such registration statement for the period set forth in subsection (a) above.

(c) Furnish Biogen such number of copies of a prospectus, including a preliminary prospectus, in conformity with the requirements of the Securities Act, and such other documents as it may reasonably request in order to facilitate the disposition of the registered Shares.

(d) Use its commercially reasonable efforts to register and qualify the securities covered by such registration statement under such other securities or blue sky laws of such jurisdictions as will be reasonably requested by Biogen; *provided* that Ionis will not be required in connection therewith or as a condition thereto to qualify to do business or to file a general consent to service of process in any such states or jurisdictions.

(e) In the event of any underwritten public offering, enter into and perform its obligations under an underwriting agreement, in usual and customary form, with the managing underwriter(s) of such offering. If Biogen participates in such underwriting Biogen will also enter into and perform its obligations under such an agreement.

(f) With respect to Shares covered by such registration statement, notify Biogen at any time when a prospectus relating thereto is required to be delivered under the Securities Act of the happening of any event as a result of which the prospectus included in such registration statement, as then in effect, includes an untrue statement of a material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances then existing. Ionis will use commercially reasonable efforts to amend or supplement such prospectus in order to cause such prospectus not to include any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances then existing.

(g) Use its commercially reasonable efforts to furnish, on the date that such Shares are delivered to the underwriters for sale, if such securities are being sold through underwriters, (i) an opinion, dated as of such date, of the counsel representing Ionis for the purposes of such registration, in form and substance as is customarily given to underwriters in an underwritten public offering, addressed to the underwriters, if any, and (ii) a letter, dated as of such date, from the independent certified public accountants of Ionis, in form and substance as is customarily given by independent certified public accountants to underwriters in an underwritten public offering addressed to the underwriters.

1.5 FURNISHING INFORMATION.

(a) If Biogen elects to register any Shares pursuant to Sections 1.1 and 1.2, Biogen will furnish Ionis such information regarding itself, the Shares held by it and the intended method of disposition of such securities as will be required to effect the registration of its Shares.

(b) Ionis will have no obligation with respect to any registration requested pursuant to Section 1.2 if the number of Shares or the anticipated aggregate offering price of the securities to be registered thereunder does not equal or exceed the number of shares or the anticipated aggregate offering price required to originally trigger Ionis' obligation to initiate such registration as specified in Section 1.2.

1.6 INDEMNIFICATION. If any Shares are included in a registration statement under Sections 1.1 or 1.2:

(a) To the extent permitted by law, Ionis will indemnify and hold harmless Biogen, its officers and directors, as applicable, any underwriter (as defined in the Securities Act) for Biogen and each person, if any, who controls Biogen or such underwriter within the meaning of the Securities Act or the Exchange Act, against any losses, claims, damages, or liabilities (joint or several) to which they may become subject under the Securities Act, the Exchange Act or other federal or state law, insofar as such losses, claims, damages or liabilities (or actions in respect thereof) arise out of or are based upon any of the following statements, omissions or violations (collectively a "***Violation***") by Ionis: (i) any untrue statement or alleged untrue statement of a material fact contained in such registration statement or incorporated by reference therein, including any preliminary prospectus or final prospectus contained therein or any amendments or supplements thereto, (ii) the omission or alleged omission to state therein a material fact required to be stated therein, or necessary to make the statements therein not misleading, or (iii) any violation or alleged violation by Ionis of the Securities Act, the Exchange Act, any state securities law or any rule or regulation promulgated under the Securities Act, the Exchange Act or any state securities law in connection with the offering covered by such registration statement; and Ionis will reimburse each such indemnified party for any legal or other expenses reasonably incurred by them in connection with investigating or defending any such loss, claim, damage, liability or action; *provided however*, that the indemnity agreement contained in this Section 1.6(a) will not apply to amounts paid in settlement of any such loss, claim, damage, liability or action if such settlement is effected without Ionis' consent, which consent will not be unreasonably withheld, nor will Ionis be liable in any such case for any such loss, claim, damage, liability or action to the extent that it arises out of or is based upon a Violation which occurs in reliance upon and in conformity with written information furnished expressly for use in connection with such registration by any of such indemnified parties.

(b) To the extent permitted by law, Biogen will, if Shares are included in the securities as to which such registration qualifications or compliance is being effected, indemnify and hold harmless Ionis, each of its directors, its officers and each person, if any, who controls Ionis within the meaning of the Securities Act, and any underwriter and any other third party, as applicable, selling securities under such registration statement, against any losses, claims, damages or liabilities (joint or several) to which Ionis or any such director, officer, controlling person, underwriter or other third party who may become subject under the Securities Act, the Exchange Act or other federal or state law, insofar as such losses, claims, damages or liabilities (or actions in respect thereto) arise out of or are based upon any of the following statements: (i) any untrue statement or alleged untrue statement of a material fact contained in such registration statement or incorporated reference therein, including any preliminary prospectus or final prospectus contained therein or any amendments or supplements thereto, (ii) the omission or alleged omission to state therein a material fact required to be stated therein, or necessary to make the statements therein not misleading, or (iii) any violation or alleged violation by Ionis of the Securities Act (collectively, a "***Biogen Violation***"), in each case to the extent (and only to the extent) that such Biogen Violation occurs in reliance upon and in conformity with written information furnished by Biogen under an instrument duly executed by Biogen and stated to be specifically for use in connection with such registration; and Biogen will reimburse any legal or other expenses reasonably incurred by Ionis or any such director, officer, controlling person, underwriter or other third party in connection with investigating or defending any such loss, claim, damage, liability or action if it is judicially determined that there was such a Biogen Violation; *provided, however,* that the indemnity agreement contained in this Section 1.6(b) will not apply to amounts paid in settlement of any such loss, claim, damage, liability or action if such settlement is effected without Biogen's consent, which consent will not be unreasonably withheld; *provided further*, that in no event will any indemnity under this Section 1.6 exceed the net proceeds from the offering received by Biogen, as applicable.

(c) Promptly after receipt by an indemnified party under this Section 1.6 of notice of the commencement of any action (including any governmental action), such indemnified party will, if a claim in respect thereof is to be made against any indemnifying party under this Section 1.6, deliver to the indemnifying party a written notice of the commencement thereof and the indemnifying party will have the right to participate in, and, to the extent the indemnifying party so desires, jointly with any other indemnifying party similarly noticed, to assume the defense thereof with counsel mutually satisfactory to the parties; *provided, however,* that an indemnified party will have the right to retain its own counsel, with the fees and expenses thereof to be paid by the indemnifying party, if representation of such indemnified party by the counsel retained by the indemnifying party would be inappropriate due to actual or potential differing interests between such indemnified party and any other party represented by such counsel in such proceeding. The failure to deliver written notice to the indemnifying party within a reasonable time of the commencement of any such action will relieve such indemnifying party of any liability to the indemnified party under this Section 1.6 to the extent, and only to the extent, prejudicial to its ability to defend such action, but the omission so to deliver written notice to the indemnifying party will not relieve it of any liability that it may have to any indemnified party otherwise than under this Section 1.6.

(d) If the indemnification provided for in this Section 1.6 is held by a court of competent jurisdiction to be unavailable to an indemnified party with respect to any losses, claims, damages or liabilities referred to herein, the indemnifying party, in lieu of indemnifying such indemnified party thereunder, will to the extent permitted by applicable law contribute to the amount paid or payable by such indemnified party as a result of such loss, claim, damage or liability in such proportion as is appropriate to reflect the relative fault of the indemnifying party on the one hand and of the indemnified party on the other in connection with the Violation(s) or Biogen Violation(s) that resulted in such loss, claim, damage or liability, as well as any other relevant equitable considerations. The relative fault of the indemnifying party and of the indemnified party will be determined by a court of law by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission to state a material fact relates to information supplied by the indemnifying party or by the indemnified party and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission; *provided*, *that* in no event will any contribution by Biogen hereunder exceed the net proceeds from the offering received by Biogen.

(e) The obligations of Ionis and Biogen under this Section 1.6 will survive completion of any offering of Shares, as applicable, in a registration statement and, with respect to liability arising from an offering to which this Section 1.6 would apply that is covered by a registration filed before termination of this Agreement, such termination. No indemnifying party, in the defense of any such claim or litigation, will, except with the consent of each indemnified party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to such indemnified party of a release from all liability in respect to such claim or litigation.

1.7 Assignment of Registration Rights. The rights to cause Ionis to register Shares pursuant to this Appendix 2 may be assigned by a Holder to a single transferee or assignee of Shares (for so long as such registration rights remain in effect) that (a) is an Affiliate of Biogen that is a corporation, partnership or limited liability company, or (b) acquires all of Biogen's Shares in connection with the sale of all or substantially all of such Biogen's business; *provided, however*, (i) the transferor will, within ten 10 days after such transfer, furnish Ionis written notice of the name and address of such transferee or assignee and the securities with respect to which such registration rights are being assigned and (ii) such transferee will agree to be subject to all restrictions set forth in this Agreement.

1.8 "Market Stand-Off" Agreement. Biogen hereby agrees that, if requested by the underwriters in any offering in which Biogen includes Shares, it will execute a customary lockup agreement in connection with any Shares that are not included in such underwritten offering.

1.9 Agreement to Furnish Information. Biogen hereby agrees to execute and deliver such other agreements as may be reasonably requested by Ionis or the underwriter that are consistent with Biogen's obligations under Section 1.8, as applicable, or that are necessary to give further effect thereto. In addition, if requested by Ionis or the representative of the underwriters of Ionis' Common Stock, Biogen will provide, within ten days of such request, such information as may be required by Ionis or such representative in connection with the completion of any public offering of Ionis' securities pursuant to a registration statement filed under the Securities Act. The obligations described in Section 1.8 and this Section 1.9 will not apply to a Special Registration Statement. Ionis may impose stop-transfer instructions with respect to the shares of Common Stock (or other securities) subject to the foregoing restriction until the end of said ten (10) day period. The underwriters of Ionis' Common Stock (or other securities) are intended third party beneficiaries of Sections 1.8 and 1.9 and will have the right, power and authority to enforce the provisions hereof as though they were a party hereto.

1.10 Rule 144 Reporting. With a view to making available to Biogen the benefits of certain rules and regulations of the SEC which may permit the sale of the Shares to the public without registration, Ionis agrees to use its reasonable best efforts to:

(a) Make and keep public information available, as those terms are understood and defined in SEC 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 Ionis for an offering of its securities to the general public; and

(b) File with the SEC, in a timely manner, all reports and other documents required of Ionis under the Exchange Act.

1.11 Termination of Registration Rights. Biogen's right to request registration or inclusion of Shares in any registration pursuant to Sections 1.1 or 1.2 hereof will terminate upon such time as all Shares may be sold pursuant to Rule 144 during any 90 day period.

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 7, 2018

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 7, 2018

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

CERTIFICATION

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

1. The Company's Quarterly Report on Form 10-Q for the period ended June 30, 2018, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: August 7, 2018

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	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.