UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 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 April 30, 2018 was 125,520,380.

IONIS PHARMACEUTICALS, INC.
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TRADEMARKS

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

	March 31, 2018	December 31, 2017 (as revised*)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 227,505	$ 129,630
Short-term investments	807,796	893,085
Contracts receivable	36,858	62,955
Inventories	9,060	9,982
Other current assets	62,064	73,082
Total current assets	1,143,283	1,168,734
Property, plant and equipment, net	123,188	121,907
Patents, net	22,914	22,004
Deposits and other assets	10,175	10,129
Total assets	$ 1,299,560	$ 1,322,774
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 13,833	$ 24,886
Accrued compensation	12,166	25,151
Accrued liabilities	66,470	66,618
Current portion of long-term obligations	47	1,621
Current portion of deferred contract revenue	120,127	125,336
Total current liabilities	212,643	243,612
Long-term deferred contract revenue	85,446	108,026
1 percent convertible senior notes	541,635	533,111
Long-term obligations, less current portion	12,946	12,974
Long-term mortgage debt	59,789	59,771
Total liabilities	912,459	957,494
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 125,448,746 and 124,976,373 shares issued and outstanding at March 31, 2018 and December 31, 2017, respectively	125	125
Additional paid-in capital	1,576,954	1,553,681
Accumulated other comprehensive loss	(33,234)	(31,759)
Accumulated deficit	(1,242,454)	(1,241,034)
Total Ionis stockholders' equity	301,391	281,013
Noncontrolling interest in Akcea Therapeutics, Inc.	85,710	84,267
Total stockholders' equity	387,101	365,280
Total liabilities and stockholders' equity	$ 1,299,560	$ 1,322,774

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

See accompanying notes.

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

	Three Months Ended March 31, 2017	
	2018	**2017**
Revenue:		**(as revised*)**
Commercial revenue:		
SPINRAZA royalties	$ 41,081	$ 5,211
Licensing and other royalty revenue	942	2,590
Total commercial revenue	42,023	7,801
Research and development revenue under collaborative agreements	102,396	107,999
Total revenue	144,419	115,800
Expenses:		
Research, development and patent	104,067	82,638
Selling, general and administrative	43,653	13,677
Total operating expenses	147,720	96,315
Income (loss) from operations	(3,301)	19,485
Other income (expense):		
Investment income	3,610	2,280
Interest expense	(10,938)	(11,363)
Other expenses	(168)	(1,438)
Income (loss) before income tax expense	(10,797)	8,964
Income tax expense	(15)	—
Net income (loss)	(10,812)	8,964
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	9,392	—
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (1,420)	$ 8,964
Basic net income (loss) per share	$ (0.01)	$ 0.07
Shares used in computing basic net income (loss) per share	125,330	122,861
Diluted net income (loss) per share	$ (0.01)	$ 0.07
Shares used in computing diluted net income (loss) per share	125,330	124,972

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

See accompanying notes.

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

	Three Months Ended March 31,	
	2018	**2017**
		(as revised*)
Net income (loss)	$ (10,812)	$ 8,964
Unrealized gains (losses) on debt securities, net of tax	(1,530)	266
Reclassification adjustment for realized gains included in net income (loss)	—	(374)
Currency translation adjustment	55	(6)
Comprehensive income (loss)	(12,287)	8,850
Comprehensive loss attributable to noncontrolling interests	9,423	—
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. stockholders	$ (2,864)	$ 8,850

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

See accompanying notes.

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

	Three Months Ended March 31,	
	2018	**2017**
Operating activities:		**(as revised*)**
Net income (loss)	$ (10,812)	$ 8,964
Adjustments to reconcile net income (loss) to net cash provided by operating activities:		
Depreciation	2,363	1,980
Amortization of patents	443	393
Amortization of premium on investments, net	1,192	1,608
Amortization of debt issuance costs	441	396
Amortization of convertible senior notes discount	8,083	7,506
Amortization of long-term financing liability for leased facility	—	1,675
Stock-based compensation expense	28,451	20,912
Gain on investment in Regulus Therapeutics, Inc.	—	(374)
Non-cash losses related to patents, licensing and property, plant and equipment	175	93
Changes in operating assets and liabilities:		
Contracts receivable	26,097	38,686
Inventories	922	688
Other current and long-term assets	11,422	(14,077)
Accounts payable	(13,144)	472
Accrued compensation	(12,985)	(15,919)
Accrued liabilities and deferred rent	(1,695)	(6,273)
Deferred contract revenue	(27,788)	75,935
Net cash provided by operating activities	13,165	122,665
Investing activities:		
Purchases of short-term investments	(91,157)	(266,185)
Proceeds from the sale of short-term investments	173,724	99,223
Purchases of property, plant and equipment	(2,343)	(3,237)
Acquisition of licenses and other assets, net	(738)	(983)
Proceeds from the sale of Regulus Therapeutics stock	—	2,507
Net cash provided by (used in) investing activities	79,486	(168,675)
Financing activities:		
Proceeds from equity awards	5,675	6,324
Proceeds from the issuance of common stock to Novartis	—	71,640
Stock issuance costs paid	(451)	(778)
Principal payments on debt and capital lease obligations	—	(1,640)
Net cash provided by financing activities	5,224	75,546
Net increase in cash and cash equivalents	97,875	29,536
Cash and cash equivalents at beginning of period	129,630	84,685
Cash and cash equivalents at end of period	$ 227,505	$ 114,221
Supplemental disclosures of cash flow information:		
Interest paid	$ 644	$ 106
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 2,091	$ 1,648
Unpaid deferred offering costs	$ —	$ 319

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

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three months ended March 31, 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 subsidiary, Akcea Therapeutics, Inc., which we formed in December 2014. In July 2017, Akcea completed an initial public offering, or IPO. As of July 19, 2017, the closing of the IPO, and at March 31, 2018, we owned approximately 68 percent of Akcea.

In April 2018, we received 8 million shares of Akcea's stock for the license of TEGSEDI (inotersen) 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. We will reflect this increase in our ownership percentage in the second quarter of 2018. Refer to the noncontrolling interest in Akcea section 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 subsidiary, 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. Below is a summary of the change from our first quarter 2017 revenue under Topic 605 to the new Topic 606 guidance:

The following table summarizes the adjustments we were required to make to revenue we originally reported at March 31, 2017 to adopt Topic 606 (in thousands):

	Three Months Ended March 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 5,211	$ —	$ 5,211
Licensing and other royalty revenue	3,547	(957)	2,590
Total commercial revenue	8,758	(957)	7,801
Research and development revenue under collaborative agreements	101,546	6,453	107,999
Total revenue	$ 110,304	$ 5,496	$ 115,800

During the first quarter of 2017, our revenue increased $5.5 million 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 a $10.3 million increase in our revenue for the first quarter of 2017.
- 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 $3.8 million decrease in our revenue for the first quarter of 2017.

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.

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 in exchange for upfront fees, license fees, milestone payments, royalties and/or profit sharing arrangements. 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 in certain cases 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.

Additionally, 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, royalties or profit share arrangements. At the start of an agreement, our transaction price usually only consists of 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.

Our most common type of variable consideration are milestone payments. 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 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 appropriate 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
- An appropriate 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 and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the R&D 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 that if they change over the course of the collaboration, may affect the timing and amount of revenue that we recognize in the current and future periods.

During the three months ended March 31, 2017, we recognized $8.2 million of additional revenue related to changes in our estimates. The additional revenue was primarily from our Biogen collaboration for IONIS-DMPK$_{Rx}$ because we shortened our estimated period of performance. Slightly offsetting this increase was a decrease in revenue related to changes in estimates for our collaboration with Roche for IONIS-HTT$_{Rx}$ (RG6042) because we increased our estimated total effort required to satisfy our performance obligation. During the three months ended March 31, 2018, we recognized $0.5 million of additional revenue related to changes in our estimated period of performance under our neurology collaboration with Biogen.

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

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, therefore, 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 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 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.

Royalties

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.

Amendments to Agreements

From time to time we amend our collaboration agreements. For these agreements, 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 under the amendment are distinct 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 under the amendment, we then assess whether the additional goods or services are distinct under the original agreement. If the goods and/ or services are distinct under the original agreement 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 they are not distinct from the original agreement, 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 the 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 are 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 we are required to account for them as a combined arrangement.

For example, in the first quarter of 2017, we and Akcea entered into two separate agreements with Novartis at the same time: a collaboration agreement and a stock purchase agreement, or SPA. We evaluated the Novartis 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 Novartis collaboration.

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 the instances in which we have billed our customers or received payment from our customers in advance of satisfying our performance obligation, we include the amounts in deferred revenue on our condensed consolidated balance sheet. During the three months ended March 31, 2018 and 2017, we recognized $34.9 million and $26.7 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	$ 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's stock and consolidated 100 percent of Akcea's results in our financial statements. In connection with Akcea's IPO, Akcea sold shares of its common stock to third parties. We owned approximately 68 percent of Akcea after the IPO and at March 31, 2018. In April 2018, we received 8 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. We will reflect this increase in our ownership percentage in the second quarter of 2018. 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 for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses 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 March 31, 2018, we held an equity investment in one publicly held company, Antisense Therapeutics Limited, or ATL. Our other investments were in five privately-held companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Kastle Therapeutics, 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 equity investments, except those accounted for under the equity method of accounting that have a readily determinable fair value, at fair value and for us to recognize the changes in fair value in our consolidated statement of operations. Prior to 2018, we recognized unrealized gains and losses through accumulated other comprehensive income. For investments without a readily determinable fair value, beginning in 2018, we are accounting for these investments 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. Prior to 2018, we accounted for our equity investments in privately held companies under the cost method of accounting. 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 three months ended March 31, 2018 and 2017. Total inventory was $9.1 million and $10.0 million as of March 31, 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 management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Basic and diluted 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 months ended March 31, 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.

Our basic net loss per share for the three months ended March 31, 2018, was calculated as follows (in thousands, except per share amounts):

Three months ended March 31, 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Income (Loss) Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	45,448	$ (0.44)	$ (19,997)
Akcea's net loss attributable to our ownership			$ (19,997)
Ionis' stand-alone net income			18,785
Net loss available to Ionis common stockholders			$ (1,212)
Weighted average shares outstanding			125,330
Basic net loss per share			$ (0.01)

For the three months ended March 31, 2017, we owned 100 percent of Akcea. As a result, we did not have to adjust our earnings per share calculation. For the three months ended March 31, 2017, we had net income. 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 three months ended March 31, 2017 consisted of the following (in thousands except per share amounts):

Three months ended March 31, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 8,964	122,861	$ 0.07
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,674	
Shares issuable upon restricted stock award issuance	—	377	
Shares issuable related to our ESPP	—	60	
Income available to Ionis common stockholders	$ 8,964	124,972	$ 0.07

For the three months ended March 31, 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

Accumulated other comprehensive loss is primarily comprised of unrealized gains and losses on investments, net of taxes and adjustments we made 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 months ended March 31, 2018 and 2017 (in thousands):

	Three Months Ended March 31,	
	2018	2017
Beginning balance accumulated other comprehensive loss	$ (31,759)	$ (30,358)
Unrealized gains (losses) on securities, net of tax (1)	(1,530)	266
Amounts reclassified from accumulated other comprehensive income (2)	—	(374)
Currency translation adjustment	55	6
Net current period other comprehensive loss	(1,475)	(102)
Ending balance accumulated other comprehensive loss	$ (33,234)	$ (30,460)

(1) There was no tax benefit for other comprehensive loss for the three months ended March 31, 2018 and 2017.

(2) Amounts are included in investment income on our condensed consolidated statement of operations.

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 performed 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 three months ended March 31, 2018 and 2017, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2018	**2017**
Risk-free interest rate	2.2%	1.8%
Dividend yield	0.0%	0.0%
Volatility	63.2%	66.3%
Expected life	4.6 years	4.5 years

ESPP:

	Three Months Ended March 31,	
	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 three months ended March 31, 2018 was $53.22 per share.

We did not grant stock options or RSUs to our Board of Directors during the three months ended March 31, 2018 or 2017.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2018 and 2017 (in thousands). Our non-cash stock-based compensation expense includes $6.4 million and $3.2 million of stock-based compensation expense for Akcea employees for the three months ended March 31, 2018 and 2017, respectively.

	Three Months Ended March 31,	
	2018	**2017**
Research, development and patent	$ 19,682	$ 16,122
Selling, general and administrative	8,769	4,790
Total	$ 28,451	$ 20,912

As of March 31, 2018, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $90.7 million and $40.4 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 1.5 years and 1.9 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 must adopt the new standard on a modified retrospective basis, which requires us to reflect our leases on our balance sheet for the earliest comparative period presented. We plan to adopt this guidance on January 1, 2019. We are currently 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. This change will result in us remeasuring 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.

3. Investments

As of March 31, 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 March 31, 2018:

One year or less	77%
After one year but within two years	18%
After two years but within three and a half years	5%
Total	100%

As illustrated above, at March 31, 2018, 95 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 March 31, 2018, we had an ownership interest of less than 20 percent in five private companies and one public company with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Kastle Therapeutics, 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):

March 31, 2018	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 433,297	$ 1	$ (1,286)	$ 432,012
Debt securities issued by U.S. government agencies	129,235	—	(323)	128,912
Debt securities issued by the U.S. Treasury (2)	54,076	1	(43)	54,034
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	31,624	1	(194)	31,431
Total securities with a maturity of one year or less	648,232	3	(1,846)	646,389
Corporate debt securities	126,128	5	(1,807)	124,326
Debt securities issued by U.S. government agencies	21,547	—	(162)	21,385
Debt securities issued by states of the U.S. and political subdivisions of the states	52,746	—	(785)	51,961
Total securities with a maturity of more than one year	200,421	5	(2,754)	197,672
Total available-for-sale securities	$ 848,653	$ 8	$ (4,600)	$ 844,061

December 31, 2017	Cost (1)	Gross Unrealized Gains	Gross Unrealized 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 March 31, 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	420	$ 470,960	$ (2,308)	$ 71,370	$ (785)	$ 542,330	$ (3,093)
Debt securities issued by U.S. government agencies	52	124,729	(397)	25,569	(88)	150,298	(485)
Debt securities issued by the U.S. Treasury	7	32,329	(43)	—	—	32,329	(43)
Debt securities issued by states of the U.S. and political subdivisions of the states	50	48,477	(588)	32,145	(391)	80,622	(979)
Total temporarily impaired securities	529	$ 676,495	$ (3,336)	$ 129,084	$ (1,264)	$ 805,579	$ (4,600)

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 three months ended March 31, 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 March 31, 2018 and December 31, 2017 that are regularly measured and carried at fair value. 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 March 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 138,350	$ 138,350	$ —
Corporate debt securities (2)	556,338	—	556,338
Debt securities issued by U.S. government agencies (3)	150,297	—	150,297
Debt securities issued by the U.S. Treasury (3)	54,034	54,034	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	83,392	—	83,392
Total	$ 982,411	$ 192,384	$ 790,027

	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 March 31, 2018, $14.6 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 will not purchase additional shares of Ionis stock. Therefore, this asset no longer had any value and we wrote-off the remaining balance to other expenses in the third quarter of 2017.

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 three months ended March 31, 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 three months ended March 31, 2017	(1,438)
Ending balance of Level 3 instruments at March 31, 2017	$ 3,597

At March 31, 2018 and December 31, 2017, we did not have any financial instruments that were valued using Level 3 inputs.

Convertible Notes

Our 1 percent notes had a fair value of $729.1 million at March 31, 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 March 31, 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 Partnerships

AstraZeneca

Cardiac, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a strategic 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 drug development candidates 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 March 2018, we have received over $124 million in upfront fees, license fees, milestone payments, and other payments under this cardiac, renal and metabolic diseases collaboration. We will achieve the next payment of $10 million under this collaboration if we advance a drug under this collaboration.

At commencement of our 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 over our period of performance, estimated through 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 March 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 additional to danvatirsen, 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 development candidate 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 the 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 March 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 commencement of our 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 another 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 months ended March 31, 2018 and 2017, we earned R&D revenue of $68.4 million and $4.9 million, respectively, from our relationship with AstraZeneca, which represented 47 percent and 4 percent, respectively, of our total revenue for those periods. Our balance sheets at March 31, 2018 and December 31, 2017 included deferred revenue of $51.3 million and $57.7 million, respectively, related to our relationship with AstraZeneca.

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 March 2018, we have received over $800 million from our Biogen collaborations. In April 2018, we and Biogen expanded our strategic collaboration to develop novel antisense drugs or a broad range of neurological diseases. We will receive $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, upon receiving clearance under the Hart-Scott Rodino Antitrust Improvements Act.

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 March 2018, we earned $155 million in revenue from SPINRAZA royalties. In addition to SPINRAZA royalties, from inception through March 2018, we have received $436 million in payments for advancing SPINRAZA. We are receiving tiered royalties up to the mid-teens 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 the milestone payment became probable because we did not have a performance obligation related to the 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 March 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 commencement of our 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 $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 over our period of performance, estimated through December 2020. From inception through March 2018, we have included $40 million in total payments in the transaction price for our R&D services performance obligation.

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 March 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 other modalities are chosen, 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 March 2018, we have received over $165 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 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 over our period of performance, estimated through March 2019. From inception through March 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 commencement of our 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 over our period of performance, estimated through December 2020.

Expanded Strategic Neurology Collaboration

In April 2018, we and Biogen expanded our strategic collaboration to develop novel antisense drug candidates for a broad range of neurological diseases. 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. The key terms of the collaboration are as follows:

- We will receive $1 billion, which will include $625 million to purchase 11,501,153 shares of our stock at a price of $54.34 per share, an approximately 25 percent cash premium, and a $375 million upfront payment;
- We are eligible to receive significant milestone payments and license fees of up to $270 million for each successful drug, plus royalties up to 20 percent on global net sales;
- Biogen will assume responsibility for development and commercialization activities and costs once we identify a drug for development;

Our expanded collaboration is subject to customary closing conditions and clearances, including clearance under the Hart-Scott Rodino Antitrust Improvements Act.

During the three months ended March 31, 2018, we earned revenue of $51.9 million from our relationship with Biogen, comprised of $41.1 million in royalties on sales of SPINRAZA and $10.8 million in R&D revenue. Our revenue from Biogen represented 36 percent of our total revenue for the three months ended March 31, 2018. In comparison, we earned revenue of $28.7 million for the same period in 2017, comprised of $5.2 million in royalties on sales of SPINRAZA and $23.5 million in R&D revenue. Our revenue from Biogen represented 25 percent of our total revenue for the three months ended March 31, 2017. Our condensed consolidated balance sheet at March 31, 2018 and December 31, 2017 included deferred revenue of $84.6 million and $93.6 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

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 our 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 March 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 commencement of our 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 related to our R&D services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation, estimated through May 2019.

During the three months ended March 31, 2018 and 2017, we earned R&D revenue of $0.6 million and $65.2 million, respectively, from our relationship with Bayer. Our revenue from Bayer for the three months ended March 31, 2017 represented 56 percent of our total revenue for that period. Our condensed consolidated balance sheet at March 31, 2018 and December 31, 2017 included deferred revenue of $8.7 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 March 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 chooses another target to advance under this collaboration.

At commencement of our 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 are distinct from our other performance obligation. 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 months ended March 31, 2018 and 2017, we earned R&D revenue of $0.1 million and $2.5 million, respectively, from our relationship with Janssen. Our condensed consolidated balance sheet at March 31, 2018 included deferred revenue of $2.8 million, related to our relationship with Janssen. We did not have any deferred revenue from our relationship with Janssen at December 31, 2017.

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 of our common stock at a premium if an IPO did not occur by April 2018.

At commencement of our 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, currently estimated to be through December 2018 and June 2019, respectively. We recognized the amount attributed to the API supply for AKCEA-APOCIII-L_{Rx} when we delivered it to Novartis in 2017. We will recognize the amount attributed to the API supply for AKCEA-APO(a)-L_{Rx} as we deliver it to Novartis.

Akcea is responsible for the development activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue and Akcea recognizes the fees as R&D expense. On a consolidated basis, we eliminate the sublicense fees.

During the three months ended March 31, 2018 and 2017, we earned R&D revenue of $17.1 million and $6.1 million from our relationship with Novartis, respectively. Our revenue from Novartis represented 12 percent of our total revenue for the three months ended March 31, 2018. Our condensed consolidated balance sheet at March 31, 2018 and December 31, 2017 included deferred revenue of $56.7 million and $70.7 million, respectively, related to our relationship with Novartis.

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 March 2018, we have received over $105 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 commencement of our 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 months ended March 31, 2018 we earned R&D revenue of $2.0 million from our relationship with Roche. During the three months ended March 31, 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 March 31, 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 March 2018, we have received more than $162 million in payments under this alliance with GSK. We will achieve the next payment of up to $15 million if GSK initiates a Phase 3 study for the HBV program.

At commencement of our 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 months ended March 31, 2018 and 2017, we earned R&D revenue of $0.1 million and $6.8 million, respectively, from our relationship with GSK. We did not have any deferred revenue from our relationship with GSK at March 31, 2018 or December 31, 2017.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics. In July 2017, Akcea completed an IPO and therefore beginning in July 2017, we no longer own 100 percent of Akcea. As of July 19, 2017, the closing of the IPO and at March 31, 2018, we owned approximately 68 percent of Akcea. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting a novel drug discovery platform we created 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 table shows our segment revenue and loss from operations for the three months ended March 31, 2018 and March 31, 2017 (as revised) (in thousands), respectively.

Three Months Ended March 31, 2018	**Ionis Core**	**Akcea Therapeutics**	**Elimination of Intercompany Activity**	**Total**
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 41,081	$ —	$ —	$ 41,081
Licensing and other royalty revenue	942	—	—	942
Total commercial revenue	$ 42,023	$ —	$ —	$ 42,023
R&D revenue under collaborative agreements	$ 90,517	$ 17,108	$ (5,229)	$ 102,396
Total segment revenue	$ 132,540	$ 17,108	$ (5,229)	$ 144,419
Total operating expenses	$ 105,544	$ 47,435	$ (5,259)	$ 147,720
Income (loss) from operations	$ 26,996	$ (30,327)	$ 30	$ (3,301)

Three Months Ended March 31, 2017 (as revised)	**Ionis Core**	**Akcea Therapeutics**	**Elimination of Intercompany Activity**	**Total**
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 5,211	$ —	$ —	$ 5,211
Licensing and other royalty revenue	2,590	—	—	2,590
Total commercial revenue	$ 7,801	$ —	$ —	$ 7,801
R&D revenue under collaborative agreements	$ 153,382	$ 6,094	$ (51,477)	$ 107,999
Total segment revenue	$ 161,183	$ 6,094	$ (51,477)	$ 115,800
Total operating expense	$ 78,352	$ 69,470	$ (51,507)	$ 96,315
Income (loss) from operations	$ 82,831	$ (63,376)	$ 30	$ 19,485

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

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
March 31, 2018	$ 1,349,044	$ 252,466	$ (301,950)	$ 1,299,560
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 March 31,	
	2018	2017 (as revised)
Partner A	47 %	4 %
Partner B	36 %	25 %
Partner C	12 %	5 %
Partner D	0%	56%

Contracts receivables from one significant partner comprised approximately 87 percent of our contracts receivables at March 31, 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 $155 million in commercial revenue from SPINRAZA royalties.

Our pipeline also contains two near-term, potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential, TEGSEDI and WAYLIVRA. We licensed both of these drugs to Akcea Therapeutics, or Akcea, our affiliate focused on developing and commercializing drugs to treat patients with rare and serious diseases with leading-edge, RNA-targeted medicines. By licensing these drugs to Akcea, we believe we will maximize the commercial potential of each drug, while optimizing our commercial participation.

We believe TEGSEDI has the potential to become the preferred treatment option for many people with hereditary TTR amyloidosis, or 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. In May 2017, we reported positive top-line data from our Phase 3 study of TEGSEDI, NEURO-TTR, in patients with hATTR with polyneuropathy. More than half of these patients also have cardiomyopathy. We are advancing TEGSEDI to the market based on the positive data from our NEURO-TTR study. TEGSEDI is currently under regulatory review for marketing authorization in the U.S., EU, and Canada. The Food and Drug Administration, or FDA, accepted the TEGSEDI New Drug Application, or NDA, for Priority Review. In the second quarter of 2018 the FDA decided they needed additional time to review some of our responses to their standard information requests. As such, the FDA extended the review period for TEGSEDI. The new Prescription Drug User Fee Act, or PDUFA, date is October 6, 2018. The European Medicines Agency, or EMA, granted accelerated assessment to TEGSEDI, which may reduce standard review time. The EMA also granted Orphan Drug Designation to TEGSEDI. In Canada, our New Drug Submission, or NDS, was granted Priority Review by Health Canada. We and Akcea are on track in our pre-commercial preparations for a potential launch this year, assuming TEGSEDI is approved. Additionally, we and Akcea are continuing to build our TTR franchise by moving AKCEA-TTR-L_{Rx} forward rapidly.

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 our 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 and an advisory committee meeting is scheduled for May 10, 2018. WAYLIVRA was granted Priority Review in Canada. Akcea is on track in its pre-commercial preparations for a potential launch this year, assuming WAYLIVRA is approved.

In addition to preparing to commercialize TEGSEDI and WAYLIVRA, Akcea is focused on developing and commercializing 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 April 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 are continuing to advance our mid-stage drugs in development, which have the potential to enter late-stage clinical development and progress toward the market over the next several years, like IONIS-HTT_{Rx}. IONIS-HTT_{Rx} is the first drug in clinical development to target the cause of Huntington's disease, or HD, by reducing the production of toxic mutant huntingtin, or mHTT, protein. In addition to IONIS-HTT_{Rx}, we have multiple drugs that we or our partners plan to advance into pivotal studies in the next year or so. These include IONIS-STAT3-2.5_{Rx} for patients with head and neck cancer 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 strategic partnerships with Biogen and AstraZeneca through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas.

In April 2018, we and Biogen expanded our strategic collaboration to develop novel antisense drug candidates for a broad range of neurological diseases. We will receive $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 upon receiving Hart-Scott Rodino clearance. We believe this collaboration will provide us with the opportunity to continue to build a strong pipeline for Biogen and for our own account. We also have partnerships with 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. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through royalty and profit share arrangements. 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. We also have the potential to further increase our commercial revenue with WAYLIVRA and TEGSEDI, assuming they are approved. We believe we have the key elements in place to achieve sustained, long-term financial growth, with multiple drivers of revenue; a mature, broad and rapidly-advancing clinical pipeline; a partnership strategy that leverages our partner resources; and an innovative drug discovery technology platform that we continue to deploy across a range of therapeutic areas to address both rare and large patient populations.

Financial Highlights

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

	Three Months Ended March 31,	
	2018	**2017**
		(as revised)
Total revenue	$ 144,419	$ 115,800
Total operating expenses	$ 147,720	$ 96,315
Income (loss) from operations	$ (3,301)	$ 19,485
Net income (loss)	$ (10,812)	$ 8,964
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	(1,420)	8,964
Cash, cash equivalents and short-term investments	1,035,301	1,022,715

Our revenue for the three months ended March 31, 2018 was $144.4 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 also plan to add product revenue from TEGSEDI and WAYLIVRA this year, assuming they are approved.

Our operating expenses for the three months ended March 31, 2018 were $147.7 million and increased compared to $96.3 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 WAYLIVRA and TEGSEDI in 2018 and reflect the investment we are making in advancing and expanding our pipeline. Our SG&A expenses also increased in the first quarter of 2018 compared to 2017 because of fees we owed under our in-licensing agreements related to SPINRAZA. R&D expenses accounted for a smaller portion of the increase in operating expenses. R&D expenses increased primarily from medical affairs expenses and increases in manufacturing costs related to TEGSEDI for our planned launch this year.

During the first quarter of 2018, we received more than $155 million in payments from our partners, primarily from Biogen from SPINRAZA royalties we earned in the fourth quarter of 2017, Roche for its license of IONIS-HTT_{Rx} in late 2017 and AstraZeneca for its license of IONIS-AZ5-2.5_{Rx}. In addition to cash and revenue, our partners provide expertise and additional resources, which we believe will maximize the commercial value of our partnered drugs.

In April 2018, we and Biogen expanded our strategic collaboration to develop novel antisense drugs for a broad range of neurological diseases. We will receive $1 billion, including an upfront payment and equity investment at a 25 percent cash premium, upon receiving Hart-Scott Rodino clearances.

Recent Events

Our Corporate and Drug Development Highlights *(Q1 2018 and subsequent activities)*

Business Highlights

- *Expanded strategic research collaboration with Biogen for neurological diseases – one of the largest research-stage collaborations ever*
  - $1 billion upfront to us, including $625 million to purchase our stock at a 25 percent cash premium of $125 million and a $375 million upfront payment
    - Together, the cash premium and upfront payment represent a $500 million technology access fee
  - We are eligible to receive milestone payments and license fees up to $270 million per drug and royalties up to 20 percent on net sales
  - Disease areas include dementia, neuromuscular diseases, movement disorders, ophthalmology, diseases of the inner ear, and neuropsychiatry
- *SPINRAZA® for SMA – one of the most successful orphan disease drug launches in history*
  - SPINRAZA®, commercialized by Biogen, continued to generate growth with global revenues of $364 million in Q1 2018
  - Increase of over 25 percent from last quarter in number of patients on SPINRAZA, including a 16 percent increase in number of patients treated in the U.S. and a more than 50 percent increase outside the US
  - Access expanding outside the U.S. with reimbursement in 24 countries; Biogen expects reimbursement in at least seven more countries by the end of 2018
  - Presented data from the SHINE open-label study at the American Academy of Neurology, or AAN, annual meeting demonstrating continued benefit, improved motor function and mobility, and longer event-free survival for the most severely affected patients treated with SPINRAZA
  - Presented data from the NURTURE study at the Muscular Dystrophy Association, or MDA, Clinical Conference demonstrating continued benefit in motor function for infants, teens and young adults treated with SPINRAZA

- *TEGSEDI (inotersen) for hereditary transthyretin amyloidosis, or hATTR – potential to transform the lives of people with hATTR; on-track to launch in 2018*
    - Invested in global commercialization of TEGSEDI by licensing TEGSEDI to our majority-owned affiliate, Akcea
    - Optimized our commercial participation with up to $1.5 billion in milestone payments and a 60 percent profit share
    - Early access program enrolling in the U.S. and Europe
    - Global commercial organization staffed and focused on disease education; robust patient support program in place; supply chain in place and launch supplies ready to be labeled
    - Presented data from the Phase 3 NEURO-TTR study, the open label extension study and an investigator sponsored Phase 2 study at the International Symposium on Amyloidosis annual meeting and the AAN annual meeting

- *WAYLIVRA (volanesorsen) for FCS and FPL – potential first treatment for people with FCS; on-track to launch in 2018*
    - Early access program enrolling in the U.S. and Europe
    - Global commercial organization staffed and focused on disease education; robust patient support program in place; supply chain in place and launch supplies ready to be labeled
    - Positive scientific opinion to initiate Early Access to Medicines Scheme, or EAMS, by the UK's Medicines and Healthcare Products Regulatory Agency, or MHRA, for the treatment of people with FCS
- *Collaboration with AstraZeneca for Cardiovascular, Renal and Metabolic Diseases*
    - Earned $60 million for the license of second and third antisense drugs, IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L$_{Rx}$, to treat a genetically associated form of kidney disease and nonalcoholic steatohepatitis, or NASH, respectively, to AstraZeneca
    - As IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L$_{Rx}$ advance, we may receive up to $300 million for each drug in additional development and regulatory milestone payments, as well as tiered royalties on sales of each drug

Pipeline and Technology Progress

- Presented positive IONIS-HTT$_{Rx}$ (RG6042) Phase 1/2 data in people with Huntington's disease, or HD at the annual CHDI HD conference. IONIS-HTT$_{Rx}$ is the first drug in development to lower the disease-causing protein in people with HD
- Presented data at the AAN annual meeting that demonstrated broad potential of antisense drugs for neurological diseases with 14 presentations on our drugs to treat neurological diseases, including SMA, hATTR amyloidosis, Huntington's disease, Alzheimer's disease, and ALS
    - Presented additional data from the Phase 1/2 study of IONIS-HTT$_{Rx}$ that demonstrated correlations between reductions in mutant huntingtin, or mHTT, and improvements in clinical measures of HD
- Published review paper titled, "RNA-targeted Therapeutics" in Cell Metabolism, authored by Stanley Crooke, M.D., Ph.D.; highlights antisense and other RNA-targeting therapeutics as important platforms for drug discovery across multiple diseases.

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 involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with 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."

During 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. Below is a summary of the change from our first quarter 2017 revenue under Topic 605 to the new Topic 606 guidance:

The following table summarizes the adjustments we were required to make to revenue we originally reported at March 31, 2017 to adopt Topic 606 (in thousands):

	Three Months Ended March 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 5,211	$ —	$ 5,211
Licensing and other royalty revenue	3,547	(957)	2,590
Total commercial revenue	8,758	(957)	7,801
Research and development revenue under collaborative agreements	101,546	6,453	107,999
Total revenue	$ 110,304	$ 5,496	$ 115,800

During the first quarter of 2017, our revenue increased $5.5 million 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 a $10.3 million increase in our revenue for the first quarter of 2017.
- 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 $3.8 million decrease in our revenue for the first quarter of 2017.

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.

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 in exchange for upfront fees, license fees, milestone payments, royalties and/or profit sharing arrangements. Our collaboration agreements typically contain multiple elements, or performance obligations, including technology licenses or options to obtain technology licenses, R&D services, and in certain cases 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 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.

Additionally, 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, royalties or profit share arrangements. At the start of an agreement, our transaction price usually only consists of 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.

Our most common type of variable consideration are milestone payments. 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 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 appropriate 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
- An appropriate 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 and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the R&D 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 that if they change over the course of the collaboration, may affect the timing and amount of revenue that we recognize in the current and future periods.

During the three months ended March 31, 2017, we recognized $8.2 million of additional revenue related to changes in our estimates. The additional revenue was primarily from our Biogen collaboration for IONIS-DMPK$_{Rx}$ because we shortened our estimated period of performance. Slightly offsetting this increase was a decrease in revenue related to changes in estimates for our collaboration with Roche for IONIS-HTT$_{Rx}$ (RG6042) because we increased our estimated total effort required to satisfy our performance obligation. During the three months ended March 31, 2018, we recognized $0.5 million of additional revenue related to changes in our estimated period of performance under our neurology collaboration with Biogen.

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

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, therefore, 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 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 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.

Royalties

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.

Amendments to Agreements

From time to time we amend our collaboration agreements. For these agreements, 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 under the amendment are distinct 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 under the amendment, we then assess whether the additional goods or services are distinct under the original agreement. If the goods and/ or services are distinct under the original agreement 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 they are not distinct from the original agreement, 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 the 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 are 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 we are required to account for them as a combined arrangement.

For example, in the first quarter of 2017, we and Akcea entered into two separate agreements with Novartis at the same time: a collaboration agreement and a SPA. We evaluated the Novartis 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 Novartis collaboration.

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 months ended March 31, 2018 was $144.4 million compared to $115.8 million for the same period in 2017 and was comprised of the following (amounts in thousands):

	Three Months Ended March 31, 2017	
	2018	2017 (as revised)
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 41,081	$ 5,211
Licensing and other royalty revenue	942	2,590
Total commercial revenue	42,023	7,801
R&D revenue:		
License fees	62,326	64,468
Milestone payments	1,500	2,500
Amortization from:		
Upfront payments	27,363	19,761
Milestone payments	4,829	17,065
Other services	6,378	4,205
Total R&D revenue	102,396	107,999
Total revenue	144,419	115,800

License fees in the first quarter of 2018 were $62.3 million primarily from AstraZeneca for the license of IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L$_{Rx}$. The first quarter of 2017 included $64.5 million in a license fee from Bayer for the license of IONIS-FXI-L$_{Rx}$.

Operating Expenses

Operating expenses for the three months ended March 31, 2018 were $147.7 million, and increased compared to $96.3 million for the same period in 2017. Our operating expenses increased year over year principally due to higher SG&A expenses as we prepare to commercialize WAYLIVRA and TEGSEDI and reflect the investment we are making in advancing and expanding our pipeline. Our SG&A expenses also increased year over year because of fees we owed under our in-licensing agreements related to SPINRAZA, which increase as our SPINRAZA revenue increases. 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 in manufacturing costs related to TEGSEDI for the planned launch this year. As this year progresses, we expect our operating expenses to continue to increase primarily related to the commercialization of WAYLIVRA and TEGSEDI.

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

	Three Months Ended March 31,	
	2018	2017
Ionis Core	$ 83,476	$ 60,620
Akcea Therapeutics	41,052	66,290
Elimination of intercompany activity	(5,259)	(51,507)
Subtotal	119,269	75,403
Non-cash compensation expense related to equity awards	28,451	20,912
Total operating expenses	$ 147,720	$ 96,315

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 March 31,	
	2018	2017
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 84,385	$ 66,516
Non-cash compensation expense related to equity awards	19,682	16,122
Total research, development and patent expenses	$ 104,067	$ 82,638

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

	Three Months Ended March 31,	
	2018	2017
Ionis Core	$ 63,988	$ 54,829
Akcea Therapeutics	25,656	63,194
Elimination of intercompany activity	(5,259)	(51,507)
Subtotal	84,385	66,516
Non-cash compensation expense related to equity awards	19,682	16,122
Total research, development and patent expenses	$ 104,067	$ 82,638

For the three months ended March 31, 2018, our total research, development and patent expenses were $84.4 million and increased compared to $66.5 million for the same period 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 were as follows (in thousands) and are part of our Ionis Core business segment:

	Three Months Ended March 31,	
	2018	2017
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 13,904	$ 12,598
Non-cash compensation expense related to equity awards	4,376	3,963
Total antisense drug discovery expenses	$ 18,280	$ 16,561

Antisense drug discovery expenses for the three months ended March 31, 2018 were $13.9 million, and were higher compared to $12.6 million for the same period in 2017, due to expenses we incurred related to advancing our early stage research programs. 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 March 31,	
	2018	2017
SPINRAZA	$ 60	$ 5,648
WAYLIVRA	6,401	4,258
TEGSEDI	5,836	6,786
Other antisense development projects	20,593	10,417
Development overhead expenses	11,978	10,303
Total antisense drug development, excluding non-cash compensation expense related to equity awards	44,868	37,412
Non-cash compensation expense related to equity awards	8,092	6,456
Total antisense drug development expenses	$ 52,960	$ 43,868

Antisense drug development expenses were $44.9 million for the three months ended March 31, 2018, compared to $37.4 million for the same period in 2017. Expenses for the three months ended March 31, 2018 increased compared to the same period in 2017. During the first quarter of 2018, we advanced our pipeline, including AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea completed enrollment of its Phase 2 clinical study of AKCEA-APO(a)-L_{Rx} during the first quarter of 2018. Akcea also initiated a Phase 2 clinical study of AKCEA-APOCIII-L_{Rx} in patients with hypertriglyceridemia and established cardiovascular disease. 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. 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 March 31,	
	2018	2017
Ionis Core	$ 27,626	$ 27,711
Akcea Therapeutics	17,242	58,996
Elimination of intercompany activity	—	(48,394)
Subtotal	44,868	38,313
Non-cash compensation expense related to equity awards	8,092	7,012
Total antisense drug development expenses	$ 52,960	$ 45,325

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 March 31,	
	2018	2017
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 5,132	$ 901
Non-cash compensation expense related to equity awards	766	556
Total medical affairs expenses	$ 5,898	$ 1,457

Medical affairs expenses were $5.1 million for three months ended March 31, 2018 and were higher compared to $0.9 million for the same period 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 and 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 March 31,	
	2018	2017
Ionis Core	$ 3,346	$ —
Akcea Therapeutics	1,786	901
Subtotal	5,132	901
Non-cash compensation expense related to equity awards	766	556
Total medical affairs expenses	$ 5,898	$ 1,457

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 March 31,	
	2018	2017
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 12,309	$ 8,805
Non-cash compensation expense related to equity awards	2,402	1,705
Total manufacturing and operations expenses	$ 14,711	$ 10,510

Manufacturing and operations expenses were $12.3 million for the three months ended March 31, 2018 compared to $8.8 million for the same period in 2017. Manufacturing and operations expenses increased primarily related to TEGSEDI for the planned launch this year. 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 March 31,	
	2018	2017
Ionis Core	$ 11,642	$ 8,104
Akcea Therapeutics	5,896	3,784
Elimination of intercompany activity	(5,229)	(3,083)
Subtotal	12,309	8,805
Non-cash compensation expense related to equity awards	2,402	1,705
Total manufacturing and operations expenses	$ 14,711	$ 10,510

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 March 31,	
	2018	2017
Personnel costs	$ 3,103	$ 2,852
Occupancy	1,759	1,878
Patent expenses	701	499
Depreciation and amortization	101	67
Insurance	470	346
Other	2,038	1,158
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	8,172	6,800
Non-cash compensation expense related to equity awards	4,046	3,442
Total R&D support expenses	$ 12,218	$ 10,242

R&D support expenses for the three months ended March 31, 2018 were $8.2 million, and increased compared to $6.8 million for the same period 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 March 31,	
	2018	2017
Ionis Core	$ 7,470	$ 6,416
Akcea Therapeutics	732	414
Elimination of intercompany activity	(30)	(30)
Subtotal	8,172	6,800
Non-cash compensation expense related to equity awards	4,046	3,442
Total R&D support expenses	$ 12,218	$ 10,242

Selling, General and Administrative Expenses

Selling, general and administrative expenses include costs associated with the pre-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, 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 owed under our in-licensing agreements related to SPINRAZA in our SG&A expenses.

The following table sets forth information on selling, general and administrative expenses (in thousands):

	Three Months Ended March 31,	
	2018	2017
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 34,884	$ 8,887
Non-cash compensation expense related to equity awards	8,769	4,790
Total selling, general and administrative expenses	$ 43,653	$ 13,677

Selling, general and administrative expenses were $34.9 million for the three months ended March 31, 2018, and increased significantly compared to $8.9 million for the same period in 2017. The increase in SG&A expenses was principally due to the cost of preparing to commercialize WAYLIVRA and TEGSEDI this year, assuming approval, and from fees we owed under our in-licensing agreements related to SPINRAZA. We project our expenses will increase as we continue to prepare to launch TEGSEDI and 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 March 31,	
	2018	2017
Ionis Core	$ 19,488	$ 5,791
Akcea Therapeutics	15,396	3,096
Non-cash compensation expense related to equity awards	8,769	4,790
Total selling, general and administrative expenses	$ 43,653	$ 13,677

Akcea Therapeutics, Inc.

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

	Three Months Ended March 31,	
	2018	2017
Development and patent expenses	$ 25,656	$ 63,194
General and administrative expenses	15,396	3,096
Total operating expenses, excluding non-cash compensation expense related to equity awards	41,052	66,290
Non-cash compensation expense related to equity awards	6,383	3,180
Total Akcea Therapeutics operating expenses	$ 47,435	$ 69,470

Operating expenses for Akcea were $41.1 million for the three months ended March 31, 2018, and decreased compared to $66.3 million for the same period in 2017.

In the first quarter 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 $10.9 million in the first quarter of 2018 compared to the same period in 2017 as Akcea made investments in advancing its pipeline, including AKCEA-APO(a)-L_{Rx} 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 quarter 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 WAYLIVRA this year, assuming approval. Akcea's G&A expenses also include costs related to the TEGSEDI licensing agreement with us. 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 to continue to increase in 2018, as they prepare to launch TEGSEDI and WAYLIVRA.

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

Investment Income

Investment income for the three months ended March 31, 2018 was $3.6 million compared to $2.3 million for 2017. The increase in investment income was primarily due to a higher average cash balance and an improvement in the market conditions during the three months ended March 31, 2018 compared to same period in 2017. We expect our investment income to increase in 2018 with the addition of $1 billion from our expanded strategic collaboration with Biogen.

Interest Expense

Interest expense for the three months ended March 31, 2018 was $10.9 million and decreased compared to $11.4 million for the same period 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 March 31,	
	2018	**2017**
Convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 8,524	$ 7,902
Interest expense payable in cash	1,714	1,715
Non-cash interest expense for long-term financing liability	—	1,675
Interest on mortgage for primary R&D and manufacturing facilities	594	—
Other	106	71
Total interest expense	$ 10,938	$ 11,363

Net Income (Loss)

We had a net loss of $10.8 million for the three months ended March 31, 2018, compared to net income of $9.0 million for the same period in 2017. Our net loss increased primarily due to increased operating expenses as we prepare to commercialize TEGSEDI and WAYLIVRA, assuming approval.

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 on July 19, 2017 through the end of the first quarter of 2018, we owned approximately 68 percent of Akcea. As a result, we adjusted our financial statements to reflect the portion of Akcea we no longer own, which was 32 percent at March 31, 2018. Accordingly, our consolidated statement of operations now includes a new line called "Net loss attributable to noncontrolling interests in Akcea", our noncontrolling interest in Akcea for the three months ended March 31, 2018 was $9.4 million. We also added a corresponding account to our consolidated balance sheet called "Noncontrolling interest in Akcea Therapeutics, Inc."

In April 2018, we received 8 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. We will reflect this increase in our ownership percentage in the second quarter of 2018.

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 $1.4 million for the three months ended March 31, 2018, compared to net income of $9.0 million for the same period in 2017. Basic and diluted net loss per share for three months ended March 31, 2018 was $0.01. Our basic and diluted net income per share for the three months ended March 31, 2017 was $0.07.

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 March 31, 2018, we have earned approximately $2.7 billion in revenue. We 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 March 31, 2018, we have raised net proceeds of approximately $1.2 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 March 31, 2018, we had cash, cash equivalents and short-term investments of $1.04 billion and stockholders' equity of $387.1 million. In comparison, we had cash, cash equivalents and short-term investments of $1.02 billion and stockholders' equity of $365.3 million at December 31, 2017. Our cash, cash equivalents and short-term investments increased in the first quarter of 2018 primarily from payments we received from Biogen, Roche and AstraZeneca. Our first quarter of 2018 cash balance did not include the $1 billion we expect to receive in the second quarter of 2018 from Biogen for our new strategic neurology collaboration.

At March 31, 2018, we had consolidated working capital of $930.6 million compared to $925.1 million at December 31, 2017. As of March 31, 2018, our debt and other obligations totaled $758.4 million compared to $759.9 million at December 31, 2017.

The following table summarizes our contractual obligations as of March 31, 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)	$ 712.9	$ 6.9	$ 13.7	$ 692.3	$ —
Building mortgage payments	82.6	2.4	4.8	5.4	70.0
Financing arrangements (principal and interest payable)	13.0	0.3	12.7	—	—
Other obligations (principal and interest payable)	1.1	0.1	0.1	0.1	0.8
Operating leases	3.1	0.9	1.5	0.6	0.1
Total	$ 812.7	$ 10.6	$ 32.8	$ 698.4	$ 70.9

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 March 31, 2018, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At March 31, 2017, 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 March 31, 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 March 31, 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, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

ITEM 4. CONTROLS AND PROCEDURES

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

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2018. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2018.

We also performed an evaluation of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. We implemented internal controls to ensure we adequately evaluated our contracts and properly assessed the impact of the of 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 control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control 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. 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 establish 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.

We plan to commercialize TEGSEDI through Akcea, if approved. 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 it 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 achieve or 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 achieve or 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, TEGSEDI, and additional approvals for SPINRAZA, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including WAYLIVRA and TEGSEDI, will be considered safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA 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 and TEGSEDI for marketing or additional marketing authorizations for SPINRAZA. 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.

The FDA's Division of Metabolism and Endocrinology Products advisory committee is scheduled to discuss and advise the FDA on the risk-benefit profile of WAYLIVRA for the treatment of FCS on May 10, 2018. In advance of this advisory committee meeting, we, Akcea and the FDA will submit briefing documents for the committee's review, and these briefing documents will be made available to the public and may include information from the WAYLIVRA development program that have not previously been disclosed. Historically, for some companies, disclosure of information in this manner has led to increased volatility in their stock price. The advisory committee and FDA may interpret nonclinical and clinical data differently than we and our experts have. Press coverage and public scrutiny of the materials that will be discussed at the advisory committee meeting may negatively affect the potential for the NDA for WAYLIVRA to receive approval or the trading price of our securities. Even if we and Akcea ultimately obtain approval for WAYLIVRA, the matters discussed at the advisory committee meeting could limit Akcea's ability to successfully commercialize WAYLIVRA.

Failure to receive marketing authorization for our drugs, WAYLIVRA and TEGSEDI, or additional authorizations for SPINRAZA, 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 and TEGSEDI or additional authorizations for SPINRAZA.

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 March 31, 2018, we had an accumulated deficit of approximately $1.2 billion and stockholders' equity of approximately $387.1 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 partners 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 March 31, 2018, we had cash, cash equivalents and short-term investments equal to $1.0 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;
- marketing approvals for WAYLIVRA and 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 March 31, 2018, the market price of our common stock ranged from $37.26 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 recently passed 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	Strategic Advisory Services Agreement, dated as of January 15, 2018, by and between B. Lynne Parshall and Ionis Pharmaceuticals, Inc.
10.2	Development, Commercialization, Collaboration, and License Agreement, dated as of March 14, 2018, by and between Ionis Pharmaceuticals, Inc. and Akcea Therapeutics, Inc.
10.3	Amended and Restated Services Agreement, dated as of March 14, 2018, by and between Ionis Pharmaceuticals, Inc. and Akcea Therapeutics, 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 March 31, 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)	May 4, 2018
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 4, 2018

Exhibit 10.1

IONIS PHARMACEUTICALS, INC.
STRATEGIC ADVISORY SERVICES AGREEMENT
(*"SUMMARY PAGE"*)

Date of Strategic Advisory Services Agreement: ("***Agreement***")	January 15, 2018 ("***Effective Date***").
Name of Strategic Advisor:	B. Lynne Parshall (hereinafter "***Strategic Advisor***").
Scope of Strategic Advisory Services:	As set forth on Schedule A attached hereto.
Duration of Strategic Advisory Services (the "***Strategic Advisory Period***"):	Until termination by Ionis or Strategic Advisor in accordance with Section 8 of Exhibit A below.
Consideration for Strategic Advisory Services:	As set forth on Schedule B attached hereto.
Time Provided by Strategic Advisor:	As set forth on Schedule A attached hereto.

In addition to such compensation, Ionis Pharmaceuticals, Inc. ("***Ionis***") will reimburse Strategic Advisor for Ionis approved travel and other out-of-pocket costs reasonably incurred in the course of performing Strategic Advisory Services under this Agreement as further described on Schedule B attached hereto.

Strategic Advisor agrees to provide Ionis with Strategic Advisory Services on the terms described above and according to the additional terms attached hereto as Exhibit A. In this Agreement references to Ionis, including but not limited to Sections 3-6 of Exhibit A, will include Ionis' affiliate companies where applicable.

	Strategic Advisor	**Ionis Pharmaceuticals, Inc.**
By (Signature):		
Date:		
Printed Name:	B. Lynne Parshall	
Title:	Individual	
Address:	Provided Separately	2855 Gazelle Court, Carlsbad, CA 92010
Telephone:	Provided Separately	760-931-9200
Fax:	Provided Separately	760-603-3820
e-mail:	Provided Separately	

Social Security or Employer Tax ID Number to be provided separately via W-9 form or foreign equivalent.

EXHIBIT A

TERMS OF STRATEGIC ADVISORY AGREEMENT

1. **Engagement of Services**

Strategic Advisor is retained to perform certain services, as needed and requested by Ionis, which services are specifically described on Schedule A attached hereto ("***Strategic Advisory Services***"). Strategic Advisor will perform such Strategic Advisory Services to the best of Strategic Advisor's talent and ability.

2. **Compensation**

As full and complete compensation for Strategic Advisory Services and for the discharge of all of Strategic Advisor's obligations hereunder, Ionis will pay Strategic Advisor at the rate set forth on Schedule B attached hereto. Strategic Advisor will invoice Ionis on a quarterly basis for Strategic Advisor fees and reimbursable expenses, and Ionis, upon its approval, will pay all undisputed fees and expenses within 30 days after Ionis' receipt of the invoice.

3. **Independent Contractor**

Strategic Advisor is an independent contractor and not an employee of Ionis. Strategic Advisor has no authority to obligate Ionis by contract or otherwise. Strategic Advisor will not be eligible for any employee benefits. Taxes will be the sole responsibility of Strategic Advisor.

4. **Additional Activities**

(a) Strategic Advisor agrees that during the Strategic Advisory Period and for one year thereafter, Strategic Advisor will not attempt to induce any employee or employees of Ionis to terminate their employment with, or otherwise cease their relationship with Ionis.

(b) Strategic Advisor acknowledges that Ionis has developed, through an extensive acquisition process, valuable information regarding actual or prospective partners, licensors, licensees, clients, customers and accounts of Ionis ("***Trade Secret Information***"). Strategic Advisor acknowledges that Strategic Advisor's use of such Trade Secret Information after the termination of the Strategic Advisory Period would cause Ionis irreparable harm. Therefore, Strategic Advisor also agrees that Strategic Advisor will not utilize any Trade Secret Information to solicit the business relationship or patronage of any of the actual or prospective partners, licensors, licensees, clients, customers or accounts of Ionis.

(c) The restrictions set forth in this Section 4 are considered by the parties to be reasonable for the purposes of protecting Ionis' business. However, if any such restriction is found by a court of competent jurisdiction to be unenforceable because it extends for too long a period of time or over too great a range of activities or in too broad a geographic area, it will be interpreted to extend only over the maximum period of time, range of activities or geographic areas as to which it may be enforceable.

5. **Confidential Information**

(a) Ionis possesses confidential information that has been created, discovered, developed by, or otherwise become known to Ionis (including, without limitation, information created, discovered, developed or made known by Strategic Advisor arising from the Strategic Advisory Services).

(i) All such information is hereinafter referred to as "***Confidential Information***." By way of illustration, but not limitation, Confidential Information includes: (A) inventions, developments, designs, improvements, trade secrets, ideas, formulas, source and object codes, programs, other works of authorship, organisms, plasmids, expression vectors, know-how, processes, cell lines, discoveries, techniques, data and documentation systems (hereinafter collectively referred to as "***Inventions***"); and (B) information regarding plans for research, development, new products, clinical data, pre-clinical product data, clinical trial patient data, marketing and selling, business plans, budgets and unpublished financial statements, licenses, prices and costs, as well as information regarding the skills and compensation of employees of Ionis.

(ii) All Confidential Information will be the sole property of Ionis and its assigns, and Ionis and its assigns will be the sole owner of all patents, copyrights and other rights in connection with such Confidential Information. At all times, both during the term of this Agreement and for five years after its termination, Strategic Advisor will keep in confidence and trust all Confidential Information and will not use, disclose, lecture upon or publish any Confidential Information or anything related to such information without Ionis' prior written consent. Any permitted disclosures will be made in strict compliance with the Ionis publication and presentation clearance policy.

(b) Strategic Advisor also understands that Ionis has received and in the future, will receive valuable information from third parties that is confidential or proprietary ("***Third-Party Information***") subject to a duty on the part of Ionis to maintain the confidentiality of such information and to use it only for certain limited purposes. During the term of this Agreement and for five years thereafter, Strategic Advisor will hold Third-Party Information in the strictest confidence and will not disclose or use Third-Party Information except as permitted by the agreement between Ionis and such third party, unless expressly authorized to act otherwise by an officer of Ionis in writing. Any permitted disclosures will be made in strict compliance with Ionis publication and presentation clearance policy.

(c) The obligations of Section 5 will not apply to information that Strategic Advisor can establish by written records: (i) was known by Strategic Advisor prior to the receipt of Confidential Information; (ii) was disclosed to Strategic Advisor by a third party having the right to do so; (iii) was, or subsequently became, in the public domain through no fault of Strategic Advisor, its officers, directors, affiliates employees or agents; (iv) was independently developed by Strategic Advisor without use of Confidential Information; or (v) was disclosed by Strategic Advisor pursuant to any judicial, governmental or stock exchange request, requirement or order, so long as Strategic Advisor provided Ionis with sufficient prior notice in order to allow Ionis to contest such request, requirement or order.

6. **Inventions**

In the course of performing Strategic Advisory Services for Ionis, Strategic Advisor may develop new ideas or Inventions or make other contributions of value to Ionis.

(a) Strategic Advisor hereby assigns to Ionis Strategic Advisor's entire right, title and interest in and to any and all Inventions (and all patent rights, copyrights, and all other rights in connection therewith, hereinafter referred to as "***Proprietary Rights***") whether or not patentable or registrable under patent, copyright or similar statutes, made or conceived of or reduced to practice or learned by Strategic Advisor, either alone or jointly with others, as a result of performing Strategic Advisory Services hereunder. All Inventions assigned to Ionis pursuant to this section will be known as "***Company Inventions***". Strategic Advisor agrees that all Proprietary Rights and Company Inventions are Ionis' sole property. Strategic Advisor agrees, upon request, to execute, verify and deliver assignments of such Proprietary Rights to Ionis or its designee. Strategic Advisor understands that, to the extent this Agreement will be construed in accordance with the laws of any state which precludes a requirement in an agreement to assign certain classes of inventions made by an individual acting as a Strategic Advisor, this section will be interpreted not to apply to any inventions that a court rules and/or Ionis agrees falls within such classes.

(b) Strategic Advisor further agrees to assist Ionis in every proper way to obtain, from time to time, and to enforce United States and foreign Proprietary Rights relating to Company Inventions in any and all countries. To that end Strategic Advisor will execute, verify and deliver such documents and perform such other acts (including appearances as a witness) as Ionis may reasonably request for use in applying for, obtaining, sustaining and enforcing such Proprietary Rights relating to Company Inventions. Strategic Advisor's obligation to assist Ionis in obtaining and enforcing Proprietary Rights relating to Company Inventions in any and all countries will continue beyond the termination of this Agreement, but Ionis will compensate Strategic Advisor at a reasonable rate after such termination for the time actually spent by Strategic Advisor at Ionis' request in connection with such assistance. If Ionis is unable, after reasonable effort, to secure Strategic Advisor's signature on any document needed to apply for or prosecute any Proprietary Rights relating to a Company Invention, Strategic Advisor hereby irrevocably designates and appoints Ionis and its duly authorized officers and agents as her agent and attorney in fact, to act for and on Strategic Advisor's behalf to execute, verify and file any such applications and to do all other lawfully permitted acts to further the prosecution and issuance of any such Proprietary Rights with the same legal force and effect as if executed by Strategic Advisor.

(d) During the term of this Agreement, Strategic Advisor will promptly disclose to Ionis, or any persons designated by it, fully and in writing and will hold in trust for the sole right and benefit of Ionis any and all Company Inventions, whether or not patentable or protectable by copyright. At the time of each such disclosure, Strategic Advisor will advise Ionis in writing of any Inventions that Strategic Advisor believes are not subject to the assignment provisions of Section 6(a) above, and Strategic Advisor will at that time provide to Ionis in writing all evidence necessary to substantiate that belief. Strategic Advisor will not be obligated to disclose information received by Strategic Advisor from others under a contract of confidentiality. In addition, after termination of this Agreement, Strategic Advisor will disclose to Ionis all patent applications filed by Strategic Advisor relating to any Company Inventions or relating to any work performed by Strategic Advisor on behalf of Ionis.

7. **Previous Strategic Advisory Relationships**

Strategic Advisor represents that Strategic Advisor's performance of Strategic Advisory Services, as well as Strategic Advisor's performance of the rest of Strategic Advisor's obligations under the terms of this Agreement, will not breach any agreement to keep in confidence any proprietary information acquired by Strategic Advisor in confidence or in trust from another entity prior to the date of this Agreement. Strategic Advisor agrees not to bring to Ionis or to use in the performance of Strategic Advisory Services for Ionis any materials or documents of a present or former employer or client of Strategic Advisor, or any materials or documents obtained by Strategic Advisor under a confidentiality agreement imposed by reason of another of Strategic Advisor's Strategic Advisory relationships, unless such materials or documents are generally available to the public or Strategic Advisor has authorization from such present or former employer or client for the possession and unrestricted use of such materials.

8. **Termination; Survival**

(a) The term of this Agreement will begin on January 15, 2018 and will end when terminated by either Ionis or Strategic Advisor. Ionis may terminate this Agreement at any time for any reason by providing Strategic Advisor at least 120 days advance written notice. Strategic Advisor may terminate this Agreement at any time for any reason by providing Ionis at least 120 days advance written notice; *provided*, once Strategic Advisor delivers such a termination notice, Ionis may elect to accelerate the effective date of such termination. Upon any termination, Ionis will pay Strategic Advisor for any Strategic Advisory Services appropriately rendered and for any out of pocket expenses reasonably incurred on behalf of Ionis, up to and including the termination date.

(b) The last sentence of the second paragraph of Schedule B and the last paragraph of Schedule B will survive termination of this Agreement. In addition, upon expiration or termination of this Agreement, each party will be released from all obligations and liabilities to the other occurring or arising after the date of such expiration or termination, except that any termination or expiration of this Agreement will not relieve Strategic Advisor of Strategic Advisor's obligations under Sections 4, 5, 6, 7 and 9 hereof, nor will any such expiration or termination relieve Strategic Advisor or Ionis from any liability arising from any breach of this Agreement. Upon expiration or termination of this Agreement for any reason whatsoever, Strategic Advisor will promptly surrender and deliver to Ionis any and all notes, business records, memoranda, specifications, devices, formulas, molecules, cells, storage media, including calculations, sequences, data and other materials of any nature pertaining to Strategic Advisory Services for Ionis, as well as any documents or data of any description (or any reproduction of any documents or data) containing or pertaining to any Trade Secret Information, Ionis' Confidential Information or Third Party Information.

9. **Arbitration**

(a) Ionis and Strategic Advisor agree to resolve by arbitration all disputes, claims or controversies ("***Claims***"), past, present or future, whether or not arising out of this Agreement or its termination, that Ionis may have against Strategic Advisor or that Strategic Advisor may have against any of the following (i) Ionis; (ii) Ionis officers, directors; employees or agents; (iii) Ionis' subsidiary or affiliated entities, joint ventures, or joint employers; (iv) Ionis' benefit plans or the plans' sponsors, fiduciaries, administrators, affiliates and agents; and/or (v) all successors and assigns of any of the foregoing. The Claims covered by this Agreement include all disputes that Ionis or Strategic Advisor could otherwise pursue in state or federal court including, but not limited to, Claims based on any state, federal, or local statute, regulation or ordinance (including Claims for discrimination, retaliation, harassment, unpaid wages or violation of state or federal wage and hour laws), as well as common law Claims (including Claims for breach of contract, breach of the implied covenant of good faith and fair dealing, wrongful discharge, defamation, misrepresentation, fraud, or infliction of emotional distress). Ionis and Strategic Advisor anticipates that this Section 9 provides the benefits of a speedy, less formal, impartial, final and binding dispute resolution procedure.

(b) To the maximum extent permitted by law, Strategic Advisor hereby waives any right to bring on behalf of persons other than Strategic Advisor, or to otherwise participate with other persons in, any class, collective or representative action (i.e. a type of lawsuit in which one or several persons sue on behalf of a larger group of persons).

(c) The arbitration will be conducted by a single neutral arbitrator in accordance with the then-current Commercial Arbitration and Mediation Procedures of the American Arbitration Association ("***AAA***"). The arbitration will take place in San Diego, California. Ionis will pay the arbitrator's fee and will bear all administrative charges by AAA. All parties will be entitled to engage in reasonable pre-hearing discovery to obtain information to prosecute or defend the asserted claims. Any disputes between the parties regarding the nature or scope of discovery will be decided by the arbitrator. The arbitrator will hear and issue a written ruling upon any dispositive motions brought by either party, including but not limited to, motions for summary judgment or summary adjudication of issues. After the hearing, the arbitrator will issue a written decision setting forth the award, if any, and explaining the basis therefore. The arbitrator will have the power to award any type of relief that would be available in court. The arbitrator's award will be final and binding upon the parties and may be entered as a judgment in any court of competent jurisdiction. If there is conflict in the arbitration procedures set forth in this Agreement and the AAA rules specified above, the AAA rules will control. Notwithstanding the foregoing, and regardless of what is provided by the AAA rules, the arbitrator will not have authority or jurisdiction to consolidate claims of different individuals or entities into one proceeding, nor will the arbitrator have authority or jurisdiction to hear the arbitration as a class action. As noted above, Strategic Advisor has agreed to waive any right to bring any class, collective or representative action. To the extent that the class, collective or representative action waiver described above is not enforceable, the issue of whether to certify any alleged or putative class for a class action proceeding must be decided by a court of competent jurisdiction. The arbitrator will not have authority or jurisdiction to decide class certification, collective or representative action issues. Until any class certification, collective, or representative action issues are decided by the court, all arbitration proceedings will be stayed, and the arbitrator will take no action with respect to the matter. However, once any issues regarding class certification, collective, or representative action have been decided by the court, the arbitrator will have authority to decide the substantive claims.

10. **Miscellaneous**

(a) The rights and liabilities of the parties hereto will bind and inure to the benefit of their respective successors, heirs, executors and administrators, as the case may be; *provided that*, as Ionis has specifically contracted for Strategic Advisor's services, Strategic Advisor may not assign or delegate Strategic Advisor's obligations under this Agreement either in whole or in part without Ionis' prior written consent.

(b) Because Strategic Advisor's services are personal and unique and because Strategic Advisor has access to and become acquainted with Ionis' Confidential Information, the parties agree that in the event of a threatened or actual material breach of this Agreement by Strategic Advisor injunctive relief would be appropriate. As such, Ionis has the right to enforce this Agreement and any of its provisions by injunction, specific performance or other equitable relief without prejudice to any other rights and remedies that Ionis may have for a breach of this Agreement.

(c) This Agreement will be governed by and construed according to the laws of the State of California as such laws are applied to contracts entered into and performed entirely within such State. If any provision of this Agreement is held to be or becomes invalid, illegal or unenforceable, such provision will be validly reformed to approximate as nearly as possible the intent of the parties and the remainder of this Agreement will not be affected thereby and will remain valid and enforceable to the greatest extent permitted by law.

(d) This Agreement, and all other documents mentioned herein, constitute the final, exclusive and complete understanding and agreement of the parties hereto and supersedes all prior understandings and agreements. Any waiver, modification or amendment of any provision of this Agreement will be effective only if in writing and signed by the parties hereto.

(e) Any notices required or permitted hereunder will be given to the appropriate party at the address specified on the Summary Page or at such other address as the party will specify in writing. Such notice will be deemed given upon personal delivery to the appropriate address, or by facsimile transmission (receipt verified and with confirmation copy followed by another permitted method), sent by express courier service, or, if sent by certified or registered mail, three (3) days after the date of mailing.

[END OF EXHIBIT A]

SCHEDULE A

Strategic Advisory Services

Ionis Board of Directors
You will serve on the Ionis board of directors as a nonemployee director until your resignation or removal in accordance with Ionis' corporate charter. Ionis will recommend that you serve on the Agenda committee of the Board, and periodically evaluate your ability to serve on other Board committees to the extent permitted by applicable SEC and Nasdaq rules. You will participate in other Board Committee meetings as requested as a non-member.

Akcea Board of Directors
Ionis will recommend that you serve on the Akcea board of directors as a nonemployee director until your resignation or removal in accordance with Akcea's corporate charter. You will serve on the Audit Committee as permitted by applicable SEC and Nasdaq rules, and participate in other committees as a member or non-member as requested.

Strategic Neurology/Rare Disease Subsidiary Board of Directors
When Ionis forms a strategic neurological/rare disease/and/or inotersen focused subsidiary, you will serve on the board of directors of such subsidiary as a non employee director on the same terms as other non employee directors until your resignation or removal in accordance with the subsidiary's corporate charter.

Additional Strategic Advisory Services

You will provide Ionis strategic advice regarding Ionis' business, including but not limited to the following:

Through July 1, 2018, you will provide approximately eight business days of strategic advice each month. After July 1, 2018 through the end of 2018 you will provide approximately five business days of strategic advice each month. For each year following 2018, you and Ionis will mutually agree on the approximate number of business days each month you will provide strategic advice during such year. You will make yourself generally available for conference calls and in person meetings Ionis invites you to attend. You will travel to locations as reasonably requested by Ionis, including to Ionis, Akcea, Ionis' partners, or other locations where Ionis is conducting corporate development activities (e.g. JP Morgan conference or strategic off-site meetings). You and Ionis expect that, you will participate in Ionis' development management committee (DMC) meetings, Ionis' affiliate's and Biogen joint steering committee meetings, and through July 1, 2018 and thereafter when requested, Ionis' strategic management meetings (e.g. G8 meetings). As requested by Ionis, you will facilitate Ionis' strategic partnerships and help develop Ionis' subsidiaries' and affiliates' senior management teams. You will help Ionis' new CBO be trained and assimilated into Ionis' business team. You will help Ionis' new COO as requested be trained and assimilated into Ionis' business team. You will work with the CEO, COO and others on strategic planning and direction for the Company. You will participate in major corporate communication initiatives, including business/financial messaging and rebranding project. You will participate in structuring and negotiating as requested new strategic alliances.

You and Ionis will reasonably coordinate to have you present on site for board of directors meetings, and a few days before and/or after such meetings to perform strategic advisory services. The time you spend preparing for or attending board of directors or board committee meetings for Ionis, Akcea or any subsidiary will not count towards your commitment to perform additional strategic advisory services outlined above.

While you are providing such services, Ionis will make an appropriate level of administrative and technical personnel available to facilitate your performance of Advisory Services at no cost to you, including, without limitation IT support and access to Ionis' electronic calendar and IT systems that are necessary to perform your duties.

SCHEDULE B

Compensation for Strategic Advisory Services

Ionis Board of Directors
For your service on the Ionis board of directors, starting with the first quarter of 2018, you will receive the same compensation as Ionis provides its other nonemployee directors. You will not receive an initial nonemployee director award. Starting in 2018, you will receive the same annual equity awards as Ionis' other nonemployee directors. You will also be eligible for any benefits (including any applicable health benefits) Ionis provides to its nonemployee directors.

Akcea Board of Directors
For your service on the Akcea board of directors, you will receive the same compensation as Akcea provides its other nonemployee directors. On January 15, 2018, you will receive an initial nonemployee director stock option award of 52,837 shares with an option exercise price equal to the fair market value of Akcea's stock on that day. Thereafter, you will receive the same annual equity awards as Akcea's other nonemployee /outside directors.

Strategic Neurology/Rare Disease Subsidiary Board of Directors
For your service on the board of directors of Ionis' strategic neurological/rare/and/or inotersen disease subsidiary (if formed), you will receive the same compensation (including equity awards) as such subsidiary provides its other nonemployee /outside directors.

Additional Strategic Advisory Services

For your other strategic advisory services, for the fiscal year ending in 2018, Ionis will pay you at the rate of $250,000 per year, payable in equal quarterly installments. Payment for services after 2018 will be set by mutual written agreement between you and Ionis, based on the expected services for such year.

Since you are transitioning seamlessly from an Ionis employee to a nonemployee director, the stock options and RSUs you received for your previous service as an Ionis employee will continue to vest so long as your Continuous Service (as defined in the applicable equity plan) continues. Once you are no longer serving on the Ionis board and no longer providing strategic advisory services, to the extent permitted by the terms of the applicable stock option agreement, your vested stock options will not terminate until the earlier of 18 months following your retirement or the expiration of the original term of such stock option.

For Ionis-directed travel and lodging Ionis will reimburse you for such travel, lodging and related expenses or reasonable rate equivalents for lodging, car and meals you provide. All such reimbursements will be in accordance with Ionis' travel policy and you will provide Ionis reasonably acceptable supporting documentation.

For the 18 months following the end of your Ionis board of directors services, if you are eligible for continued health coverage under COBRA, Ionis will pay your COBRA premium payments sufficient to continue your coverage at your then current level, or if COBRA is not available, Ionis will pay you an amount equal to the cost of comparable replacement coverage.

Exhibit 10.2

LICENSE AGREEMENT

DEVELOPMENT, COMMERCIALIZATION, COLLABORATION, AND LICENSE AGREEMENT

between

IONIS PHARMACEUTICALS, INC.

and

AKCEA THERAPEUTICS, INC.

Dated March 14, 2018

DEVELOPMENT, COMMERCIALIZATION, COLLABORATION, AND LICENSE AGREEMENT

THIS DEVELOPMENT, COMMERCIALIZATION, COLLABORATION, AND LICENSE AGREEMENT is made and entered into as of March 14, 2018 (the "***Execution Date***"), by and between **Akcea Therapeutics, Inc.**, a Delaware corporation ("***Akcea***"), and **Ionis Pharmaceuticals, Inc.**, a Delaware corporation ("***Ionis***"). Akcea and Ionis each may be referred to herein individually as a "***Party***," or collectively as the "***Parties.***"

RECITALS

WHEREAS, Ionis has rights to, and has filed an NDA and MAA to support commercial launch of, inotersen for hereditary transthyretin amyloidosis ("***hATTR***");

WHEREAS, Ionis seeks a partner that has expertise in Commercializing human therapeutics and, in particular, experience treating patients with rare diseases to globally Commercialize inotersen;

WHEREAS, Ionis formed Akcea as a subsidiary to serve as the Commercialization entity for Ionis' portfolio of lipid drugs, and Akcea is focusing its efforts primarily on Commercializing on its own the rare disease assets in this portfolio, including volanesorsen;

WHEREAS, Akcea is building an organization with resources and expertise to globally Commercialize volanesorsen, and Akcea and Ionis desire to leverage Akcea's commercial resources to globally Commercialize inotersen;

WHEREAS, Akcea and Ionis desire to enter into a strategic TTR collaboration under which Akcea will Commercialize inotersen in accordance with a global strategic plan;

WHEREAS, in addition to Commercializing inotersen, the Parties will conduct a Development program to Develop a follow-on drug to inotersen, IONIS-TTR-L_{Rx}, to expand and extend Ionis' and Akcea's leadership position in the TTR amyloidosis market; and

WHEREAS, following receipt of marketing approval of IONIS-TTR-L_{Rx}, Akcea will Commercialize IONIS-TTR-L_{Rx} in accordance with the Strategic Plan.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants herein contained, the Parties do hereby agree as follows.

ARTICLE 1
DEFINITIONS

The terms used in this Agreement with initial letters capitalized (and the term "*inotersen*"), whether used in the singular or the plural, will have the meaning set forth in Appendix 1, or if not listed in Appendix 1, the meaning designated in places throughout this Agreement.

ARTICLE 2
AGREEMENT OVERVIEW

The intent of the strategic Collaboration is (a) for Akcea to Commercialize inotersen in accordance with the Strategic Plan approved by the Joint Steering Committee and for the Parties to share profits from the Commercialization of inotersen, (b) for the Parties to develop IONIS-TTR-L_{Rx} under the Strategic Plan approved by the JSC through completion of all Pivotal Studies necessary to obtain Approval throughout the world, and (c) following receipt of Approval of IONIS-TTR-L_{Rx}, for Akcea to Commercialize IONIS-TTR-L_{Rx} in accordance with the Strategic Plan and for the Parties to share profits from the Commercialization of IONIS-TTR-L_{Rx}. The JSC will review and determine whether to approve all Material Changes in the Strategic Plan. The purpose of this ARTICLE 2 is to provide a high-level overview of the roles and responsibilities and rights and obligations of each Party under this Agreement and therefore this ARTICLE 2 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

ARTICLE 3
DEVELOPMENT AND COMMERCIALIZATION - STRATEGY AND MANAGEMENT

Section 3.1 **Initial Development and Commercialization**. Prior to approval of the initial Strategic Plan the Parties will conduct the Development and Commercialization of the Products in accordance with those plans and budgets for the Products as may be agreed and updated by the Parties from time to time (the "***Initial 2018 Plans and Budgets***").

Section 3.2 **Strategic Plan**.

3.2.1 The Strategic Plan. The Parties will Develop and Commercialize the Products in accordance with this Agreement and pursuant to a global strategic Development and Commercialization plan (the "***Strategic Plan***").

(a) ***Development and Commercialization***. The Strategic Plan will provide that Akcea will be responsible for Commercializing inotersen in each country where it receives Approval and for conducting all Akcea Non-Commercial Activities for inotersen, and Ionis will be responsible for Developing inotersen until the receipt of Approval in certain countries throughout the world, other than the performance of Akcea Non-Commercial Activities. The Strategic Plan will also provide that Ionis will be responsible for Developing IONIS-TTR-L_{Rx} through completion of all Pivotal Studies, and Akcea will be responsible for Commercializing IONIS-TTR-L_{Rx} in each country where it receives Approval and for conducting all Akcea Non-Commercial Activities for IONIS-TTR-L_{Rx}; *provided that* the JSC will periodically evaluate each Party's experience, expertise, and resources and may determine to allocate any such Development activities for IONIS-TTR-L_{Rx} to either Party (and include such allocation in the Strategic Plan) based on such experience, expertise, and resources of each Party at such time. The Strategic Plan will cover both the long-term global Development and Commercialization strategy for each of the Products separately and collectively as a suite of products and will also detail the specific Development and Commercialization activities to be performed over the course of the upcoming 24 months, on a rolling basis. Without limiting the foregoing, Schedule 3.2.1 contains a list of examples of content that may be included in the Strategic Plan, as appropriate, based on the stage of Development or Commercialization of the applicable Product.

(b) ***Manufacture and Supply***. The Strategic Plan will provide that Akcea will be responsible for the Manufacture and supply of API and Drug Product (i) of inotersen to support Commercialization and Akcea Non-Commercial Activities, other than any inotersen API and Drug Product purchased by Akcea from Ionis pursuant to Section 3.8, and (ii) of IONIS-TTR-L_{Rx} to support Commercialization and Akcea Non-Commercial Activities under the Strategic Plan, in each case ((i) and (ii)), subject to Ionis' compliance with Section 3.8.2(a). The Strategic Plan will provide that Ionis will be responsible for the Manufacture and supply of API and Drug Product of IONIS-TTR-L_{Rx} to support Development activities under the Strategic Plan through completion of all Pivotal Studies for IONIS-TTR-L_{Rx}. In addition, to facilitate the foregoing allocation of responsibilities between the Parties for the Manufacture and supply of the Products, the Strategic Plan will include the strategy for Manufacturing and supply of API and Drug Product sufficient to support Commercialization of each Product (and to perform any Akcea Non-Commercial Activities) and a sequence of activities and associated timelines for the orderly transition from Ionis to Akcea of CMC activities for each Product on or before the receipt of Approval for each such Product from the FDA and the EMA, including, as contemplated under Section 3.8.2(a), the assignment from Ionis to Akcea of Ionis' supply agreements with CMOs for inotersen API and Drug Product as of the Effective Date and, at the applicable time, Ionis' supply agreements with CMOs for IONIS-TTR-L_{Rx} API and Drug Product.

(c) ***Commercial Activities and Budget***. The Strategic Plan will address, among other important Commercial matters, (i) pre-launch, launch, and subsequent Commercialization activities for inotersen (which may include, as appropriate at any given time based on the stage of Commercialization, market access strategy, messaging, branding, pricing, advertising, education, publication planning, marketing, compliance, and field force training), (ii) key decisions and timelines for Commercialization activities, (iii) key strategies and tactics for implementing those activities, and (iv) a budget approved by the JSC for all inotersen Commercial activities set forth in the Strategic Plan, which budget will include costs associated with each Party's FTEs and out of pocket expenses (consistent with the terms set forth in Schedule 6.4.1) necessary for each Party to conduct its Commercialization activities under the Strategic Plan (such budget, the "***Commercial Budget***"). The Commercial activities and strategy in the Strategic Plan will be driven by the shifting competitive landscape over time, reimbursement environment, medical factors that impact

Commercialization strategies, patient experiences that inform TTR amyloidosis treatment, and emerging data generated from Clinical Trials of IONIS-TTR-L_{Rx}. As such, the Parties anticipate that the Commercial components of the Strategic Plan for each Product will evolve over time and become more detailed as inotersen and IONIS-TTR-L_{Rx} move closer to launch in, and thereafter penetrate, each market. The Commercialization activities under the Strategic Plan will initially cover inotersen only and at the appropriate time the Commercial sections of the Strategic Plan will be updated to include Commercial activities for IONIS-TTR-L_{Rx} as set forth in Section 3.2.3. In addition to the Commercial activities to be included for IONIS-TTR-L_{Rx}, at the appropriate time, the Parties will also discuss and update the Strategic Plan to reflect strategies and activities for Commercializing both Products, including synergies that may result from having each Product on the market.

(d) ***Development Activities and Budget***. The Strategic Plan will address, among other important Development matters, (i) all non-clinical and preclinical studies and Clinical Trials to be conducted through completion of the last Pivotal Study for IONIS-TTR-L_{Rx}, (ii) all Akcea Non-Commercial Activities for each Product, and (iii) a budget approved by the JSC for all such activities for each Product set forth in the Strategic Plan, which budget will include costs associated with each Party's FTEs and out of pocket expenses (consistent with the terms set forth in Schedule 6.4.1) necessary for each Party to conduct the foregoing activities set forth under the Strategic Plan (such budget, the "***Development Budget***").

(e) ***Regulatory Matters under the Strategic Plan***. The Strategic Plan will also address, among other important regulatory matters, regulatory strategy and communication management, transfer of Regulatory Documentation, submissions to Regulatory Authorities, meetings with Regulatory Authorities, regulatory communications, Product labeling, and safety reporting and pharmacovigilance, in each case, which regulatory matters included in the Strategic Plan will be subject to and in accordance with Section 3.5 (Interactions with, and Submissions to, Regulatory Authorities).

3.2.2 Developing the Initial Strategic Plan. The JSC will review, discuss, and determine whether to approve the initial Strategic Plan (other than the Development Budget and Commercial Budget to be included therein), which will be a separate written document from this Agreement, by September 1, 2018. Following such approval of the initial Strategic Plan, the Parties will prepare and submit to the JSC for its review, discussion, and approval by November 15, 2018 (as part of its annual budget process) (a) an initial Commercial Budget and Development Budget for Calendar Year 2019, in each case, that reflect the Commercialization and Development activities set forth in the initial Strategic Plan to be performed in Calendar Year 2019, and (b) a preliminary forecast of the budgets for the Development and Commercial activities (including all Akcea Non-Commercial Activities) set forth in the initial Strategic Plan for Calendar Year 2020. Akcea will have primary responsibility for developing those sections of the initial Strategic Plan related to the Commercialization activities and Akcea Non-Commercial Activities for each Product and the associated Commercial Budget and portion of the Development Budget covering the Akcea Non-Commercial Activities, in each case, other than regulatory matters. Ionis will have primary responsibility for developing those sections of the initial Strategic Plan that set forth the (i) Development activities for IONIS-TTR-L_{Rx} through completion of the first Phase 1 Clinical Trial for IONIS-TTR-L_{Rx} (other than the Akcea Non-Commercial Activities) and the associated Development Budget (other than the portion of the Development Budget covering the Akcea Non-Commercial Activities), other than regulatory matters, and (ii) the strategy for Manufacturing and supply of API and Drug Product sufficient to support Commercialization of inotersen (and any Akcea Non-Commercial Activities) and a sequence of activities and associated timelines for the orderly transition from Ionis to Akcea of CMC activities for inotersen. The Regulatory Sub-Committee will have primary responsibility for developing those sections of the Strategic Plan that set forth important regulatory matters for the Products and the portion of the Development Budget or Commercial Budget (as applicable) covering such regulatory matters. The JSC will review, discuss, and determine whether to approve each section of the initial Strategic Plan, which discussion will afford each Party the opportunity to review and comment on those sections of the Strategic Plan developed by the other Party.

3.2.3 Updating the Strategic Plan. Following the JSC's approval of the initial Strategic Plan, each Party (including through the Regulatory Sub-Committee) will develop updates to those sections of the Strategic Plan for which it is responsible every six months to account for the progression of Development, Manufacturing, and Commercialization of each Product, which updates will include an update to the Strategic Plan prior to completion of the first Phase 1 Clinical Trial for IONIS-TTR-L_{Rx} and an update in September of each Calendar Year (to enable each Party to timely complete its internal annual budget process). Akcea will also be responsible,

following Ionis' development of such section in the initial Strategic Plan, for updating the Strategic Plan to include (a) the strategy for Manufacturing and supply of API and Drug Product (i) of inotersen sufficient to support Commercialization (and any Akcea Non-Commercial Activities), and (ii) of IONIS-TTR-L_{Rx},following receipt of Approval therefor in the U.S., and (b) a sequence of activities and associated timelines for the orderly transition from Ionis to Akcea of CMC activities for IONIS-TTR-L_{Rx} following receipt of Approval therefor in the U.S. Ionis will remain responsible for updating such strategy for the Manufacturing and supply of IONIS-TTR-L_{Rx} through receipt of Approval therefor in the U.S. Without limiting the generality of the foregoing, the Parties will discuss (through the JSC), and Ionis will take into consideration and not unreasonably refuse to implement Akcea's comments relating to aspects of Development (including designs and protocols of Clinical Trials) of IONIS-TTR-L_{Rx} that are likely to affect Commercializing of IONIS-TTR-L_{Rx}, such as trial site selection, health economic outcomes, quality of life measures, endpoints, market access, and optimal reimbursement. In addition, at the appropriate time, but no later than at the completion of the first Phase 1 Clinical Trial for IONIS-TTR-L_{Rx}, Akcea will update the Development section of the Strategic Plan to account for Akcea Non-Commercial Activities for IONIS-TTR-L_{Rx} and the Commercial section of the Strategic Plan to account for Commercial activities for IONIS-TTR-L_{Rx}.Each Party or the Regulatory Sub-Committee, as applicable, will submit those sections of the proposed updated Strategic Plan developed by it to the other Party at least 15 days prior to the next JSC meeting. Subject to Section 3.4.4, the JSC must determine whether to approve any material changes to the Strategic Plan included in any update (each, a "***Material Change***").

Section 3.3 **Diligence**. Akcea will use Commercially Reasonable Efforts to (a) conduct the Commercialization activities assigned to Akcea as set forth in the Strategic Plan in accordance with the timelines specified therein, and (b) Commercialize the Products following receipt of Approval therefor in a country. Both Parties will use Commercially Reasonable Efforts to Develop the Products, including conducting the activities assigned to each Party as set forth in the Strategic Plan in accordance with the timelines specified therein.

Section 3.4 **Development and Commercialization Management**.

3.4.1 Joint Steering Committee. The Parties will establish a Joint Steering Committee (the "***JSC***") to oversee and manage the conduct of activities related to the Development and Commercialization of the Products. The JSC will consist of four representatives appointed by Ionis and four representatives appointed by Akcea each with Development or Commercialization expertise with one JSC representative from each Party being such Party's chief financial officer. The JSC will determine the JSC operating procedures at its first meeting, including policies for participation by additional representatives or consultants invited to attend JSC meetings, and the timing and location of meetings, which will be codified in the written minutes of the first JSC meeting. Each Party may replace one or more of its representatives on the JSC from time to time upon written notice to the other Party.

3.4.2 Meetings. During the first 12 months after the Execution Date the JSC will meet on an ongoing basis (as often as reasonably necessary but at least monthly) to prepare for and to effectively execute the launch of inotersen, which will include the review and discussion of and determination as to whether to approve the initial Strategic Plan and associated Development Budget and Commercial Budget. Thereafter, the JSC will meet on a quarterly basis. The JSC may hold meetings in person or by audio or video conference as determined by the JSC. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JSC meetings. Each Party will be responsible for the costs of its own representatives attending such meetings, and such costs will not be "*Expenses*" under Schedule 6.4.1.

3.4.3 Role of the JSC. Without limiting any of the foregoing, the JSC will perform the following functions, some or all of which may be addressed directly at any given JSC meeting:

(a) review Akcea's progress on performing the Commercialization and Akcea Non-Commercial Activities under the Strategic Plan;

(b) review each Party's progress on performing the Development activities for IONIS-TTR-L_{Rx} assigned to it under the Strategic Plan;

(c) review and discuss the strategy for Manufacturing and supply of API and Drug Product sufficient to support Commercialization of each Product (and to perform any Akcea Non-Commercial Activities) and a sequence of activities and associated timelines for the orderly transition from Ionis to Akcea of CMC activities for each Product;

(d) review and provide advice on the execution of activities and strategies set forth under the Strategic Plan with respect to each Product;

(e) review, discuss, and determine whether to approve the initial Strategic Plan and all updates thereto that contain Material Changes, as described in Section 3.2.2;

(f) discuss key regulatory interactions and strategy for the Products;

(g) review, discuss, and determine whether to approve the Commercial Budget for each Product, including any updates thereto, as described in Section 3.2.2;

(h) review, discuss, and determine whether to approve the Development Budget, including any updates thereto, as described in Section 3.2.2;

(i) establish the Allowable Overage for each Calendar Year;

(j) review and provide advice on Clinical Trial designs for each Product;

(k) if referred by a Party following the JPC's failure to reach consensus, determine the strategy with regard to the defense against actual or potential allegations of infringement of any Patent Controlled by a Third Party, including the institution of any *inter partes* review, opposition or other proceeding related to any such Patent;

(l) establish subcommittees as necessary to conduct the activities set forth in the Strategic Plan, including a Regulatory Sub-Committee, and, as may be determined necessary by the JSC, clinical development sub-committee, a manufacturing sub-committee, and a clinical operations sub-committee (with the expectation that such sub-committees will evolve as required by the status of Development or Commercialization of the Products); and

(m) such other review, approval, and advisory responsibilities as may be assigned to the JSC under this Agreement.

3.4.4 Decision Making.

(a) Committee Decision-Making. Decisions by the JSC will be made by unanimous consent of each Party with each Party's representatives having, collectively, one vote. At any given meeting of any such committee, a quorum will be deemed reached if two voting representatives of each Party 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 to be approved by the JSC if the JSC has not reached unanimous consensus.

(b) Final Decision-Making. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the JSC regarding the conduct of the activities under the Strategic Plan. The JSC will endeavor in good faith to reach consensus on all decisions, *however*, if the JSC cannot unanimously agree on a matter to be decided or approved by the JSC, then, except as otherwise set forth in Schedule 6.4.1, the matter may be referred to the Senior Representatives for resolution. If the Senior Representatives cannot reach agreement, then (i) without limiting Akcea's obligations under Section 3.3, Akcea will have final-decision making authority with respect to (A) matters relating to the Commercialization or Akcea Non-Commercial Activities (other than Pre-Approval Akcea Development Activities) of any Product and Manufacture of the Products for such purposes, including approval of those sections of the Strategic Plan covering Commercialization, Akcea Non-Commercial Activities (other than Pre-Approval Akcea Development Activities), and Manufacturing of the Products for such activities (but not the Commercial Budget), and how to implement the JSC's recommendations with respect thereto, and (B) matters relating to the strategy with regard to the defense against actual or potential allegations of infringement of any Patent Controlled by a Third Party, including the institution of any *inter partes* review, opposition, or other proceeding related to any such Patent, and (ii) Ionis will have final-decision making authority with respect to matters relating to the Development (other than Akcea Non-Commercial Activities that are not Pre-Approval Akcea Development Activities) of any Product and the Manufacture of the

Product for such purposes, including approval of those sections of the Strategic Plan covering Development other than Akcea Non-Commercial Activities that are not Pre-Approval Akcea Development Activities (but not the Development Budget) and Manufacturing of the Products for such purposes, and how to implement the JSC's recommendations with respect thereto.

(c) Limitations on Decision-Making. Notwithstanding anything to the contrary set forth in this Agreement, a Party may not exercise its final decision-making right to (i) increase the Commercial Budget or Development Budget or the other Party's Internal Expenses, External Expenses, or obligations under the Strategic Plan, or (ii) increase the other Party's commitments to a Regulatory Authority; *provided, however*, that neither Party will unreasonably withhold its consent to an increase in the Commercial Budget or Development Budget that is reasonably necessary to fund the activities contemplated by the most recent Strategic Plan approved by the JSC. In addition, and notwithstanding anything to the contrary set forth in this Agreement, Ionis may not exercise its final decision-making authority with respect to Pre-Approval Akcea Development Activities in a manner that causes or would reasonably be expected to cause Akcea to violate or act in a manner inconsistent with any of Akcea's standard operating procedures or codes of conduct or Applicable Law. The JSC will solely have the decision-making authority expressly assigned to it under this Agreement, and, notwithstanding anything to the contrary set forth in this Agreement, will not have the authority to make any decision (A) in a manner that excuses a Party from any obligation specifically enumerated under this Agreement, (B) in a manner that negates any consent right or other right specifically allocated to a Party under this Agreement, (C) to resolve any dispute involving the breach or alleged breach of this Agreement or to amend or modify this Agreement or any of the Parties' respective rights and obligations hereunder, (D) to resolve a matter if the provisions of this Agreement specify that unanimous or mutual agreement of the Parties (and not the JSC) is required for such matter, or (E) in a manner that would require a Party to perform any act that would cause such Party to breach any of its obligations hereunder.

3.4.5 Term of the JSC. Each Party's obligation to participate in the JSC will continue for the Agreement Term.

3.4.6 Briefing the JSC. At each regularly scheduled meeting of the JSC each Party will provide to the JSC a progress update on each Party's performance of activities related to each Product under the Strategic Plan, which progress update can take the form of a PowerPoint presentation.

3.4.7 Alliance Managers. Each Party will appoint a representative to act as its alliance manager, which alliance manager will promote the overall health of the relationship between the Parties and oversee the conduct of the Collaboration.

3.4.8 Dispute Resolution. Other than those matters to be approved or determined by the JSC, disputes related to regulatory matters, or as otherwise set forth in Schedule 6.4.1, the Parties will resolve all Disputes related to the Development or Commercialization of the Products in accordance with Section 13.4.

3.4.9 Status Updates to the Ionis Board of Directors. Upon Ionis' reasonable request, Akcea will present updates to Ionis' board of directors (and answer any reasonable questions posed by such directors) regarding the status of the Development or Commercialization of the Products, including presenting any proposed Commercial Budget or Development Budget for the upcoming Calendar Year.

Section 3.5 **Interactions with, and Submissions to, Regulatory Authorities**.

3.5.1 Regulatory Strategy and Communication Management. The Parties will, through the JSC, establish a committee comprised of two members from each of Akcea and Ionis with requisite experience in Regulatory strategy and communications (the "***Regulatory Sub-Committee***"). The Parties acknowledge that, subject to Section 3.5.6 and Section 3.5.8 (a) Ionis and Akcea will share responsibilities related to devising and implementing regulatory strategy under this Agreement, (b) Akcea will lead all regulatory activities related to Akcea Non-Commercial Activities (other than Pre-Approval Akcea Development Activities), (c) the Party that holds the IND (and the NDA following receipt of Approval for the Product in a country) (the "***Regulatory Responsible Party***") for the applicable Product will lead all other regulatory activities for such Product (including with respect to Manufacturing), (d) Ionis will be responsible for filing the NDA, MAA, and other marketing authorization applications with Regulatory Authorities for inotersen until such time as the Parties may

agree to transfer such responsibilities to Akcea, and (e) Akcea will be responsible for filing the NDA, MAA, and other marketing authorization applications with Regulatory Authorities for IONIS-TTR-L_{Rx}. The Regulatory Sub-Committee will be responsible for determining by mutual agreement:

(a) The overall regulatory strategy for each of the Products;

(b) The content of each submission to a Regulatory Authority related to the Products;

(c) The attendees, roles, and responsibilities of such attendees and strategy for all important interactions with Regulatory Authorities related to the Development and Commercialization of the Products; and

(d) The strategy and content of all material correspondence with Regulatory Authorities related to the Development and Commercialization of the Products.

3.5.2 Transfer of Regulatory Documentation. No later than 30 days after the receipt of Approval for a Product in a country, unless otherwise agreed by the Parties, Ionis will assign to Akcea all rights, title, and interests in and to each IND and NDA for such Product filed in such country. The date of such transfer will be the "***NDA Transfer Date***." After the NDA Transfer Date for a Product in a country, Ionis will transfer to Akcea in accordance with the regulatory plan to be established by the Regulatory Sub-Committee copies (in electronic or other format) of other Regulatory Documentation (including drafts) Controlled by Ionis as of the NDA Transfer Date related to such Product (collectively, with the Regulatory Documentation transferred to Akcea pursuant to this Section 3.5.2 the "***Assigned Regulatory Documentation***"). Ionis will execute all letters, attestations, forms, confirmatory assignments, and other documentation reasonably requested by Akcea to give effect to the assignment and transfer of INDs, NDAs, and Assigned Regulatory Documentation contemplated by this Section 3.5.2. If any Approval for a Product in a country cannot be transferred to Akcea within such 30 day period, then, to the extent it would be helpful to hasten the Commercialization of such Product in such country, at Akcea's request, Ionis will appoint Akcea as its exclusive distributor of the applicable Product in such country and grant Akcea the right to appoint sub-distributors until such time as such Approval in such country has been transferred to Akcea, and the Parties will enter into a distribution agreement on reasonable and customary terms to memorialize such appointment.

3.5.3 Submissions to Regulatory Authorities. Subject to Section 3.5.6, the Parties will mutually agree on the content of all important written submissions to Regulatory Authorities for the Products, including INDs, Investigator Brochures, CTDs, and NDAs. The Regulatory Sub-Committee will mutually develop and agree to a detailed plan for coordination and preparation of regulatory filings for market approval for the Products (including establishing responsibilities for provision of all sections of the electronic common technical document ("***eCTD***") modules, and plan activity timelines) to accelerate eCTD completion and facilitate rapid completion of regulatory filings to obtain Approval for the Products. Once the Parties mutually agree upon such a plan, each Party will use Commercially Reasonable Efforts to execute its respective tasks and responsibilities under such plan in accordance with the time frames set forth in such plan.

3.5.4 Meetings with Regulatory Authorities. The Parties will mutually agree on the strategy for all meetings with Regulatory Authorities, including pre-IND meetings, end of Phase 2 Clinical Trial meetings, scientific advice in the EU, and the preparatory sessions therefor. The Regulatory Sub-Committee will mutually agree on the attendees for each such meeting (with Ionis having up to three representatives and the goal of equal representation from Akcea and Ionis), each attendee's role and responsibilities, and the strategy for addressing the issues to be discussed with the Regulatory Authority for each such meeting. In addition, Akcea will promptly disclose to the Regulatory Sub-Committee any planned substantive interactions with a Regulatory Authority in a Major Market reasonably in advance of such interaction to provide the Parties with sufficient time to discuss the strategy with respect to such interaction.

3.5.5 Regulatory Communications for Products. The receiving Party will provide to the other Party for its review all important documents and communications received from Regulatory Authorities in Major Market countries that impact the Development, Commercialization, or potential Approval of Products as soon as reasonably practicable. Akcea and Ionis will mutually agree on the content of all responses to such documents and communications received from any Regulatory Authorities in a Major Market country.

3.5.6 Product Label and Class Generic Claims. The Parties will work collaboratively, and Akcea will lead the effort, to create the label for each Product for submission to Regulatory Authorities, including the

proposed label for inotersen and IONIS-TTR-L_{Rx} included in each NDA. Akcea will submit any proposed Product label to Ionis for Ionis' review and comment and the Parties will endeavor to mutually agree on the final label for each Product to be submitted to each Regulatory Authority in each country. If the Parties cannot mutually agree on a Product label, then Akcea will have final decision-making authority with respect thereto, other than with respect to any statement to be included in the proposed label for a Product that Ionis reasonably determines is not supported by the data generated from Clinical Trials of such Product, for which statements Ionis will have final decision-making authority. In addition, to the extent Akcea intends to make any claims in a label or regulatory filing for a Product that are class generic to antisense oligonucleotides, Ionis' generation 2.0 or 2.5 chemistry platform(s), or Conjugate Technology the Regulatory Sub-Committee will adopt Ionis' language for such class generic claim in such label or regulatory filing.

3.5.7 Safety Reporting, Pharmacovigilance, and Regulatory Coordination. The Parties acknowledge and agree that Ionis and Akcea will coordinate their respective Development activities for the Products, including with respect to the conduct of all Clinical Trials (including the collection and reporting of adverse events and pharmacovigilance), regulatory activities, and nonclinical and pre-clinical activities.

3.5.8 Disputes Related to Regulatory Matters. If the Parties cannot come to a mutual agreement through the Regulatory Sub-Committee on an issue related to regulatory matters, then the Regulatory Responsible Party for the applicable Product at such time will have the final decision-making authority over such matter, except as otherwise set forth in Section 3.5.6 with respect to decisions regarding the label for a Product and class generic claims included in any regulatory filings for a Product.

Section 3.6 **Collaboration Costs**. Costs incurred by Ionis or Akcea associated with inotersen or IONIS-TTR-L_{Rx} under this Agreement will be handled in accordance with Schedule 6.4.1.

Section 3.7 **Subcontracting**. Subject to the terms of this Section 3.7, each Party will have the right to engage Third Party subcontractors to perform 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 granted to the other Party under this Agreement.

Section 3.8 **Manufacturing, Supply and CMC**.

3.8.1 Sale of Existing Inotersen Supply. Ionis will sell to Akcea, and Akcea will purchase from Ionis, the commercial and clinical-grade inventory of API and Drug Product for inotersen set forth on the inventory schedule disclosed by Ionis to Akcea via the electronic data room hosted in connection with the transactions contemplated hereunder, in each case, in accordance with a purchase schedule to be mutually agreed by the Parties. The price for such inotersen API and Drug Product is the price equal to Ionis' Cost of Goods (or, if made by a Third Party, the price Ionis was charged for such material) calculated based on the pricing methodology Ionis uses for its other partners, which cost will be handled in accordance with Schedule 6.4.1. Akcea will take delivery of such material at times to be agreed by the Parties.

3.8.2 Manufacturing Agreements.

(a) ***Assignment of Existing CMO Agreements***. In accordance with the process and timelines set forth in the Strategic Plan with respect to the applicable Product, Ionis will assign to Akcea any agreements with Ionis' CMOs for the applicable Product, unless any such agreement with a CMO expressly prohibits such assignment, in which case Ionis will cooperate with Akcea in all reasonable respects to secure the consent of the applicable Third Party to such assignment. If any such consent cannot be obtained with respect to such an agreement with a CMO, then Ionis will facilitate the introduction of Akcea to the applicable CMO and obtain for Akcea substantially all of the practical benefit and burden under such CMO agreement until such time as Akcea is able to enter into its own agreements with one or more CMOs for the supply of the applicable Product sufficient to enable Akcea to comply with its Manufacturing obligations for such Product set forth under this Agreement and the Strategic Plan, including by (i) entering into appropriate and reasonable alternative arrangements on terms agreeable to each of Ionis and Akcea, and (ii) subject to the consent and control of Akcea, enforcing for the account of Akcea, any and all rights of Ionis against the other party thereto arising out of the breach or cancellation thereof by such other party or otherwise.

(b) ***Additional Manufacturing Agreements***. In connection with Akcea's selecting and engaging one or more CMOs to perform its Manufacturing obligations set forth in the Strategic Plan with respect to each Product, the Parties will cooperate in good faith to negotiate and execute any agreements with CMOs for the Manufacture of API or Drug Product for use in the Commercialization of a Product and the performance of Akcea Non-Commercial Activities (each such agreement, a "***Manufacturing Agreement***"). Akcea will have the final decision-making authority regarding the selection of the CMO and the terms of any such Manufacturing Agreement. As between the Parties, Akcea will enter into such Manufacturing Agreements with CMOs. Under each Manufacturing Agreement at Akcea's election, Ionis will either (i) grant a license to the selected CMO under the Ionis Manufacturing Patents and Ionis Manufacturing and Analytical Know-How to the extent necessary for such CMO to Manufacture Products in such Third Party's own manufacturing facility, or (ii) permit Akcea to grant a sublicense from Akcea to the selected CMO under the Ionis Manufacturing Patents and Ionis Manufacturing and Analytical Know-How. Each Manufacturing Agreement will include provisions permitting Ionis to elect to have such agreements assigned to Ionis in the event of a termination of this Agreement. Other than in connection with such an assignment upon termination of this Agreement, and except as set forth in the Strategic Plan, Ionis will have no obligations under such Manufacturing Agreements. Prior to execution of any such Manufacturing Agreement, Akcea will provide a copy of any proposed Manufacturing Agreement to Ionis for Ionis' review and will consider in good faith all comments and recommendations provided by Ionis with respect to such Manufacturing Agreement. Akcea will provide Ionis with a true and complete copy of any Manufacturing Agreement that it enters into with a CMO within 30 days after the execution thereof.

Section 3.9 **Ionis Internal Oligonucleotide Safety Database**.

3.9.1 Ionis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Ionis Internal Oligonucleotide Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Ionis' compounds, Akcea will reasonably cooperate in connection with populating the Ionis Internal Oligonucleotide Safety Database. To the extent collected by Akcea and in the form in which Akcea uses/stores such information for its own purposes, Akcea will provide Ionis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events, and other safety information related to a Product reasonably promptly following the date such information is available to Akcea (but not later than 90 days after Akcea's receipt of such information). In connection with any reported serious adverse event, Akcea will provide Ionis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to a Product, Akcea will provide Ionis with copies of annual safety updates filed with each IND and the safety sections of any final Clinical Trial reports within 90 days following the date on which such information is filed or is available to Akcea, as applicable. Furthermore, Akcea will promptly provide Ionis with reasonable supporting data and answers to follow-up questions requested by Ionis. All such information disclosed by Akcea to Ionis will be Akcea Confidential Information; *provided*,*however*, that Ionis may disclose any such Akcea Confidential Information to (a) Ionis' other partners if such information is regarding class generic properties of oligonucleotides pursuant to Section 3.5.6, or (b) any other Third Party, in each case, so long as Ionis does not disclose the identity of a Product or Akcea or any information from which the identity of a Product or Akcea can be derived. Akcea will deliver all such information to Ionis for the Ionis Internal Oligonucleotide Safety Database to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
Attention: Head of Drug Safety Monitoring

(or to such other address/contact designated in writing by Ionis). Akcea will also require its Affiliates and Sublicensees to comply with this Section 3.9.

3.9.2 From time to time, Ionis utilizes the information in the Ionis Internal Oligonucleotide Safety Database to conduct analyses to keep Ionis and its partners informed regarding class generic properties of oligonucleotides, including with respect to safety, without compromising the confidential information of the contributing partners. 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 inform Akcea of such issues and, if requested, provide the data supporting Ionis' conclusions.

3.9.3 During the Agreement Term, Akcea may submit written requests to Ionis for Ionis to run queries of the Ionis Internal Oligonucleotide Safety Database relevant to one or more Products, and Ionis will use Commercially Reasonable Efforts to promptly run such queries and deliver to Akcea the results of such queries. Any information disclosed between the Parties under this Section 3.9.3 will be treated as Confidential Information in accordance with ARTICLE 8.

ARTICLE 4
GRANT OF RIGHTS

Section 4.1 **License Grants From Ionis to Akcea**. Subject to the terms and conditions of this Agreement, including the conditions and limitations set forth in Section 4.5 below, Ionis hereby grants to Akcea:

4.1.1 an exclusive, world-wide, royalty-bearing license, with the right to grant sublicenses as set forth in Section 4.2 below, under Ionis' rights in the Ionis Product-Specific Patents, Ionis Product-Specific Know-How, Ionis Core Technology Patents, Ionis Core Technology Know-How, and Joint Patents to Develop, make, have made, use, sell, have sold, offer for sale, import and otherwise Commercialize Products; and

4.1.2 a non-exclusive, world-wide, royalty-bearing license, with the right to grant sublicenses as set forth in Section 4.2 below, under the Ionis Manufacturing Patents and Ionis Manufacturing and Analytical Know-How to Manufacture Products (a) by Akcea in Akcea's own manufacturing facility, (b) by a CMO previously granted licenses to practice the Ionis Manufacturing Patents, or (c) in the facility of a CMO selected and engaged by Akcea under a Manufacturing Agreement and subsequently granted licenses or sublicenses in accordance with Section 3.8.2(b), as applicable, to practice the Ionis Manufacturing Patents and Ionis Manufacturing and Analytical Know-How.

Section 4.2 **Sublicenses**. The licenses granted to Akcea under Section 4.1 are sublicensable only in connection with the grant of rights to any Third Party or Affiliate, in each case, for the continued Development and Commercialization of a Product in accordance with the terms of this Agreement. Akcea will not enter any agreement with a Third Party that sublicenses, transfers, grants a security interest in, or otherwise encumbers any of the Products, including the Patents or Know-How licensed to Akcea under this Agreement Covering such Products, in each case, without Ionis' prior written consent (including with respect to the terms of any such an agreement with a Third Party), such consent not to be unreasonably withheld, delayed, or conditioned. Akcea will provide Ionis with written notice of any Sublicense granted pursuant to this Section 4.2 within 30 days after the execution thereof together with a true and complete copy of any such Sublicense or any other Sublicense entered into by Akcea, subject to Akcea being entitled to make such appropriate redaction for information that does not relate to a Product to the extent not relevant to Ionis' enforcement of such Sublicense and not reasonably necessary for Ionis to determine Akcea's compliance with the terms of this Agreement. Notwithstanding the foregoing, Ionis' consent will not be required for Akcea to enter into a Distribution Agreement with respect to one or more countries outside of the Major Market countries that is consistent with the scope of the licenses granted to Akcea hereunder (with or without packaging rights).

Section 4.3 **Enforcing Sublicense Agreements**. If Akcea fails to take any action to enforce the applicable terms of a Sublicense granted pursuant to Section 4.2 for a period of 15 days following receipt of written notice of such failure from Ionis, which failure, in Ionis' good faith determination, could cause a material adverse effect on Ionis or Ionis' technology, then Akcea hereby grants Ionis the right to enforce such Sublicense terms on Akcea's behalf and will cooperate with Ionis (which cooperation will be at Akcea's sole expense and will include Akcea 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.

Section 4.4 **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, then any Sublicensee 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 Akcea; *so long as* (a) such Sublicensee is not in breach of its Sublicense, (b) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by Akcea, and (c) 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 Akcea. Akcea agrees that it will confirm clause (a) of the foregoing in writing at the request and for the benefit of Ionis and if requested, the Sublicensee.

Section 4.5 **License Limitations; Retained Rights**.

4.5.1 The licenses granted under this ARTICLE 4 are subject to and limited by the (a) Prior Agreements, (b) Existing In-License Agreements, and (c) Future In-License Agreements, in each case ((a) – (c)), to the extent the provisions of such obligations or agreements have been specifically disclosed to Akcea in writing (or via electronic data room).

4.5.2 All rights in and to Ionis Licensed Technology not expressly licensed to Akcea under this Agreement are hereby retained by Ionis or its Affiliates. All rights in and to Akcea Technology not expressly licensed to Ionis under this Agreement are hereby retained by Akcea or its Affiliates. In addition, notwithstanding the exclusive licenses granted under this ARTICLE 4, Ionis retains the right to: (a) perform any activities pursuant to the Prior Agreements as in effect on the Effective Date; and (b) grant licenses to any Third Party under the Ionis Core Technology Patents to (i) conduct pre-clinical research, or (ii) enable such Third Party to Manufacture or formulate oligonucleotides, where 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.

Section 4.6 **Technology Transfer**.

4.6.1 Ionis Know-How. Ionis will promptly deliver to Akcea or one or more designated Affiliates all Know-How in Ionis' possession related to the Products that has not previously been provided to Akcea for use solely in accordance with the licenses granted to Akcea under Section 4.1.1 and Section 4.1.2.

4.6.2 Ionis Manufacturing and Analytical Know-How. Ionis will promptly deliver to Akcea or one or more designated Affiliates or any mutually agreed upon Third Party CMOs all Ionis Manufacturing and Analytical Know-How in Ionis' Control relating to the Products that is necessary for the exercise by Akcea, its Affiliates, or a Third Party of the Manufacturing rights granted to Akcea under Section 4.1.2, in each case, solely for use by Akcea, its Affiliates, or a Third Party acting on Akcea's behalf under a Manufacturing Agreement (or an agreement with a Third party CMO assigned by Ionis to Akcea) to Manufacture API or Drug Product (including any mutually agreed upon contract manufacturers). Upon Akcea's request, and provided such request is consistent with the supply chain strategy set forth in the Strategic Plan, Ionis will provide Ionis personnel to transfer such Manufacturing and Analytical Know-How under this Section 4.6.2 to any Third Party Manufacturing API or Drug Product on Akcea's behalf solely to enable such Third Party to Manufacture API or Drug Product in accordance with the terms of this Agreement.

Section 4.7 **No Implied License**. Except as expressly provided in this Agreement no Party will be deemed by estoppel or implication to have granted to the other Party any license or other right with respect to any intellectual property.

Section 4.8 **License to Ionis under Akcea Collaboration Technology**. Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 5.1.2 and without limiting the licenses granted to Akcea under Section 4.1), Akcea hereby grants Ionis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable license under any Akcea Collaboration Technology to Develop, Manufacture, have Manufactured, and Commercialize products that include an oligonucleotide as an active pharmaceutical ingredient, other than a Competing Product.

ARTICLE 5
EXCLUSIVITY COVENANTS

Section 5.1 **Exclusivity; Limitations**.

5.1.1 Akcea's Exclusivity Covenants. Akcea, its Affiliates, and its Sublicensees will not work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to the Development or Commercialization of any product (including an ASO) that (a) is a Competing Product, or (b) is reasonably expected to decrease the market share for a Product and treats or is intended to treat transthyretin amyloidosis or any other Indication for which a Product is being Developed or Commercialized under this Agreement, in each case ((a) and (b)), until, on a Product-by-Product and country-by-country basis, the expiration of the last Valid Claims in an Ionis Patent Covering a Product in a country.

5.1.2 Ionis' Exclusivity Covenants. Except in the exercise of its retained rights under Section 4.5.2 or the exercise of its right in accordance with the last sentence of this Section 5.1.2, Ionis, its Affiliates, and its Sublicensees will not practice any Ionis Licensed Technology or Joint Patents or grant any license to any Third

Party to practice any Ionis Licensed Technology or Joint Patents to Develop or Commercialize any Competing Product until, on a Product-by-Product and country-by-country basis, the expiration of the last Valid Claims in an Ionis Patent Covering a Product in such a country. Notwithstanding the foregoing, if Ionis alleges that Akcea has materially breached its obligations under Section 3.3 and Akcea disputes the occurrence of such a material breach and submits such dispute for resolution pursuant to Section 13.4, then, during the pendency of such dispute in any country in which this Section 5.1.2 applies, Ionis, its Affiliates, and its Sublicensees may practice the Ionis Licensed Technology and Joint Patents and grant licenses to Third Parties to practice the Ionis Licensed Technology and Joint Patents, in each case, to Develop (but not Commercialize) any Competing Product.

5.1.3 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 completion of such Change of Control, is Developing or Commercializing a product that would violate the terms of Section 5.1.1 or Section 5.1.2, as applicable (such pre-existing competitive product, a "***Pre-Existing Competing Product***,"), then such Party shall not be deemed in breach of its obligations under Section 5.1.1 or Section 5.1.2, as applicable, with respect to such Pre-Existing Competing Product (and the restrictions set forth therein will not apply to such Pre-Existing Competing Products); *provided* that, following such Change of Control, such acquired Party will separate its Development and Commercialization activities under this Agreement from its development and commercialization activities relating to such Pre-Existing Competing Product ("***Competing Activities***") and such Party will, and (if applicable) will cause the acquiring Affiliate to, (a) establish separate teams to conduct Development activities under this Agreement and development activities related to such Pre-Existing Competing Product, (b) prevent any Know-How that is Confidential Information relating to the Development or Commercialization of the applicable Product from being disclosed to, or used by, individuals performing such Competing Activities, and (c) not use or reference any Know-How that is Confidential Information or conduct any activities Covered by any Patents, 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, as applicable, in the development, manufacture, or commercialization of the Pre-Existing Competing Product.

ARTICLE 6
FINANCIAL PROVISIONS

Section 6.1 **Up-Front Fee**. In partial consideration for the licenses granted under Section 4.1, on the Effective Date, Akcea will pay to Ionis an up-front fee equal to $150,000,000 through the issuance of Akcea common stock in accordance with the terms of the Stock Purchase Agreement.

Section 6.2 **Inotersen Commercialization Funding**. To support Commercialization of inotersen and IONIS-TTR-L_{Rx}, in addition to the Akcea common stock issued to Ionis under Section 6.1, on the Effective Date, Ionis will purchase $200,000,000 of Akcea common stock in cash in accordance with the terms of the Stock Purchase Agreement.

Section 6.3 **Milestone Payments**.

6.3.1 Milestone Payments for Achievement of Regulatory Milestone Events by inotersen. Akcea will pay to Ionis the Regulatory Milestone Payments set forth in Table 6.3.1 below when Akcea, its Affiliates, or its Sublicensees first achieve a Regulatory Milestone Event listed in Table 6.3.1 for inotersen.

TABLE 6.3.1 – INOTERSEN REGULATORY MILESTONES

Inotersen Milestone Event	Milestone Payment	
NDA Approval of inotersen in the U.S.	$	50M
MAA Approval of inotersen in the EU	$	40M
JNDA Approval of inotersen in Japan	$	20M

6.3.2 Milestone Payments for Achievement of Regulatory Milestone Events by IONIS-TTR-L_{Rx}. Akcea will pay to Ionis the Regulatory Milestone Payments set forth in Table 6.3.2 below when Akcea, its Affiliates, or its Sublicensees first achieve a Regulatory Milestone Event listed in Table 6.3.2 for IONIS-TTR-L_{Rx}.

TABLE 6.3.2 - IONIS-TTR-LRx REGULATORY MILESTONES

IONIS-TTR-LRx Milestone Event	Milestone Payment
Acceptance of Filing for IONIS-TTR-L_{Rx} in the U.S.	$ 20M
Acceptance of Filing for IONIS-TTR-L_{Rx} in the EU	$ 15M
NDA Approval of IONIS-TTR-L_{Rx} in the U.S.	$ 50M
MAA Approval of IONIS-TTR-L_{Rx} in the EU	$ 40M
JNDA Approval of IONIS-TTR-L_{Rx} in Japan	$ 20M

6.3.3 Payment for Achievement of Regulatory Milestone Events. Akcea will notify Ionis promptly upon achievement of a Regulatory Milestone Event, and will pay to Ionis the applicable Milestone Payment within 45 days after the date of achievement of such Regulatory Milestone Event. Each Regulatory Milestone Payment shall be payable no more than one time.

6.3.4 Milestone Payments for First Achievement of Sales Milestone Event. Akcea will pay to Ionis the milestone payments set forth in Table 6.3.4 below (each, a "***Sales Milestone Payment***" and, together with the Regulatory Milestone Payments, the "***Milestone Payments***") when any combination of Akcea, its Affiliates, or its Sublicensees first achieve a sales milestone event set forth in Table 6.3.4 (each, a "***Sales Milestone Event***" and, together with the Regulatory Milestone Events, the "***Milestone Events***"). Notwithstanding the definition of "*Net Sales*," for the purposes of this Section 6.3.4, "*Net Sales*" will includes sales of the Products by Sublicensees as determined in accordance with GAAP and reported by such Sublicensees to Akcea.

TABLE 6.3.4 – SALES MILESTONES

Sales Milestone Event	Sales Milestone Payment
$400M in aggregate worldwide Net Sales of Products in a Calendar Year	$ 50M
$750M in aggregate worldwide Net Sales of Products in a Calendar Year	$ 75M
$1B in aggregate worldwide Net Sales of Products in a Calendar Year	$ 100M
$1.5B in aggregate worldwide Net Sales of Products in a Calendar Year	$ 150M
$2B in aggregate worldwide Net Sales of Products in a Calendar Year	$ 200M
$3B in aggregate worldwide Net Sales of Products in a Calendar Year	$ 300M
$4B in aggregate worldwide Net Sales of Products in a Calendar Year	$ 400M

6.3.5 Payment for Achievement of Sales Milestone Events. A Sales Milestone Payment for a Sales Milestone Event will be considered earned and accrued under this Agreement once the applicable requisite amount of aggregate worldwide Net Sales of all Products added together (including all Net Sales of Products made by any Sublicensee) achieves the applicable Sales Milestone Event set forth in Table 6.3.4 above in the applicable Calendar Year. Akcea will notify Ionis of the achievement of a Sales Milestone Event as soon as reasonably practicable after Akcea becomes aware of such achievement (but no later than 15 days after the end of the Calendar Quarter in which such Sales Milestone Event is achieved). Except as otherwise set forth in Section 6.3.7(d) below, Akcea will pay each Sales Milestone Payment for a Sales Milestone Event within 10 days after the date on which Akcea notifies Ionis of the achievement of such Sales Milestone Event. Each Sales Milestone Payment shall be payable no more than one time.

6.3.6 Further Assurances. If (i) Akcea elects to or is required to make any Milestone Payment in shares of Akcea common stock pursuant to this Section 6.3 and (ii) the number of shares of Akcea common stock required to pay for such Milestone Payment exceeds the number of shares of Akcea common stock that is authorized pursuant to its certificate of incorporation less the sum of the number of shares of common stock outstanding and the number of shares otherwise reserved for issuance, then:

(a) Akcea will use its reasonable efforts to amend its certificate of incorporation to sufficiently increase the number of authorized shares of Akcea common stock to pay such Milestone Payment in shares of Akcea common stock;

(b) Ionis will vote in favor of any stockholder approval sought by Akcea to amend Akcea's certificate of incorporation in accordance with the foregoing; and

(c) *provided that* Akcea is in compliance with clause (a) above, Akcea's obligation to make such Milestone Payment shall be suspended until such time as such amendment occurs and such shares become available for issuance.

6.3.7 Payment Mechanics for Milestone Payments.

(a) ***Milestone Payments Are Not Expenses***. Milestone Payments will not be considered "*Expenses*" for purposes of the Profit/Loss Share.

(b) ***Milestone Payment Election Notices***. Akcea may elect, at its option, to pay any Milestone Payment in cash or Akcea common stock at fair market value by providing written notice of such election (each, a "***Payment Election Notice***") to Ionis within 15 days after the date on which Akcea, its Affiliates, or its Sublicensees achieve such Milestone Event. If Akcea's Payment Election Notice indicates that Akcea elects to pay a particular Milestone Payment in cash, then Ionis will have the right, by providing written notice to Akcea within 15 days after Ionis' receipt of such Payment Election Notice, to require Akcea to pay such Milestone Payment to Ionis through the issuance of Akcea common stock rather than cash. If Akcea does not deliver a Payment Election Notice to Ionis with respect to a particular Milestone Payment within 15 days after the date of achievement of such Milestone Event, then subject to Section 6.3.7(d), Akcea will be deemed to have elected to pay, and will pay, the applicable Milestone Payment in Akcea common stock. Notwithstanding any provision to the contrary in this Section 6.3.7(b), once any combination of Akcea, its Affiliates, or Sublicensees has achieved the "*$750M in aggregate worldwide Annual Net Sales of Products*" Sales Milestone Event, then Akcea will pay all subsequent Milestone Payments for achievement of any Milestone Event in cash.

(c) ***Payments in Stock***. For any Milestone Payment to be paid to Ionis in Akcea common stock rather than cash, the price of such common stock will be the trailing 20 trading day average measured from the date on which Akcea provides notice to Ionis of the achievement of the corresponding Milestone Event and Akcea will issue to Ionis common stock pursuant to a stock purchase agreement consistent with the Stock Purchase Agreement, with appropriate modifications for the circumstance.

(d) ***Limitation on Sales Milestone Payments***. Akcea will not be required to pay more than two Sales Milestone Payments for the achievement of Sales Milestone Events earned in any single Calendar Year. Akcea will pay to Ionis any Sales Milestone Payment due for the achievement of a Sales Milestone Event that is unpaid in the Calendar Year in which it is earned and accrued as a result of the payment limitation set forth in the foregoing sentence by March 31st of the subsequent Calendar Year. For example, if, in Calendar Year 2020, the "*$400M in aggregate worldwide Net Sales of Products in a Calendar Year*" Sales Milestone Event is achieved on March 1, 2020, the "*$750M in aggregate worldwide Net Sales of Products in a Calendar Year*" Sales Milestone Event is achieved on June 1, 2020, and the "*$1B in aggregate worldwide Net Sales of Products in a Calendar Year*" Sales Milestone Event is achieved on August 1, 2020, then Akcea will pay to Ionis the $50M Sales Milestone Payment no later than April 25, 2020, the $75M Sales Milestone Payment no later than July 25, 2020, and the $100M Sales Milestone Payment no later than March 31, 2021.

Section 6.4 **Profit Sharing for Products Sold by Akcea and its Affiliates.**

6.4.1 Profit Sharing. The Parties will share all Net Profits or Losses (as applicable) for each Product in accordance with the Profit/Loss Share as further specified in Schedule 6.4.1, which will govern each Party's rights and obligations with respect to Net Profits or Losses relating to each Product. Schedule 6.4.1 sets forth the procedures for monthly and quarterly reporting of actual results and review and discussion of potential discrepancies, quarterly reconciliation, reasonable forecasting, and other finance and accounting matters.

6.4.2 Ionis' Right to Terminate Profit Sharing on a Change of Control of Akcea. Ionis will have the right to terminate the Profit/Loss Share and replace such profit and loss sharing with the alternative royalty provisions set forth on Schedule 6.4.2 by providing written notice to Akcea of such election within 90 days

following the closing of a Change of Control of Akcea. If Ionis does not provide such written notice to Akcea within 90 days following the closing of a Change of Control of Akcea, then the Parties will continue to share Net Profits or Losses for each Product in accordance the Profit/Loss Share as set forth in Section 6.4.1 and on Schedule 6.4.1.

Section 6.5 **Third Party Payment Obligations**. Akcea will be responsible for, and will pay for, all Third Party Obligations that arise from Akcea's practice of in-licensed technology necessary to Commercialize a Product, including any royalty payable under the GSK Agreement. Any amounts paid by Akcea to a Third Party in accordance with this Section 6.5 will be considered "*Expenses*" for purposes of the Profit/Loss Share. If any Third Party Obligations arise under any Existing In-License Agreement or Future In-License Agreement with respect to which a Party is a party that benefit the Product and one or more other products, then such Party's board of directors will determine a *pro rata* portion of such payment that will be considered "*Expenses*" for purposes of the Profit/Loss Share, which *pro rata* portion will be calculated based on the number of products with respect to which such payment obligations arise. If the other Party disagrees with such allocation, then such matter will be resolved by Expedited Arbitration.

Section 6.6 **Mode of Payment**. All payments under this Agreement will be (a) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (b) made by wire transfer of immediately available funds to an account designated by Ionis in writing, and (c) non-creditable, irrevocable, and non-refundable. Whenever for the purposes of calculating any payment due under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by applying the monthly average rate of exchange calculated by using the foreign exchange rates published in Bloomberg during the applicable month starting two Business Days before the beginning of such month and ending two Business Days before the end of such month.

Section 6.7 **Records Retention**. Akcea (and Ionis with respect to its Expenses reported to Akcea for calculating Profit Share Payments) will keep, and will require its Affiliates and Sublicensees to keep (all in accordance with GAAP, consistently applied), complete and accurate records pertaining to Net Sales, Profit Share Payments (including underlying data), Sublicense Revenue, and any other payment due pursuant to this ARTICLE 6 for the longer of (i) seven years after the year in which such Net Sales, Profit Share Payment, Sublicense Revenue, or any other payment due pursuant to this ARTICLE 6 arose, or (ii) such period of time required by Applicable Law, and in sufficient detail to permit Ionis to confirm the accuracy of the Net Sales, Profit Share Payment, or Sublicense Revenue paid by Akcea hereunder.

Section 6.8 **Audits and Interim Reviews**. Either Party will have the right to request that an independent certified public accountant selected by it (but excluding its own accountant) and reasonably acceptable to the other Party perform an audit, not more than once in any four consecutive Calendar Quarters during the Agreement Term, but including one post-termination audit and, if any such audit results in a material restatement of records (*i.e.*, a discrepancy of 5% or more for any Calendar Year), such Party will be permitted an additional examination within such four-quarter period, of the other Party's books of accounts covering the preceding three-year period for the sole purpose of verifying compliance with the payment provisions of this Agreement. Such audits will be conducted at the expense of the requesting Party at reasonable times during regular business hours and upon at least 20 Business Days' prior notice. Audit results will be shared with both Parties, subject to ARTICLE 8 (Confidentiality); *provided*, *however*, that the accounting firm may not disclose copies of the audited Party's books of accounts (or excerpts thereof) to the other Party. Any accounting firm conducting such an audit will enter into a confidentiality agreement with both Parties containing restrictions substantially similar to the confidentiality provisions of ARTICLE 8 (Confidentiality) limiting the disclosure and use of information contained in such books and records for the purposes expressly permitted by this Section 6.8. Any inspection or audit pursuant to this Section 6.8 will be at the expense of the Party initiating the audit; *provided*, *however*, that if the Party's accountants reasonably determine that Net Profits or Losses have been understated or Expenses have been overstated by an amount equal to or greater than 5%, for any Calendar Year, then the audited Party will pay the reasonable fees of such accountants for such audit, in addition to remitting the Net Profits or refund of Net Losses, Expenses with interest thereon computed in accordance with Section 6.11.

Section 6.9 **Taxes**.

6.9.1 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.

6.9.2 Withholding Tax. The Parties agree to cooperate with one another and use reasonable efforts to lawfully avoid or reduce tax withholding or similar obligations in respect of payments made by Akcea to Ionis under this Agreement. To the extent Akcea is required to deduct and withhold taxes, interest, or penalties on any payment, Akcea will pay the amounts of such taxes to the proper governmental authority for the account of Ionis and remit the net amount to Ionis in a timely manner. Akcea will promptly furnish Ionis 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, then the Parties will provide such documentation to the extent they are entitled to do so.

6.9.3 Tax Cooperation. Ionis will provide Akcea with any and all tax forms that may be reasonably necessary in order for Akcea to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following Akcea's timely receipt of such tax forms from Ionis, Akcea will not withhold tax or will withhold tax at a reduced rate under the applicable bilateral income tax treaty, if appropriate under Applicable Law. Ionis will provide any such tax forms to Akcea 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 6.9.

6.9.4 The provisions of this Section 6.9 are to be read in conjunction with the provisions of Section 13.1.

Section 6.10 **Blocked Currency**. In each country where the local currency is blocked and cannot be removed from the country, royalties accrued in that country will be paid to Ionis in the country in local currency by deposit in a local bank designated by Ionis, unless the Parties otherwise agree.

Section 6.11 **Interest**. If Akcea fails to make any payment due to Ionis under this Agreement by the deadline specified in this ARTICLE 6, then interest will accrue on a daily basis thereafter at an annual rate equal to 1.0% above the then-applicable prime commercial lending rate of Citibank, N.A. San Francisco, California, or at the maximum rate permitted by Applicable Law, whichever is lower, and any such interest will not be considered "*Expenses*" for purposes of the Profit/Loss Share.

ARTICLE 7
PRESS RELEASES AND PUBLICATIONS

Section 7.1 **Press Releases; Public Disclosure**. The Parties will agree upon and issue as joint press releases all releases or public disclosures under this Agreement related to (a) this Agreement, or (b) any of the Products (including any discussion of clinical data related to a Product). Akcea and Ionis will agree on talking points and a communication plan with respect to the Commercialization of the Products and the commercial potential thereof to be used in communications to customers, specialty pharmacies, physicians, regulatory authorities, patient advocacy groups, and clinical study investigators, and each Party will make all such communications to such entities in accordance with such talking points and communication plan and will not make any statement related to the Commercialization of the Products or the commercial potential thereof, in each case, that is inconsistent with such talking points and communication plan. In addition, Akcea will not disclose any material clinical data or commercial information related to a Product without first informing Ionis' Vice President, Corporate Communications and the JSC that it plans to so disclose such data or information at least 48 hours prior to any planned disclosure of such data or information. Notwithstanding the foregoing, each Party may make disclosures permitted by, and in accordance with, ARTICLE 8. The contents of any announcement or similar publicity can be re-released by either Party without a requirement for re-approval so long as the information in such announcement remains true and correct as of the time of such re-release.

7.1.1 Significant Events. Each Party will immediately notify the other Party of any event that is material to the Development, Manufacture, or Commercialization of a Product including any starting/stopping of a Clinical Trial, any Clinical Hold, clinical data or results, material regulatory discussions, submission of any NDA, MAA, or JNDA, receipt of Approval, or a material change in Akcea's sales projections (each a "***Significant Event***") so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event. In all such cases, the Parties will mutually agree on a communications strategy for such Significant Event and will make any such disclosure in accordance with Section 7.1.

7.1.2 Scientific or Clinical Presentations. The Parties agree to use Commercially Reasonable Efforts to control public scientific disclosures of results of the Development activities under this Agreement with respect to

the Products to prevent any potential adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, whether they are to be presented orally or in written form.

7.1.3 Acknowledgment. Akcea will acknowledge in any press release, public presentation, or publication regarding a Product that such Product is under license from Ionis and Ionis' stock ticker symbol (*e.g.*, Nasdaq: IONS). Ionis may include any Product in Ionis' drug pipeline. To the extent permitted by Applicable Law, Akcea will prominently include the words "*Discovered by Ionis Pharmaceuticals*" in relevant scientific, medical and other Product-related communications to the extent such communications address the research, discovery or commercialization of a Product. Notwithstanding the foregoing, Akcea shall have no obligation to include such attribution language in any of the following: (a) communications or materials where such inclusion would be prohibited by Applicable Law or applicable Third Party institutional, corporate, or other policies; (b) communications that Akcea does not control, such as publications with non-Akcea lead authors; or (c) materials primarily focused on or directed to patients, or other materials in which Akcea branding is not prominently featured, *provided that*, in each case,Akcea will use reasonable efforts to have such attribution language included in any such communication, consistent with the efforts that Akcea uses to have statements regarding its own contributions to the Product included in such communication.

7.1.4 Not Limiting; No Conflict. With respect to communications by Akcea, this ARTICLE 7 will not modify or amend any separate agreement between Ionis and Akcea regarding public communications. In case of a conflict between this ARTICLE 7 and such other agreement, the stricter standard will apply.

ARTICLE 8
CONFIDENTIALITY

Section 8.1 **Disclosure and Use Restriction**. Each Party agrees that, for so long as this Agreement is in effect and for a period of five years thereafter, a Party (the "***Receiving Party***") receiving Confidential Information of the other Party (the "***Disclosing Party***") will (a) maintain in confidence such Confidential Information, (b) not disclose such Confidential Information except to the Receiving Party's employees having a need-to-know such Confidential Information, (c) not disclose such Confidential Information to any Third Party without the prior written consent of the Disclosing Party, except for disclosures expressly permitted by this Agreement, and (d) not use such Confidential Information for any purpose except those expressly permitted by this Agreement.

Section 8.2 **Authorized Disclosure**. To the extent that it is reasonably necessary or appropriate to fulfill its obligations or exercise its rights under this Agreement, a Party may disclose Confidential Information belonging to the other Party in the following instances:

(a) filing or prosecuting patent applications in accordance with this Agreement;

(b) communicating with Regulatory Authorities as necessary for the Development or Commercialization of a Product in a country, in accordance with this Agreement and as required in connection with any filing, application, or request for Approval; *provided*, *however*, that reasonable measures will be taken to assure confidential treatment of such information;

(c) prosecuting or defending litigation;

(d) complying with Applicable Laws and regulations (including the rules and regulations of the Securities and Exchange Commission or any national securities exchange, and compliance with tax laws and regulations) and with judicial process, if (i) in the reasonable opinion of the Receiving Party's counsel, such disclosure is necessary for such compliance and (ii) such disclosure is made in accordance with Section 8.3 or Section 8.4 as applicable;

(e) disclosure, in connection with the exercise of its rights and performance of its obligations under this Agreement and solely on a need-to-know basis, to Affiliates, potential or actual collaborators (including potential and actual Sublicensees), potential or actual investment bankers, investors, lenders, or acquirers, or employees, independent contractors, or agents, each of whom prior to disclosure must be bound by written obligations of confidentiality and non-use no less restrictive than the obligations set forth in this ARTICLE 8; *provided*, *however*, that the Receiving Party will remain responsible for any failure by any Person who receives Confidential Information pursuant to this ARTICLE 8 to treat such Confidential Information as required under this ARTICLE 8; and

(f) in the case of Akcea, its Affiliates, and its Sublicensees, use and disclosure of Ionis Know-How in the ordinary course of the exercise of the rights and licenses and performance of its obligations under this Agreement.

If Confidential Information is disclosed in accordance with this Section 8.2, then such disclosure will not cause any such information to cease to be Confidential Information except to the extent that such permitted disclosure results in a public disclosure of such information (other than by breach of this Agreement). Where reasonably possible and subject to Section 8.3 and Section 8.4, the Receiving Party will notify the Disclosing Party of the Receiving Party's intent to make such disclosure pursuant to clauses (a) through (d) of this Section 8.2 prior to making such disclosure to allow the Disclosing Party adequate time to take whatever action it may deem appropriate to protect the confidentiality of the information.

Section 8.3 **Required Disclosure**. A Receiving Party may disclose Confidential Information pursuant to interrogatories, requests for information or documents, subpoena, civil investigative demand issued by a court or governmental agency or as otherwise required by Law; *provided*, *however*, that, unless legally prohibited from doing so, the Receiving Party will notify the Disclosing Party promptly upon receipt thereof, giving (where practicable) the Disclosing Party sufficient advance notice to permit it to oppose, limit, or seek confidential treatment for such disclosure, and to file for patent protection if relevant; and *provided*, *further*, that the Receiving Party will furnish only that portion of the Confidential Information that it is advised by counsel is legally required whether or not a protective order or other similar order that is obtained by the Disclosing Party.

Section 8.4 **Securities Filings**. If either Party proposes to file with the Securities and Exchange Commission or the securities regulators of any state or other jurisdiction a registration statement, periodic report, or any other disclosure document that describes or refers to this Agreement under the Securities Act of 1933, as amended, the Securities Exchange Act, of 1934, as amended, or any other applicable securities Law, then the Party will notify the other Party of such intention and will provide such other Party with a copy of relevant portions of the proposed filing not less than five Business Days prior to such filing. In such case such Party will seek to obtain confidential treatment of any information concerning the Agreement that such other Party requests be kept confidential (except to the extent advised by counsel that confidential treatment is not available for such information), and such Party will only disclose Confidential Information that it is advised by counsel is legally required to be disclosed. No such notice will be required under this Section 8.4 if the substance of the description of or reference to this Agreement contained in the proposed filing has been included in any previous filing made by either Party hereunder or otherwise approved by the other Party.

ARTICLE 9
PATENTS

Section 9.1 **Joint Patent Committee**

9.1.1 The Parties will establish a joint patent committee that will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement (the "***Joint Patent Committee***" or "***JPC***"), and the Parties will cooperate with respect to the activities set forth in this ARTICLE 9. The JPC will discuss the strategy with regard to (a) prosecution, maintenance, defense, and enforcement of Ionis Product-Specific Patents and Joint Product-Specific Patents that are licensed to Akcea under Section 4.1 in connection with a Product, (b) defense against actual or potential allegations of infringement of any Patent Controlled by a Third Party, including the institution of any *inter partes* review, opposition, or other proceeding related to any such Patent, and (c) licenses to Third Party Patents or Know-How. Each Party will promptly disclose to the JPC in writing, and will cause its Affiliates to so disclose, the discovery, development, invention, or creation of any Joint Patents. The JPC will also be responsible for identifying new inventions related to Products, determining the inventorship thereof in accordance with United States patent law, and setting a filing strategy for such inventions. Except with respect to the defense of a Third Party Claim that is the subject of indemnification pursuant to Section 11.1, if the JPC cannot reach consensus regarding the strategy with regard to a matter referred to in clause (b), then either Party may refer such matter to the JSC for resolution. With respect to the defense of a Third Party Claim that is the subject of indemnification pursuant to Section 11.1, the Indemnifying Party will control the defense of such Third Party Claim as provided in Section 11.3.

9.1.2 The JPC will be comprised of 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 9. The JPC will determine the JPC operating procedures at its first

meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which operating procedures will be codified in the written minutes of the first JPC meeting. If either Party deems it reasonably advisable, then the Parties will enter into a mutually agreeable common interest agreement covering the intellectual property matters contemplated by this Agreement.

Section 9.2 **Prosecution and Maintenance of Patents**.

9.2.1 Patents Owned or Controlled by a Party. Except as otherwise expressly set forth in Section 9.2.2, Section 9.2.3, or Section 9.2.5, each Party will have the right, at its cost and expense and at its discretion, to file, prosecute, maintain, and enforce throughout the world any Patents Controlled by such Party.

9.2.2 Ionis First Right. Ionis will have the first right, at its cost and expense and at its discretion, to file, prosecute, maintain, and enforce throughout the world the (a) Ionis Core Technology Patents, (b) Ionis Manufacturing Patents, (c) Joint Core Technology Patents, and (d) until completion of the first Phase 1 Clinical Trial for IONIS-TTR-L_{Rx}, the Ionis Product-Specific Patents Covering IONIS-TTR-L_{Rx} that do not also Cover inotersen. To the extent it has not already done so in a country where Ionis has filed other Ionis Core Technology Patents or Ionis Product-Specific Patents, Ionis will use Commercially Reasonable Efforts to file a continuation or divisional (or the foreign equivalent) of a patent application related to PCT/US14/036463 and prosecute such continuation or divisional application in a manner that renders it an Ionis Product-Specific Patent, which Akcea will have the first right to prosecute and maintain such patent application pursuant to Section 9.2.3.

9.2.3 Product-Specific Patents. Except as otherwise expressly set forth in Section 9.2.2 and Section 9.2.5, Akcea, either directly or through its Affiliates and Sublicensees, will have the first right, at its expense, to file, prosecute, and maintain throughout the world all Product-Specific Patents. Until such time that Akcea hires in-house patent counsel or engages outside patent counsel, Ionis will provide to Akcea patent management services under the Services Agreement, including preparation and prosecution of all Product-Specific Patents world-wide and management of outside patent counsel world-wide. After Akcea retains its own patent counsel, Akcea will provide Ionis with an update of the filing, prosecution, and maintenance status for each such Product-Specific Patent on a periodic basis and will reasonably consult with and cooperate with Ionis with respect to the preparation, filing, prosecution, and maintenance of such Product-Specific Patents, including providing Ionis with drafts of material filings in sufficient time to allow Ionis' review and comment before such filings are due. Akcea or its outside counsel will provide to Ionis copies of any material papers relating to the filing, prosecution, and maintenance of such Product-Specific Patents promptly upon their being filed or received. If Akcea determines that it is not commercially reasonable to continue prosecuting or maintaining particular applications or patents within such Product-Specific Patents in selected jurisdictions, then Akcea may cease such efforts (in which case the terms of Section 9.2.5 will apply).

9.2.4 Notice of Disputes. Each Party will notify the other Party within a reasonable period of time if any action, suit, claim, dispute, or proceeding concerning the Ionis Product-Specific Patents licensed hereunder or any other Product-Specific Patents, or a Product has been initiated, in each case, that would have a material adverse effect on the licenses granted by Ionis to Akcea under this Agreement, or that would have a material adverse effect on or would materially impair a Party's rights under this Agreement, if determined adversely to a Party. Any information communicated pursuant to this Section 9.2.4 will be treated as Confidential Information subject to the terms of ARTICLE 8.

9.2.5 Discontinued Patents. If the Party responsible for prosecution and maintenance of the Product-Specific Patents under Section 9.2.2 or Section 9.2.3, as applicable (the "***Prosecuting Party***") elects to not pursue or continue the filing, prosecution, or maintenance of any particular applications or patents, or subject matter included in the Product-Specific Patents in any jurisdiction (a "***Discontinued Patent***"), then the Prosecuting Party will give as much advance written notice as reasonably practicable (but in no event less than 30 days or, in the case of an applicable impending deadline, 45 days prior to such deadline) to the other Party of any decision not to pursue or continue such preparation, filing, prosecution, or maintenance. In such case, the other Party may elect to continue preparation, filing, prosecution, or maintenance of such Discontinued Patent in the applicable jurisdiction at its expense and such Party will become the Prosecuting Party with respect to such Discontinued Patent in such jurisdiction. The Party that is discontinuing the prosecution or maintenance of a Discontinued Patent will execute such documents and perform such acts as may be reasonably necessary for the

other Party to continue prosecution or maintenance of the applicable Discontinued Patent in the applicable jurisdiction. If a Party that continues the prosecution and maintenance of a Discontinued Patent wishes to cease prosecution, then such Party does not need to provide notice to the Party that originally decided to discontinue prosecution of such Product-Specific Patent.

9.2.6 Cooperation. Each Party will cooperate reasonably in the preparation, filing, prosecution, and maintenance of the Product-Specific Patents and Joint Core Technology Patents. Such cooperation includes (a) promptly executing all papers and instruments and requiring employees to execute such papers and instruments as reasonable and appropriate so as to enable such responsible Party, to file, prosecute, and maintain such Patents in any country; and (b) promptly informing such other Party of matters that may affect the preparation, filing, prosecution, or maintenance of any such Patents.

Section 9.3 **Enforcement of Patents**.

9.3.1 Notification of Competitive Infringement. If either Party learns of an infringement, unauthorized use, misappropriation, or threatened infringement by a Third Party with respect to any Product-Specific Patents or Ionis Core Technology Patent by reason of the Development, Manufacture, use, or Commercialization of a Competing Product ("***Competitive Infringement***"), then such Party will promptly notify the other Party in writing (and in any event within 10 days for cases of Competitive Infringement under Section 9.3.7) and will provide such other Party with available evidence of such Competitive Infringement.

9.3.2 Product-Specific Patents. Akcea will have the first right, but not the obligation, at Akcea's expense, to enforce the Product-Specific Patents against any such Competitive Infringement or to defend against any challenge to the validity, scope, or enforceability of a Product-Specific Patent, including any opposition or *inter partes* review proceeding against any Product-Specific Patent. If Ionis requests that Akcea take action to enforce any Product-Specific Patent against a Competitive Infringement, and Akcea believes that it is not commercially appropriate to take such actions, then the Parties will meet and discuss in good faith such circumstances and seek to reach agreement on what appropriate steps to take to cause such infringement to end in a commercially appropriate manner. If Akcea brings an action to enforce a Product-Specific Patent against a Competitive Infringement, then Ionis as the owner of such Product-Specific Patent, will be permitted to join the litigation with respect thereto and any communications between the Parties will be governed by the common interest privilege.

9.3.3 Ionis Core Technology Patents. If the Parties learn that a Third Party is infringing one or more Valid Claims of an Ionis Core Technology Patent or Joint Core Technology Patent by selling a Competing Product (including any Competitive Infringement) and such infringement is likely to have a material adverse effect on the Product, then Ionis will have the sole right, but not the obligation, at Ionis' expense, to enforce the Ionis Core Technology Patents or Joint Core Technology Patent against any such Competitive Infringement. If Akcea requests that Ionis take action to enforce any Ionis Core Technology Patent or Joint Core Technology Patent against a Competitive Infringement, and Ionis believes that it is not commercially appropriate to take such actions, then the Parties will meet and discuss in good faith such circumstances and seek to reach agreement on what appropriate steps to take to cause such infringement to end in a commercially appropriate manner.

9.3.4 Cooperation. The Party not enforcing the applicable Patent against a Competitive Infringement or not defending the applicable Patent against any challenge to the validity, scope, or enforceability thereof (including in any opposition or *inter partes* review proceeding), in each case, will provide reasonable assistance to the other Party (at such other Party's expense), including providing access to relevant documents and other evidence, making its employees available at reasonable business hours in deposition and at trial, and joining the action as a named party to the extent necessary to allow the enforcing or defending Party to bring or maintain the action or establish damages. Subject to Section 11.3, each Party will provide similar cooperation to the other Party in furtherance of the execution of any strategy determined in accordance with Section 3.4 or Section 9.1 (as applicable) with respect to the defense against actual or potential allegations of infringement of any Patent Controlled by a Third Party, including the institution of any *inter partes* review, opposition, or other proceeding related to any such Patent. If any Third Party asserts in writing or in any legal proceeding that any of the Ionis Patents are unenforceable based on any term or condition of this Agreement, then the Parties shall amend this Agreement as may reasonably be required to effect the original intent of the Parties, including to preserve the enforceability of such Ionis Patents.

9.3.5 Recovery. Any damages or other monetary awards recovered with respect to any action contemplated by this Section 9.3 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) and any costs and expenses of either Party with respect to any such action will be included in Commercialization Costs for the purpose of calculating Net Profits or Losses; and

(b) any remaining proceeds will be treated as Net Profit.

9.3.6 Settlement. Notwithstanding anything to the contrary under this ARTICLE 9, neither Party may enter a settlement, consent judgment, or other voluntary final disposition of a suit under this ARTICLE 9 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 Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent.

9.3.7 35 USC 271(e)(2) Infringement. Notwithstanding anything to the contrary in this Section 9.3, solely with respect to the Patents licensed to Akcea under this Agreement for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 9.3.1 during which a Party will have the initial right to bring a proceeding will be shortened to a total of 25 days, so that, to the extent the other Party has the right pursuant to Section 9.3.1 to initiate a proceeding against such a Competitive Infringement if the first Party does not initiate such a proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement, such other Party will have such right.

Section 9.4 **Future In-License Agreements**.

9.4.1 Notice of Third Party Patents and Know-How. Each Party will notify the other Party if either Party becomes aware of Third Party Patents or Know-How that it believes are necessary or reasonably useful to Develop, Manufacture, or Commercialize a Product.

9.4.2 Approval of Future In-Licenses. Either Party may request that the other Party approve the acquisition of rights (whether by license or otherwise) with respect to a Third Party's Patents or Know-How, as applicable, for use in the Development, Manufacture, and Commercialization of Products pursuant to this Agreement. If Ionis is the requesting Party and Akcea provides such approval, then Ionis may enter into an agreement to acquire such rights, and upon its execution such agreement will become a Future In-License Agreement for purposes of this Agreement, the Patents and Know-How acquired or licensed thereunder will become Controlled by Ionis and licensed or sublicensed (as applicable) to Akcea under this Agreement, and amounts payable to the Third Party in consideration for such acquisition of rights will be Third Party Obligations for purposes of this Agreement and will be included in Expenses for the purpose of the Profit/Loss Share in accordance with Section 6.5. Similarly, if Akcea is the requesting Party and Ionis provides such approval, then Akcea may enter into an agreement to acquire such rights, and may include any amounts payable to such Third Party in consideration of the acquisition of such rights in Expenses for the purposes of the Profit/Loss Share.

9.4.3 Non-Approval. If the non-requesting Party does not approve the requesting Party's acquisition of such rights to any such Patents or Know-How Controlled by a Third Party, then, the other Party may enter into an agreement to acquire such rights (whether by license, or otherwise). However, if Ionis was the requesting Party and Akcea did not approve Ionis' acquisition of such rights, then upon the execution of such an agreement, such agreement will not become a Future In-License Agreement, the Patents and Know-How acquired or licensed thereunder will not be Controlled by Ionis for purposes of this Agreement, and will not be licensed to Akcea under this Agreement, and amounts payable by Ionis to the Third Party will not be Third Party Obligations included in Expenses for the purpose of the Profit/Loss Share. Similarly, if Akcea is the requesting Party and Ionis did not provide such approval, then Akcea may enter into an agreement to acquire such rights, but may not include any amounts payable to such Third Party pursuant to such agreement in Expenses for the purposes of the Profit/Loss Share.

Section 9.5 **Patent Listing**. During the Agreement Term, Akcea will promptly, accurately, and completely list with the applicable Regulatory Authorities all applicable Patents that Cover a Product. Prior to such listings, the Parties will meet, to evaluate and identify all applicable Patents (through the Joint Patent Committee), and Akcea will have the right to review, where reasonable, original records relating to any invention for which Patents are

being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Akcea will retain final decision-making authority as to the listing of all applicable Product-Specific Patents that are not Ionis Core Technology Patents or Ionis Manufacturing Patents.

Section 9.6 **Joint Research Agreement under the Leahy-Smith America Invents Act**. Notwithstanding anything to the contrary in this ARTICLE 9, 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 9 without the prior written consent of the other Party, which consent will not be unreasonably withheld. 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).

Section 9.7 **Patent Term Extension**. The Parties will cooperate with each other in gaining patent term extension of the optimal patent licensed under this Agreement, wherever applicable to a Product.

Section 9.8 **Rights in Bankruptcy**. All rights and licenses granted under this Agreement are, for purposes of Section 365(n) of the U.S. Bankruptcy Code (*i.e.*, Title 11 of the U.S. Code) or analogous provisions of Applicable Law outside the United States, licenses of rights to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States. The Parties agree that each Party, as licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the U.S. Bankruptcy Code or any other provisions of Applicable Law outside the United States that provide similar protection for 'intellectual property.' The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against a Party under the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States, the Party that is not subject to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) such intellectual property and all embodiments of such intellectual property, which, if not already in the non subject Party's possession, will be promptly delivered to it upon the non subject Party's written request therefor. Any agreements supplemental hereto will be deemed to be "agreements supplementary to" this Agreement for purposes of Section 365(n) of the U.S. Bankruptcy Code.

ARTICLE 10
TERM AND TERMINATION

Section 10.1 This Agreement will take effect automatically without further action of either Party upon the Effective Date; *provided, however*, that Section 3.1, Section 3.4, Section 3.5, ARTICLE 8, ARTICLE 9, this Section 10.1, Section 10.3.1, ARTICLE 11, ARTICLE 12, and ARTICLE 13 will each become binding and effective as of the Execution Date.

Section 10.2 **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 10, will continue in full force and effect until the expiration of all payment obligations under this Agreement with respect to the last Product (or Product) in all countries. The period from the Effective Date until the date of expiration or earlier termination of this Agreement pursuant to this ARTICLE 10 is the "***Agreement Term.***"

Section 10.3 **Termination of the Agreement**.

10.3.1 Termination Prior to the Effective Date. Notwithstanding anything to the contrary set forth in this Agreement, this Agreement may be terminated and the transactions contemplated herein be abandoned at any time prior to the Effective Date:

(a) by mutual written consent of Akcea and Ionis;

(b) by either Akcea or Ionis:

(i) if the Effective Date shall not have occurred on or prior to June 30, 2018; or

(ii) if any governmental authority having jurisdiction over Akcea or Ionis shall have enacted, issued, promulgated, enforced, or entered any Applicable Law or taken any other material action that has the effect of making the transactions contemplated by the Transaction Documents illegal or otherwise restraining or prohibiting the consummation of such transactions;

(c) by Akcea, upon a material breach of this Agreement by Ionis, *provided*, *however* that if such breach is capable of being cured within 90 days from the date Ionis is notified in writing by Akcea of such breach, then Akcea may not terminate this Agreement during such 90-day period or following such date if such breach is cured at or prior to such date; or

(d) by Ionis, upon a material breach of this Agreement by Akcea, *provided*, *however* that if such breach is capable of being cured within 90 days from the date Akcea is notified in writing by Ionis of such breach, then Ionis may not terminate this Agreement during such 90-day period or following such date if such breach is cured at or prior to such date.

If this Agreement is terminated under this Section 10.3.1 prior to the Effective Date, then, within 15 days after the date of such termination, the Parties will mutually agree on a transition plan to promptly affect the orderly transition to Ionis of all inotersen activities being performed by Akcea in a manner intended to support inotersen launch. Each Party will execute, acknowledge, and deliver such further instruments (including any assignments and other documents), and do all such other acts, as may be necessary or appropriate to carry out the orderly transition of inotersen activities from Akcea to Ionis described in this provision. This last paragraph of this Section 10.3.1 will survive any termination of this Agreement under this Section 10.3.1.

10.3.2 Akcea's Termination for Convenience. At any time following the Effective Date Akcea may terminate this Agreement in its entirety by providing 90 days written notice to Ionis of such termination.

10.3.3 Termination for Material Breach

(a) ***Akcea's Right to Terminate.*** At any time following the Effective Date, if Akcea believes that Ionis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 3.3, a breach of which is governed by Section 10.3.4 below), then Akcea may deliver notice of such material breach to Ionis. If the breach is curable, then Ionis will have 90 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice), which cure period may be extended for an additional 90-day period if such breach cannot be cured in the initial 90 day cure period and Ionis commences actions to cure such default within such initial 90 day period and thereafter uses diligent efforts with respect to the cure thereof. If Ionis fails to cure such breach within the 90-day, 180-day, or 30-day period (as applicable), or if the breach is not subject to cure, then Akcea may terminate this Agreement by providing written notice to Ionis.

(b) ***Ionis' Right to Terminate.*** At any time following the Effective Date, if Ionis believes that Akcea is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts to Develop and Commercialize a Product under Section 3.3, which is governed by Section 10.3.4 below), then Ionis may deliver notice of such material breach to Akcea. If the breach is curable, then Akcea will have 90 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice), which cure period may be extended for an additional 90 day period if such breach cannot be cured in the initial 90-day cure period and Akcea commences actions to cure such default within such initial 90-day period and thereafter uses diligent efforts with respect to the cure thereof. If Akcea fails to cure such breach within the 90-day, 180-day, or 30-day period (as applicable), or if the breach is not subject to cure, then Ionis may terminate this Agreement by providing written notice to Akcea.

10.3.4 Remedies for Failure to Use Commercially Reasonable Efforts.

(a) At any time following the Effective Date, if Ionis, in Akcea's reasonable determination, fails to perform its obligations under Section 3.3, then Akcea will notify Ionis and, within 30 days thereafter, Ionis and Akcea will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Ionis' failure to perform its obligations under Section 3.3. Following such a meeting, if Ionis fails to use Commercially Reasonable Efforts to conduct the mutually agreed cure plan, then Akcea will have the right to terminate this Agreement by providing written notice to Ionis.

(b) At any time following the Effective Date, if Akcea, in Ionis' reasonable determination, fails to perform its obligations under Section 3.3, then Ionis will notify Akcea and, within 30 days thereafter, Ionis

and Akcea will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable cure plan to address any outstanding issues related to Akcea's failure to perform under Section 3.3. Following such a meeting, if Akcea fails to use Commercially Reasonable Efforts as contemplated by the mutually agreeable cure plan, then Ionis will have the right, at its sole discretion, to terminate this Agreement in its entirety; *provided, however*, that, in the case where Ionis has the right to terminate this Agreement due to Akcea's failure to perform its obligations under Section 3.3 with respect to inotersen, if, at such time, (i) a First Commercial Sale of IONIS-TTR-L_{Rx} has occurred in a Major Market, and (ii) Akcea diligently performs its obligations under a Product transition plan that has been agreed by the Parties pursuant to which Akcea will transition its Commercialization efforts away from Commercialization of inotersen to focus on the Commercialization of IONIS-TTR-L_{Rx}, then Ionis may not terminate this Agreement with respect to such failure.

10.3.5 Termination for Patent Challenge. Ionis may terminate this Agreement if Akcea or its Affiliates disputes, or actively assists any Third Party to dispute, the validity of any Ionis Patents licensed to Akcea hereunder in a patent re-examination, *inter-partes* review, post grant, or other patent-office proceeding, opposition, litigation, or other court proceeding and, within 30 days after written notice from Ionis, Akcea fails to rescind any and all of such actions, *provided however* that, nothing in this clause prevents Akcea or its Affiliates from taking any of the actions referred to in this clause and *provided further* that Ionis will not have the right to terminate if Akcea or its Affiliates:

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

(b) acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against an Ionis Patent licensed to Akcea hereunder; or

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

10.3.6 Disputes Regarding Material Breach. Notwithstanding anything to the contrary set forth in this Agreement, if the Party that has been alleged pursuant to Section 10.3.1, Section 10.3.3, Section 10.3.4, or Section 10.3.5 to be in breach of this Agreement or otherwise to have triggered a termination right for the other Party (the ***"Breaching Party"*** and the other Party, the ***"Non-Breaching Party"***) disputes in good faith the existence, materiality, or failure to cure of any such breach or condition, and provides notice to the Non-Breaching Party of such dispute within the initial applicable day cure period, then the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.3.1, Section 10.3.3, Section 10.3.4, or Section 10.3.5 (as applicable) unless and until it has been determined in accordance with Section 13.4 that the Breaching Party has materially breached this Agreement (or such other condition of termination has occurred) and failed to cure such breach or condition within 90 days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.3.7 Termination for Insolvency. Either Party may terminate this Agreement if, at any time, the other Party (a) 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; (b) proposes a written agreement of composition or extension of substantially all of its debts; (c) is served with an involuntary petition against it filed in any insolvency proceeding and such petition is not be dismissed within 90 days after the filing thereof; (d) proposes or is party to any dissolution or liquidation; or (e) makes an assignment of substantially all of its assets for the benefit of creditors (each of items (a) through (e), an ***"Insolvency Event"***); *provided, however*, that Ionis will not have the right to terminate this Agreement pursuant to this Section 10.3.7 in the case where Akcea is the Party that is the subject of an Insolvency Event and such Insolvency Event was caused by Ionis.

***Section 10.4* Consequences of Termination of this Agreement**.

10.4.1 Consequences of Termination of this Agreement. If this Agreement is terminated by a Party in accordance with Sections 10.3.2, 10.3.3, 10.3.4, 10.3.5, or 10.3.7, in each case, in its entirety at any time and for any reason, then the following terms will apply to any such termination:

(a) ***Licenses.*** The licenses granted by Ionis to Akcea under this Agreement will terminate and Akcea, its Affiliates, and its Sublicensees will cease selling Products.

(b) ***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. 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.

(c) ***Accrued Rights.*** Termination 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. Such termination will not relieve a Party from obligations that are expressly indicated to survive the termination of this Agreement. For purposes of clarification, Milestone Payments accrue as of the date of achievement of the applicable Milestone Event, even if the payment is not due at that time.

(d) ***Survival.*** The following provisions of this Agreement will survive the expiration or earlier termination of this Agreement: Section 4.4 (Effect of Termination on Sublicenses); Section 4.8 (License to Ionis under Akcea Collaboration Technology); Section 6.7 (Records Retention); Section 6.8 (Audits and Interim Reviews); ARTICLE 8 (Confidentiality); Section 9.8 (Rights in Bankruptcy); Section 10.4 (Consequences of Termination of this Agreement); ARTICLE 11 (Indemnification and Insurance); Section 13.3 (Governing Law); Section 13.4 (Dispute Resolution); Section 13.6 (Notices); Section 13.9 (Entire Agreement); Section 13.11 (Interpretation); Section 13.12 (Third Party Beneficiaries); and Appendix 1 (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.4.2 Special Consequences of Certain Terminations. If Ionis terminates this Agreement under Section 10.3.3(b) (Ionis' Right to Terminate for Material Breach), Section 10.3.4(b) (Ionis' Right to Terminate for Failure to Use Commercially Reasonable Efforts), Section 10.3.5 (Termination for Patent Challenge), or Section 10.3.7 (Termination for Insolvency), then, in addition to the terms set forth in Section 10.4.1, the following additional terms will also apply:

(a) Akcea will and hereby does grant to Ionis a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all Akcea Technology Controlled by Akcea as of the effective date of such termination that Covers the Products solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import, and otherwise Commercialize the Products;

(b) Akcea will transfer to Ionis for use with respect to the Development and Commercialization of the Products, any Know-How, data, results, regulatory information, Regulatory Documentation (including the IND and all regulatory approvals), and files in the possession of and Controlled by Akcea as of the effective date of such termination that relate to such Products, and any other information or material delivered to Akcea pursuant to Section 4.6;

(c) Akcea will provide Ionis with copies of any internal or external market research reports and other market research documentation, including any meeting minutes and meeting materials from any meetings Akcea had with focus groups and payors regarding the Products;

(d) Akcea will grant to Ionis a non-exclusive, royalty-free, fully paid up license under any trademarks that are specific to any Product solely for use with such Product; *provided*, *however*, that in no event will Akcea have any obligation to license to Ionis any trademarks used by Akcea both in connection with a Product and in connection with the sale of any other Akcea product or service, including any Akcea- or Akcea-formative marks;

(e) Akcea will pay the final invoice of all outstanding Expenses accrued by Ionis prior to the effective date of termination within 45 days of receipt thereof;

(f) Upon Ionis' written request pursuant to a mutually agreed supply agreement, Akcea will sell to Ionis any bulk API and Drug Product in Akcea's possession and Control related to the Products at the time of such termination, at a price equal to Akcea's Cost of Goods therefor;

(g) Ionis may request Akcea to conduct (or cause to be conducted by Akcea's CMO) a technology transfer to Ionis (or Ionis' designated Third Party supplier) of any technology, information, and data reasonably related to Akcea's or such CMO's Manufacturing and supply of API or Drug Product for the Products, and if so requested, Akcea will conduct (or cause to be conducted by Akcea's CMO) such a technology transfer at no cost to Ionis, and Akcea will (or will cause Akcea's CMO to) continue to (i) provide reasonable support and cooperation with Ionis' regulatory filings and interactions with Regulatory Authorities related to the Manufacture of API or Drug Product by Akcea or such CMO Akcea's or such CMO's API or Drug Product Manufacturing (including any required inspections), and (ii) supply (or cause to be supplied by Akcea's CMO) API or Drug Product to Ionis, at a price equal to Akcea's Cost of Goods at the time such material was Manufactured, until such time as Ionis is able to identify and contract with a suitable Third Party API or Drug Product manufacturer, such period not to exceed 36 months; and

(h) ***Post-Termination Transition Activities.*** The Parties wish to provide a mechanism to ensure that patients who were being treated with a Product prior to such termination or who desire access to such Product can continue to have access to such Product while the regulatory and commercial responsibilities for the Product are transitioned from Akcea to Ionis. As such, Ionis may request Akcea perform transition activities that are necessary or useful to (i) transition Akcea's Commercialization activities to Ionis to minimize disruption to sales of such Products, (ii) provide patients with continued access to the applicable Products, (iii) enable Ionis (or Ionis' designee) to assume and execute the responsibilities under all Approvals and ongoing Clinical Trials for the applicable Product, and (4) ensure long-term continuity of supply for the Products, which will include some or all of the categories of services and deliverables listed on Schedule 10.4.2(h) as reasonably requested by Ionis (collectively, the ***"Post-Termination Transition Activities"***). Akcea will use Commercially Reasonable Efforts to perform such Post-Termination Transition Activities in accordance with the Termination Transition Plan for the periods set forth in Schedule 10.4.2(h), or such longer periods of time as Akcea and Ionis may agree. In furtherance of the foregoing:

(i) Ionis may elect to have Akcea perform the Post-Termination Transition Activities by providing written notice to Akcea no later than 60 days following the effective date of termination of this Agreement. If Ionis so requests Post-Termination Transition Activities, then, without limiting the provisions of Section 10.4.2, the Parties will mutually agree upon a transition plan for Akcea to perform the Post-Termination Transition Activities including delivery and transition dates for such activities (the ***"Termination Transition Plan").*** In addition, the Parties will establish a transition committee consisting of at least each Party's Alliance Managers, a representative from each Party's chemistry, manufacturing, and controls (CMC) group who was responsible for the Products prior to termination of this Agreement, and up to two additional representatives from each Party who are from other relevant functional groups to facilitate a smooth transition. While Akcea is providing Post-Termination Transition Activities under the Termination Transition Plan, Akcea and Ionis will agree on talking points and a communication plan to customers, specialty pharmacies, physicians, regulatory authorities, patient advocacy groups, and clinical study investigators, and Akcea will make all such communications to such entities in accordance with such talking points and communication plan.

(ii) Ionis will pay Akcea's internal costs to perform the Post-Termination Transition Activities in accordance with the Termination Transition Plan, calculated using the same methodology as Akcea used to calculate such expenses for such Product in its most recently audited financial statements prior to the termination date. In addition, Ionis will reimburse Akcea's out-of-pocket costs to perform such Post-Termination Transition Activities. Ionis will own all revenue derived from the Products after the effective date of termination of this Agreement and Akcea will remit all such revenues to Ionis no later than 45 days after the end of the month in which such revenue was received.

ARTICLE 11
INDEMNIFICATION AND INSURANCE

Section 11.1 **Indemnification**.

11.1.1 By Akcea. Akcea will indemnify, defend, and hold harmless Ionis and its Affiliates, and its or their respective directors, officers, employees and agents (each, an ***"Ionis Indemnitee"***), from and against any and all liabilities, damages, losses, costs, including the reasonable fees of attorneys and other professionals (collectively "***Losses***") arising out of or resulting from any and all Third Party suits, claims, actions, proceedings, or demands arising from or related to:

(a) the gross negligence, recklessness, or willful misconduct of Akcea, its Affiliates, or its or Sublicensees and its or their respective directors, officers, employees, and agents, in connection with Akcea's performance of its obligations or exercise of its rights under this Agreement; or

(b) Development, Commercialization, and Manufacturing activities that are conducted by or on behalf of Akcea or its Affiliates or Sublicensees, including handling, storage, manufacture, and sale by or on behalf of Akcea or its Affiliates or Sublicensees of any Products for the purpose of conducting Development or Commercialization by or on behalf of Akcea or its Affiliates or Sublicensees; or any breach of any representation or warranty or express covenant made by Akcea in this Agreement; or

(c) any breach of any representation, warranty, or covenant made by Akcea in this Agreement;

except, in each case above, to the extent such Losses are subject to indemnification by Ionis pursuant to Section 11.1.2.

11.1.2 By Ionis. Ionis will indemnify, defend, and hold harmless Akcea and its Affiliates, and its or their respective directors, officers, employees and agents (each, an ***"Akcea Indemnitee"***), from and against any and all Losses arising out of or resulting from any and all Third Party suits, claims, actions, proceedings, or demands arising from or related to:

(a) the gross negligence, recklessness, or willful misconduct of Ionis, its Affiliates or licensees (other than Akcea) and 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;

(b) Development, Manufacturing, and Commercialization activities that are conducted by or on behalf of Ionis or its Affiliates or licensees (other than Akcea), including handling, storage, manufacture, and sale by or on behalf of Ionis or its Affiliates or licensees (other than Akcea) of any Products for the purpose of conducting Development or Commercialization by or on behalf of Ionis or its Affiliates or licensees (other than Akcea); or

(c) any breach of any representation or warranty or express covenant made by Ionis in this Agreement;

except, in each case above, to the extent such Losses are subject to indemnification by Akcea pursuant to Section 11.1.1.

Section 11.2 **Losses as Expenses**. Except as otherwise set forth in Section 6 of Schedule 6.4.1 with respect to a Third Party Infringement Claim, any Losses that are subject to indemnification pursuant to Section 11.1 that arise from the Development, Manufacture, or Commercialization of any Product (including product liability and intellectual property infringement claims) will be treated as *Expenses* for the purposes of the Profit/Loss Share, *except* solely to the extent such Losses arise from a Party's breach of this Agreement, violation of Applicable Law, gross negligence, or willful misconduct, in which case such Party will fully bear such Losses and may not include such Losses in *Expenses* for the purpose of the Profit/Loss Share. The indemnification obligations of each Party set forth in Section 11.1.1 and Section 11.1.2 will exclude any Losses to the extent that the Indemnitee has already been reimbursed for such damages by virtue of the inclusion of such Losses in Expenses prior to receiving indemnification therefor by the Indemnifying Party. Notwithstanding anything to the contrary set forth in this Agreement, with respect to Third Party Infringement Claims filed by a Third Party within 18 months after the First Commercial Sale of a Product, 89% of any damages awarded as a final judgment by a court of competent jurisdiction will be treated as "*Expenses*" hereunder and the remaining 11% will be paid solely by Ionis.

Section 11.3 **Indemnification Procedure**. In the event of any claim, suit, proceeding, or action of a Third Party (a ***"Third Party Claim"***) giving rise to an indemnification obligation under this ARTICLE 11, the person or entity entitled to indemnification under this ARTICLE 11 (individually, an ***"Indemnitee"***), will promptly notify the Party from whom indemnification is sought (the ***"Indemnifying Party"***), in writing of the Third Party Claim (it being understood and agreed, however, that the failure by an Indemnitee to give notice of a Third Party Claim as provided in this Section 11.3 will not relieve the Indemnifying Party of its indemnification obligation under this Agreement, except and only to the extent that such Indemnifying Party is actually prejudiced as a result of such failure to give notice). The Indemnifying Party will manage and control, at its sole expense, the defense of the claim and its settlement, and all such expenses of such defense and any settlement will be considered "*Expenses*" for purposes of the Profit/Loss Share (except to the extent such expenses arise from the Indemnifying Party's breach of this Agreement (or any other agreement between the Parties), violation of Applicable Law, gross negligence, or willful misconduct). Within 30 days after delivery of such notification the Indemnifying Party may, upon written notice to the Indemnitee, assume control of the defense of such Third Party Claim with counsel reasonably satisfactory to the Indemnitee. The Indemnitee may participate therein at its own expense; *provided*, *however*, that if the Indemnifying Party assumes control of such defense and the Indemnitee reasonably concludes, based on advice from counsel, that the Indemnifying Party and the Indemnitee have conflicting interests with respect to such Third Party Claim, then the Indemnifying Party will be responsible for the reasonable fees and expenses of counsel to the Indemnitee solely in connection therewith (and any such reasonable fees and expenses of counsel will be considered "*Expenses*" for purposes of the Profit/Loss Share except to the extent the Third Party Claim arises from the Indemnitee's breach of this Agreement (or any other agreement between the Parties), violation of Applicable Law, gross negligence, or willful misconduct). Notwithstanding anything to the contrary set forth in this Agreement, in no event will the Indemnifying Party be responsible for the fees and expenses of more than one counsel in any one jurisdiction for all Indemnified Parties. If the Indemnifying Party does not assume control of the defense of the Third Party Claim within 30 days after delivery of Indemnitee's notice of such claim and request for indemnification, then the Indemnitee(s) may defend such Third Party Claim. Each Party will keep the other Party advised of the status of such Third Party Claim and the defense thereof, and the Indemnifying Party will consider recommendations made by the other Party with respect thereto. If the Indemnifying Party assumes control of the defense of the Third Party Claim, then the Indemnifying Party will not agree to any settlement of such Third Party Claim or consent to any judgment in respect thereof that does not include a complete and unconditional release of the Indemnitee from all liability with respect thereto or that imposes any liability or obligation on the Indemnitee without the prior written consent of the Indemnitee. The Indemnifying Party will not be obligated to indemnify the Indemnitee(s) for any Third Party Claim settled by the Indemnitee(s) without the Indemnifying Party's prior written consent, which consent will not be unreasonably withheld.

Section 11.4 **Insurance.** Each Party will maintain at its sole expense, a liability insurance program (including clinical trials and product liability insurance) consistent with products that are at the stage of development as the Products licensed under this Agreement to protect against potential liabilities and risk arising out of activities to be performed under this Agreement and any agreement related hereto.

Section 11.5 **LIMITATION OF CONSEQUENTIAL DAMAGES**. EXCEPT WITH RESPECT TO (I) A PARTY'S BREACH OF Section 5.1, ARTICLE 8, OR Section 12.1, (II) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER SECTION 11.1, (III) CLAIMS ARISING OUT OF A PARTY'S GROSS NEGLIGENCE OR WILLFUL MISCONDUCT UNDER THIS AGREEMENT, OR (IV) IONIS' BREACH OF Section 12.2(a), Section 12.2(b), OR SECTION 12.3.3: 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, 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.

ARTICLE 12
REPRESENTATIONS, WARRANTIES, AND COVENANTS

Section 12.1 **Representations and Warranties of the Parties**. The Parties hereby represent and warrant, as of the Execution Date and the Effective Date, to the other Party that: (a) it has the power and authority and the

legal right to enter into this Agreement and perform its obligations hereunder, and that it has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder; (b) this Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid and binding obligation of such Party and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency, or other laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity; and (c) it has all necessary consents, approvals, and authorizations of all government or regulatory bodies and other parties required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been obtained.

Section 12.2 **Ionis Representations and Warranties.** Ionis hereby represents and warrants (and where specified to the best of its knowledge, means to the best of the knowledge of Ionis' executive officers) to Akcea that, as of (i) the Execution Date and, (ii) other than any matters set forth in a letter from Ionis to Akcea dated as of the Effective Date, the Effective Date:

(a) It has sufficient legal or beneficial title and ownership or right to license (or sublicense as the case may be) with respect to the Ionis Patents as is necessary to fulfill its obligations under this Agreement and to grant the licenses (or sublicenses as the case may be) to Akcea pursuant to this Agreement.

(b) To the best of its knowledge, no actions, suits, claims, disputes, or proceedings concerning the Ionis Patents licensed hereunder are currently pending or are threatened in writing, that if determined adversely to Ionis would have an adverse effect on Ionis' ability to grant the licenses (or sublicenses as the case may be) to Akcea, or perform its obligations, under this Agreement, or that would have an adverse effect on or would impair Akcea's right to practice under the licenses (or sublicenses as the case may be) granted under this Agreement by Ionis to Akcea.

(c) All employees and contractors of Ionis that are inventors of any of the inventions claimed in the Ionis Product-Specific Patents and that have performed Development or Manufacturing activities with respect to any Product Development on behalf of Ionis have entered into written agreements pursuant to which such Persons are obligated to assign all rights, title, and interests in and to any such inventions developed by them, whether or not patentable, to Ionis or such Affiliate, respectively, as the sole owner thereof.

(d) To the best of its knowledge, there are no additional licenses (beyond those granted to Akcea under this Agreement) under any intellectual property owned or Controlled by Ionis or its Affiliates that would be required in order for Akcea to Develop, Manufacture, or Commercialize a Product.

(e) The Ionis Licensed Technology constitutes all of the Patents and Know-How Controlled by Ionis that are necessary to Develop, Manufacture, and Commercialize the Products as contemplated under this Agreement. Ionis has not previously assigned, transferred, conveyed, or otherwise encumbered its rights, title, or interests in or to the Ionis Licensed Technology in a manner that conflicts with any rights granted to Akcea hereunder with respect to the Products.

(f) Appendix 2 (Ionis Core Technology Patents), Appendix 3 (Ionis Product Specific Patents), and Appendix 4 (Ionis Manufacturing Patents), set forth true, correct, and complete lists of all Ionis Core Technology Patents, all Ionis Product-Specific Patents, and Ionis Manufacturing and Patents, respectively, and indicates whether each such Patent is owned by Ionis or licensed by Ionis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent is licensed. Ionis Controls such Patents and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Patents that it purports to grant to Akcea under this Agreement.

(g) To the best of its knowledge, (i) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude that any Ionis Product-Specific Patent is invalid or un-enforceable; (ii) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude the inventorship of each Ionis Product-Specific Patent is not properly identified on each patent; and (iii) all official fees, maintenance fees, and annuities for the Ionis Product-Specific Patents have been paid and all administrative procedures with governmental agencies have been completed. None of the Ionis Product-Specific Patents is

currently involved in any interference, reissue, re-examination, *inter partes* review, 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.

(h) Ionis has set forth on Appendix 5 (Existing In-License Agreements) a true, correct, and complete lists of all agreements pursuant to which a Third Party has granted Ionis a sublicensable license under any Know-How or Patents that is necessary to Develop, Manufacture, or Commercialize the Products, and all such Patents and Know-How are Controlled by Ionis and included in the Ionis Licensed Technology. All Existing In-License Agreements are in full force and effect, and Ionis has provided Akcea with true and complete copies of each such Existing In-License Agreement and all amendments thereto. Neither Ionis nor, to the best its knowledge, the counterparty to an Existing In-License Agreement is in default with respect to a material obligation under such Existing 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 Existing In-License Agreement.

(i) To the best of its knowledge, except as otherwise disclosed by Ionis to Akcea via the electronic data room hosted in connection with the transactions contemplated hereunder, no issued patent or published patent application owned by a Third Party will be infringed by the Development, Manufacture (as manufactured by Ionis at its facility), or Commercialization of the Products as contemplated by this Agreement (assuming with respect to such published patent application, that such application issues with the claims existing in such application as of the Effective Date), and Ionis and its Affiliates have not misappropriated any Third Party's Know-How in the course of the Development and Manufacture of the Products.

(j) All INDs, NDAs, and other material regulatory submissions made with any Regulatory Authority relating to the Development, Manufacture, marketing, distribution, or sale of the Products are set forth in the electronic data room. Except as otherwise disclosed by Ionis to Akcea via the electronic data room hosted in connection with the transactions contemplated hereunder, neither Ionis nor any of its Affiliates or licensees has received any written notice or allegation from any Regulatory Authority regarding (i) any actual, alleged, possible, or potential violation of or failure to comply with any Applicable Law, or (ii) any actual, proposed, or potential revocation, withdrawal, suspension, cancellation, termination, or modification of any regulatory filing for the Products, and to Ionis' knowledge there is no reasonable basis for any such notice or allegation.

(k) All Development of the Products has been conducted, in all material respects, in accordance with all Applicable Law. There is no legal proceeding pending or, to Ionis' knowledge, threatened, by any Regulatory Authority to suspend, investigate, or terminate Development of any Product.

(l) To the best of its knowledge, true, complete and correct copies of all material information with respect to the safety and efficacy of the Products have been provided to Akcea.

Section 12.3 **Covenants of Ionis**. From and after the Execution Date through the expiration or earlier termination of this Agreement, Ionis hereby covenants to Akcea that, except as expressly permitted under this Agreement:

12.3.1 Updates to Appendixes. Upon Akcea's request, Ionis will promptly update Appendix 2 (Ionis Core Technology Patents), Appendix 3 (Ionis Product-Specific Patents), and Appendix 4 (Ionis Manufacturing Patents) and submit such amended Appendixes to Akcea.

12.3.2 In-Licenses. Ionis will not, and will cause its Affiliates not to amend, modify, terminate, or waive any rights under any Existing In-License Agreement or Future In-License Agreement in a manner that would adversely affect Akcea's rights or obligations under this Agreement without Akcea's prior written consent. 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 Existing In-License Agreement or Future In-License Agreement in its entirety or with respect to any rights under such agreement for which such termination would adversely affect Akcea's rights or obligations under this Agreement. Ionis will notify Akcea in writing within one Business Day after any such termination of any Existing In-License Agreement or Future In-License Agreement.

12.3.3 Conflicting Agreements. Ionis will not enter into any agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case, that restricts, limits, encumbers, or conflicts with the rights granted to Akcea under this Agreement.

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

Section 12.4 **DISCLAIMER OF WARRANTY**. NEITHER PARTY WARRANTS THAT ANY PRODUCT WILL BE SUCCESSFULLY DEVELOPED OR COMMERCIALIZED HEREUNDER. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 12, AKCEA AND IONIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND AKCEA AND IONIS EACH SPECIFICALLY DISCLAIM ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 13
MISCELLANEOUS

Section 13.1 **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, except that each Party may assign this Agreement and the rights, obligations, and interests of such Party, in whole or in part, without the other Party's consent, to (a) any of its Affiliates, (b) any purchaser of all or substantially all of its business or assets to which this Agreement relates, or (c) any successor corporation resulting from any merger, consolidation, share exchange, or other similar transaction; *provided*, if Akcea or any of its Affiliates or Sublicensees transfers or assigns this Agreement or a Sublicense to one of its Affiliates that is incorporated in a jurisdiction that does not have a Bilateral Income Tax Treaty with the United States or in a jurisdiction where a Bilateral Income Tax Treaty requires withholding taxes on any payment described in this Agreement, then Akcea (or such Affiliate or Sublicensee), will increase (*i.e.*, "gross up") any payment due Ionis under ARTICLE 6 for the Incremental Tax Cost such that Ionis receives the amount Ionis would have otherwise received under ARTICLE 6 but for such transfer or assignment. In addition, Ionis may assign or transfer its rights to receive payments under this Agreement (but, subject to any right that Akcea may have under Applicable Law), without Akcea'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 13.1 will be null, void, and of no legal effect.

The ***"Incremental Tax Cost"*** shall equal the amount of IRC Sec 901 (or successor provision) foreign withholding taxes withheld under ARTICLE 6 in each year in which such tax is paid and Ionis cannot obtain a corresponding cash benefit from the foreign tax credit, grossed up by the applicable withholding tax rate based on a payment to a United States Person (unless the actual applicable treaty is lower, in which case the lower withholding tax rate shall be used) to equal the pre withholding tax payment.

To the extent Ionis utilizes a foreign tax credit or claims a deduction in any year with respect to the taxes withheld in any year, Ionis will refund to Akcea an amount equal to (i) 100% of the foreign tax credit utilized or (ii) the benefit realized by Ionis resulting from the deduction, which benefit will be calculated as the sum of (1) the amount claimed as a deduction *multiplied* by the highest marginal statutory federal corporate tax rate applicable to Ionis; *plus* (2) any state tax benefit of the deduction claimed by Ionis. To assist Akcea 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 Akcea pays Ionis an increased (*i.e.*, "gross up") payment under this Section 13.1, and each year thereafter (including, for clarity, all years in which Ionis utilizes a tax credit or claims a deduction for any foreign tax that is withheld), Ionis will provide Akcea with tax documentation reasonably required and requested by Akcea and, in years in which Ionis utilizes the federal foreign tax credit, supporting documentation for such credit. Notwithstanding the foregoing, if the increase in the withholding tax is in any way a result of the transfer or assignment by Ionis of any intellectual property or a portion of the rights under this license outside of the United States, then Akcea will only be obligated to pay Ionis such gross up to the extent such transfer or assignment by Ionis did not cause such increase in the withholding tax.

Section 13.2 **Severability**. If any provision of this Agreement is held to be illegal, invalid, or unenforceable by a court of competent jurisdiction, then such adjudication will not affect or impair, in whole or in part, the validity, enforceability, or legality of any remaining portions of this Agreement. All remaining portions will remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable, or illegal part. The Parties agree to use good faith, reasonable efforts to replace the illegal, invalid, or unenforceable provision with a legal, valid, and enforceable provision that achieves similar economic and non-economic effects as the severed provision.

Section 13.3 **Governing Law; Jurisdiction**. This Agreement will be governed by and construed and enforced in accordance with the laws of the State of New York, USA without reference to any rules of conflicts of laws. Subject to Section 13.4, each of the Parties hereby irrevocably and unconditionally submits, for itself and its property, to the exclusive jurisdiction of any federal court of the United States of America sitting in Chicago, Illinois and any appellate court having jurisdiction thereover, in any action in aid of arbitration, and each of the Parties hereby irrevocably and unconditionally agrees that all actions in aid of arbitration may be heard and determined in any such federal court in Chicago, Illinois. Notwithstanding the foregoing or anything to the contrary herein, any dispute relating to the scope, validity, enforceability, or infringement of any Patents will be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

Section 13.4 **Dispute Resolution.**

13.4.1 Resolution by Senior Representatives. The Parties will seek to settle amicably any and all disputes, controversies, or claims arising out of or in connection with this Agreement (a "***Dispute***"). Except as otherwise provided in this Agreement (including Schedule 6.4.1), any such dispute between the Parties will be promptly presented to the Chief Executive Officer of Akcea and the Chief Operating Officer of Ionis (the "***Senior Representatives"***), or their respective designees, for resolution. Such Senior Representatives, or their respective designees, will meet in-person or by teleconference as soon as reasonably possible thereafter, and use their good faith efforts to agree upon the resolution of the dispute, controversy, or claim. If a dispute between the Parties arising out of or relating to the validity or interpretation of, compliance with, breach or alleged breach of, or termination of this Agreement cannot be resolved within 30 days after presentation to the Senior Representatives, or their respective designees, for resolution, then either Party may refer such dispute to Expedited or other binding arbitration, as applicable, to be conducted as set forth in this Section 13.4. Notwithstanding anything to the contrary set forth in this Agreement, any dispute relating to the validity, construction, scope, enforceability, infringement, or other violations of Patents or other intellectual property rights will not be subject to arbitration pursuant to Section 13.4.2 or Section 13.4.3 and instead either Party may bring an action in any court of competent jurisdiction to resolve such disputes.

13.4.2 Arbitration.

(a) If the Parties fail to resolve the Dispute through Escalation, and a Party desires to pursue resolution of the Dispute, then, other than Expedited Disputes subject to resolution by Expedited Arbitration (which will be resolved in accordance with Section 13.4.3), the Dispute will be submitted by either Party for resolution in binding arbitration pursuant to the then current CPR Non-Administered Arbitration Rules (***"CPR Rules"***) (www.cpradr.org), except where they conflict with these provisions, in which case these provisions will control. The arbitration will be held in Chicago, Illinois. Except in a proceeding to enforce the results of the arbitration or as otherwise required by Applicable Law, all aspects of the arbitration will be treated as confidential.

(b) The arbitrators will be chosen from the CPR Panel of Distinguished Neutrals, unless a candidate not on such panel is approved by both Parties. Each arbitrator will be a lawyer with at least 15 years of experience with a law firm or corporate law department of over 25 lawyers or who was a judge of a court of general jurisdiction. To the extent that the Dispute requires special expertise, the Parties will so inform CPR prior to the beginning of the selection process.

(c) The arbitration tribunal will consist of three arbitrators, of whom each Party will designate one in accordance with the "screened" appointment procedure provided in CPR Rule 5.4. The chair will be chosen in accordance with CPR Rule 6.4.

(d) If, however, the aggregate award sought by the Parties is less than $25 million and equitable relief is not sought, then a single arbitrator will be chosen in accordance with the CPR Rules.

(e) Candidates for the arbitrator position(s) may be interviewed by representatives of the Parties in advance of their selection, provided that all Parties are represented.

(f) The Parties agree to select the arbitrator(s) within 45 days of initiation of the arbitration. The hearing will be concluded within six months after selection of the arbitrator(s) and the award will be rendered within 60 days of the conclusion of the hearing, or of any post hearing briefing, which briefing will be completed by both sides within 45 days after the conclusion of the hearing. If the Parties cannot agree upon a schedule, then the arbitrator(s) will set the schedule following the time limits set forth above as closely as practical.

(g) The hearing will be concluded in 10 hearing days or less. Multiple hearing days will be scheduled consecutively to the greatest extent possible. A transcript of the testimony adduced at the hearing will be made and will be made available to each Party.

(h) The arbitrator(s) will be guided, but not bound, by the CPR Protocol on Disclosure of Documents and Presentation of Witnesses in Commercial Arbitration (www.cpradr.org) (***"CPR Protocol"***). The Parties will attempt to agree on modes of document disclosure, electronic discovery, witness presentation, etc. within the parameters of the CPR Protocol. If the Parties cannot agree on discovery and presentation issues, then the arbitrator(s) will decide on presentation modes and provide for discovery within the CPR Protocol, understanding that the Parties contemplate reasonable discovery.

(i) The arbitrator(s) will decide the merits of any Dispute in accordance with the law governing this Agreement, without application of any principle of conflict of laws that would result in reference to a different law. The arbitrator(s) may not apply principles such as "amiable compositeur" or "natural justice and equity."

(j) The arbitrator(s) are expressly empowered to decide dispositive motions in advance of any hearing and will endeavor to decide such motions as would a United States District Court Judge sitting in the jurisdiction whose substantive law governs.

(k) The arbitrator(s) will render a written opinion stating the reasons upon which the award is based. The Parties consent to the jurisdiction of the United States District Court for the district in which the arbitration is held for the enforcement of these provisions and the entry of judgment on any award rendered hereunder. Should such court for any reason lack jurisdiction, any court with jurisdiction may act in the same fashion.

(l) Each Party has the right to seek from the appropriate court provisional remedies such as attachment, preliminary injunction, replevin, etc. to avoid irreparable harm, maintain the *status quo*, or preserve the subject matter of the Dispute. Rule 14 of the CPR Rules does not apply to this Agreement.

(m) EXCEPT IN THE CASE OF COURT ACTIONS PERMITTED BY SECTION 13.4.4, AND FOR CLAIMS NOT SUBJECT TO ARBITRATION PURSUANT TO SECTION 13.4.2 AS SET FORTH IN SECTION 13.4.4, EACH PARTY HERETO WAIVES: (i) ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY.

(n) Each Party will bear its own attorneys' fees, costs, and disbursements arising out of the arbitration, and will pay an equal share of the fees and costs of the arbitrator; *provided*, *however*, the arbitrator will be authorized to determine whether a Party is the prevailing party, and if so, to award to that prevailing party reimbursement for any or all of its reasonable attorneys' fees, costs and disbursements (including, for example, expert witness fees and expenses, photocopy charges, travel expenses, etc.), or the fees and costs of the administrator and the arbitrator.

13.4.3 Expedited Arbitration. If a Party exercises its rights under this Agreement to refer a Dispute to expedited arbitration (an ***"Expedited Dispute"***), then the Parties will follow the expedited dispute resolution process in this Section 13.4.3 (and not the dispute resolution process in Section 13.4.2) (***"Expedited Arbitration"***). The Parties agree and acknowledge that any good faith dispute under Expedited Arbitration will not be deemed to be a material breach of this Agreement. The Expedited Dispute will be submitted to fast-track, binding arbitration in accordance with the following:

(a) Arbitration will be conducted in Chicago Illinois under the rules of the CPR for the resolution of commercial disputes in the most expedited manner permitted by such rules. The Parties will appoint an

arbitrator in accordance with Section 13.4.2(b) through Section 13.4.2(f). Except as otherwise provided in this Agreement, the cost of the arbitration will be borne as set forth in Section 13.4.2(n). Except in a proceeding to enforce the results of the arbitration or as otherwise required by Applicable Law, all aspects of the arbitration will be treated as confidential.

(b) Within 30 days after such matter is referred to arbitration, each Party will provide the arbitrator with a proposal and written memorandum in support of its position regarding the Expedited Dispute, as well as any documentary evidence it wishes to provide in support thereof, which in the case of a dispute regarding the terms of an agreement, will include such Party's proposed agreement (each a ***"Brief"***) and the arbitrator will provide each Party's Brief to the other Party after it receives it from both Parties.

(c) Within 30 days after a Party submits its Brief, the other Party will have the right to respond thereto. The response and any material in support thereof will be provided to the arbitrator and the other Party.

(d) The arbitrator will have the right to meet with the Parties as necessary to inform the arbitrator's determination and to perform independent research and analysis. Within 30 days after the receipt by the arbitrator of both Parties' responses (or expiration of the 30-day period if any Party fails to submit a response), then the arbitrator will deliver his/her decision regarding the Expedited Dispute in writing, which decision will be made in accordance with the standard for resolution of such matter set forth in this Agreement; *provided that* the arbitrator must select the resolution proposed by one of the Parties.

13.4.4 Injunctive Relief; Court Actions. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek from any court of competent jurisdiction, in addition to any other remedy it may have at law or in equity, injunctive, or other equitable relief in the event of an actual or threatened breach of this Agreement by the other Party, without the posting of any bond or other security, and such an action may be filed and maintained notwithstanding any ongoing discussions between the Parties or any ongoing arbitration proceeding. The Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive or equitable relief would be an appropriate remedy.

Section 13.5 **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.

Section 13.6 **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), facsimile transmission (receipt verified), or overnight express courier service (receipt verified), 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
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 Akcea, addressed to:	Akcea Therapeutics, Inc. 55 Cambridge Parkway, Suite 100 Cambridge, MA 02142 Attention: Chief Executive Officer Fax: 760-602-1855
with a copy to:	Akcea Therapeutics, Inc. 55 Cambridge Parkway, Suite 100 Cambridge, MA 02142 Attention: Vice President, Legal Email: legalnotices@akceatx.com
with a copy to:	Ropes & Gray LLP Prudential Tower 800 Boylston Street Boston, MA 02199 Attention: David M. McIntosh Email: david.mcintosh@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 or facsimile transmission, then 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, then 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.

Section 13.7 **Export Clause**. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

Section 13.8 **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

Section 13.9 **Entire Agreement; Modifications**. This Agreement (including the attached Appendices and Schedules) and the Stock Purchase Agreement sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof, and all prior agreements, understanding, promises, and representations, whether written or oral, with respect to the subject matter hereof are superseded hereby. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

Section 13.10 **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.

Section 13.11 **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word "including" (in its various forms) means "*including without limitation*," (c) the words "shall" and "will" have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, "$" is in reference to United States dollars, (h) the headings contained in this Agreement, in any exhibit or schedule to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement, and (i) the word "or" is used in the inclusive sense.

Section 13.12 **Third Party Beneficiaries**. The Indemnitees are intended third party beneficiaries of this Agreement and will have the right to directly enforce Section 11.1 against the Parties. Except as expressly set forth in this Agreement, no Person other than the Parties and their respective Affiliates and permitted assignees will have any right to enforce this Agreement.

Section 13.13 **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with U.S. Generally Accepted Accounting Principles (or any successor standard), consistently applied.

Section 13.14 **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. If a Party requests any data and results generated by the other Party under this Agreement, such other Party will disclose to the requesting Party such data and results as promptly as possible.

Section 13.15 **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives 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.

Section 13.16 **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 identifying the Ionis Patents 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.

Section 13.17 **Counterparts**. This Agreement may be signed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which 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.

Section 13.18 **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

Section 13.19 **Debarment**. Neither Party is debarred under the United States Federal Food, Drug and Cosmetic Act or comparable Applicable Laws and it does not, and will not during the Agreement Term, employ or use the services of any person or entity that is debarred, in connection with the Development, Manufacture or

Commercialization of the Products. If either Party becomes aware of the debarment or threatened debarment of any person or entity providing services to such Party, including the Party itself and its Affiliates or Sublicensees, which directly or indirectly relate to activities under this Agreement, then the other Party will be immediately notified in writing.

[Remainder of Page Intentionally Left Blank]

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

IONIS PHARMACEUTICALS, INC.

By: /s/ Stanley T. Crooke
Name: Stanley T. Crooke
Title: Chief Executive Officer

AKCEA THERAPEUTICS, INC.

By: /s/ Paula Soteropoulos
Name: Paula Soteropoulos
Title: Chief Executive Officer

[Signature Page to Development, Commercialization, Collaboration, and License Agreement]

List of Appendices and Schedules

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APPENDIX 1

DEFINITIONS

"Acceptance of Filing" means, with respect to an NDA or MAA filed for IONIS-TTR-L_{Rx}, (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*," or (b) in the European Union, receipt of written notice of validation by the EMA of such MAA 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 of Filing will be determined upon the validation of such MAA by the applicable Regulatory Authority in a Major Market in Europe.

"Affiliate" of an entity means any other entity that, directly or indirectly, through one or more intermediaries, controls, is controlled by, or is under common control with such first entity, but such an entity will be deemed to be an Affiliate only for the duration of such control. For purposes of this definition only, "control" (and, with correlative meanings, the terms "controlled by" and "under common control with") means the possession, directly or indirectly, of the power to direct the management or policies of an entity, whether through the ownership of voting securities or by contract relating to voting rights or corporate governance. Ionis will not be considered an Affiliate of Akcea and Akcea will not be considered an Affiliate of Ionis for the purposes of this Agreement.

"Agreement" means this Agreement, together with all Schedules and Appendices attached hereto as the same may be amended or supplemented from time to time in accordance with the terms of this Agreement.

"Agreement Term" has the meaning set forth in Section 10.1.

"Akcea" has the meaning set forth in the opening paragraph of this Agreement.

"Akcea Collaboration Technology" means Patents and Know-How discovered, developed, invented, or created solely by or on behalf of Akcea or its Affiliate or a Third Party acting on their behalf in the performance of the Strategic Plan that is necessary or useful to Develop, Manufacture, or Commercialize a Product.

"Akcea Indemnitee" has the meaning set forth in Section 11.1.2.

"Akcea Non-Commercial Activities" means, with respect to a Product, (a) Pre-Approval Akcea Development Activities, (b) all Development activities to be conducted for such Product in a country following receipt of Approval for such Product in such country, including phase 4 trials and post-marketing commitments, and (c) Medical Affairs Activities, whether performed prior to or following the receipt of Approval for such Product in such country.

"Akcea Product-Specific Patents" means all Patents Controlled by Akcea at any time during the Agreement Term Covering (a) the composition of matter of a Product, or (b) methods of using a Product as a prophylactic or therapeutic; *provided however*, Patents Controlled by Akcea that include only claims that are directed to (i) subject matter applicable to oligonucleotide compounds or products in general, including Conjugate Technology, or (ii) an oligonucleotide compound that does not specifically modulate expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR, will not be considered Akcea Product-Specific Patents.

"Akcea Technology" means any Patents and Know-How Controlled by Akcea or its Affiliates that is necessary or useful to Develop, Manufacture, or Commercialize a Product.

"Allowable Overage" has the meaning set forth in Section 4(f) of Schedule 6.4.1.

"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 (unless expressly stated otherwise) for a Product. The quantity of API will be the as-is gross mass of the API after lyophilization (*i.e.*, including such amounts of water, impurities, salt, heavy, metals, etc. within the limits set forth in the API specifications).

"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 any Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the Development, Manufacture, or Commercialization of such Product in such jurisdiction in accordance with Applicable Law.

"ASO" means a single-stranded or double-stranded oligonucleotide, or analog, mimic, or mimetic thereof, having a sequence of at least six bases long designed to modulate the expression of the target nucleic acid transcript via binding, partially or wholly, of such compound to the nucleic acid transcript.

"Assigned Regulatory Documentation" has the meaning set forth in Section 3.5.2.

"Breaching Party" has the meaning set forth in Section 10.3.6.

"Brief" has the meaning set forth in Section 13.4.3(b).

"Business Day" means any day, other than Saturday, Sunday, or any statutory holiday or bank holiday in the United States.

"Calendar Quarter" means the respective periods of three consecutive calendar months ending on March 31, June 30, September 30, and December 31.

"Calendar Year" means each successive period of 12 months commencing on January 1 and ending on December 31.

"Change of Control" means, with respect to a Party: (a) the acquisition by any Third Party of beneficial ownership of more than 50% of the then outstanding common shares or voting power of such Party, other than acquisitions by employee benefit plans sponsored or maintained by such Party; (b) the consummation of a business combination involving such Party, unless, following such business combination, the stockholders of such Party immediately prior to such business combination beneficially own directly or indirectly more than 50% of the then outstanding common shares or voting power of the entity resulting from such business combination.

"Clinical Hold" means a clinical hold issued by the FDA (or other Regulatory Authority) in accordance with 21 CFR 312.42 (or a similar foreign counterpart law or regulation) to delay a proposed clinical investigation of a Product or to suspend an ongoing clinical investigation of a Product.

"Clinical Trial" or ***"Clinical Trials"*** means a Phase 1 Clinical Trial, Phase 2 Clinical Trial, or Phase 3 Clinical Trial, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data to obtain, support, or maintain an NDA, MAA, or other similar marketing application.

"CMC" means Chemistry, Manufacturing, and Controls as set forth 21 C.F.R.

"CMO" means a contract manufacturing organization.

"Collaboration" means the conduct of the Strategic Plan in accordance with this Agreement.

"Commercial Budget" has the meaning set forth in Section 3.2.1(c).

"Commercialize," "Commercializing," and ***"Commercialization"*** means activities directed to manufacturing, obtaining pricing and reimbursement approvals, marketing, promoting, distributing, importing, or selling a Product.

"Commercially Reasonable Efforts" means, with respect to a Product, the carrying out of Development, Manufacturing, 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 Development, Manufacturing, or Commercialization 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 regulatory approval and other relevant scientific, technical, and commercial factors.

"Competing Activities" has the meaning set forth in Section 5.1.3.

"Competing Product" means, during the Agreement Term, any product (including an ASO) that is designed to modulate expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR, other than any Product. For the avoidance of doubt, no such product will be considered a "*Competing Product*" for purposes of this Agreement after the expiration or earlier termination of this Agreement.

"Competitive Infringement" has the meaning set forth in Section 9.3.1.

"Compliance Expenses" has the meaning set forth in Section 6 of Schedule 6.4.1.

"Confidential Information" means all Know-How and other information and any tangible embodiments thereof provided by or on behalf of the Disclosing Party to the Receiving Party either in connection with the discussions and negotiations pertaining to this Agreement or in the course of performing activities under this Agreement, including data; knowledge; practices; processes; ideas; research plans; engineering designs and drawings; research data; manufacturing processes and techniques; scientific, manufacturing, marketing and business plans; and financial and personnel matters relating to the Disclosing Party or to its present or future products, sales, suppliers, customers, employees, investors, or business; regardless of whether any of the foregoing are marked "confidential" or "proprietary" or communicated to the other by the Disclosing Party in oral, written, graphic, or electronic form.

Notwithstanding the foregoing, information or Know-How of a Party will not be deemed Confidential Information for purposes of this Agreement to the extent that the Receiving Party can show by competent proof that such information or Know-How:

(a) was already known to the Receiving Party or any of its Affiliates, without any obligation to the Disclosing Party to keep it confidential or restricting its use, prior to the time of disclosure to such Receiving Party;

(b) was generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or was otherwise part of the public domain, at the time of its disclosure to the Receiving Party;

(c) became generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or otherwise became part of the public domain, after its disclosure to such Receiving Party through no fault of the Receiving Party;

(d) was disclosed to such Receiving Party or any of 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; or

(e) was independently discovered or developed by employees or (sub)contractors of the Receiving Party or any of 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.

"Conjugate Technology" means chemistry designed to enhance targeting or uptake of antisense drugs to specific tissues and cells. Conjugate Technology includes N-acetylgalactosamine (GalNAc) ligand conjugates capable of binding to the asialoglycoprotein receptor (ASGP-R) and enhancing the targeting or uptake of antisense drugs to the liver.

"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, 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 such compensation owed to such Third Party. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that later becomes an Affiliate of Ionis after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of Ionis.

"Cost of Goods" has the meaning set forth in Section 6 of Schedule 6.4.1.

"Cover" or ***"Covered"*** or ***"Covering"*** means, with respect to a Patent and a Product, that, but for rights granted to a Person under such Patent the act of making, using, or selling of such Product 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. If Ionis assigns an Ionis Product-Specific Patent to Akcea, then such Patent will still be considered an Ionis Product-Specific Patent hereunder and a Product will be deemed "*Covered*" by such Ionis Product-Specific Patent for purposes of this Agreement.

"CPR Rules" has the meaning set forth in Section 13.4.2.

"Development" or ***"Develop"*** or ***"Developing"*** means (a) any and all discovery, characterization, or preclinical (including gene function, gene expression, and target validation research, lead optimization, and which may include small pilot toxicology studies), clinical, or regulatory activities with respect to a product to obtain, support, or maintain Approval of such product (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), or any other human clinical studies conducted for a product, whether conducted prior to or after receipt of Approval for such product, and (b) Medical Affairs Activities.

"Development Budget" has the meaning set forth in Section 3.2.1(d).

"Development Expenses" has the meaning set forth in Section 6 of Schedule 6.4.1.

"Disclosing Party" has the meaning set forth in Section 8.1.

"Discontinued Patent" has the meaning set forth in Section 9.2.5.

"Dispute" has the meaning set forth in Section 13.4.1.

"Distribution Agreement" means a written agreement between Akcea or its Affiliates and a Distributor (a) that grants such Distributor the rights to buy from Akcea or its Affiliates one or more Products and distribute and resell such Products under Akcea's brand name and product marks, (b) that does not include the grant of a sublicense under any Ionis Licensed Technology or the grant of any other right to Develop, Manufacture, or Commercialize a Product, (c) pursuant to which such Distributor purchases its requirements of such Product from Akcea or its Affiliates but does not make any royalty payment or other payments to Akcea or its Affiliates, and (d) that Akcea has the right to terminate without cause on reasonable written notice to such Third Party.

"Distribution Expenses" has the meaning set forth in Section 6 of Schedule 6.4.1.

"Distributor" means a Third Party to whom Akcea grants the rights to buy from Akcea or its Affiliates one or more Products and distribute and resell such Products under Akcea's brand name and product marks pursuant to a Distribution Agreement, where title to such Product transfers to such Third Party.

"Dollars" or ***"$"*** means the lawful currency of the United States.

"Drug Product" means any drug product containing API as an active ingredient in finished bulk form or in packaged and labeled form, in each case, for the Development or Commercialization by a Party under this Agreement.

"eCTD" has the meaning set forth in Section 3.5.3.

"Effective Date" means the date on which the closing of the Stock Purchase Agreement occurs.

"EMA" means the European Regulatory Authority known as the European Medicines Agency and any successor agency thereto.

"European Union" or ***"EU"*** means each and every country or territory that is officially part of the European Union.

"Execution Date" has the meaning set forth in the opening paragraph of this Agreement.

"Existing In-License Agreement" means the agreements listed on Appendix 5.

"Expedited Arbitration" has the meaning set forth in Section 13.4.3.

"Expedited Dispute" has the meaning set forth in Section 13.4.3.

"Expenses" has the meaning set forth in Section 6 of Schedule 6.4.1.

"External Expenses" has the meaning set forth in Section 6 of Schedule 6.4.1.

"FDA" means the United States Food and Drug Administration and any successor agency thereto.

"First Commercial Sale" means the first sale of a Product by Akcea, its Affiliate, or its Sublicensee to a Third Party in a particular country after Approval of such Product has been obtained in such country.

"FTE" means a total of 47 weeks or 1,880 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.

"Fully Absorbed Cost of Goods" means the reasonable and necessary internal and third party costs with no mark-up incurred by Ionis in making or acquiring of product as determined using the methodology set forth in Schedule 3.8.1 fairly applied and as employed on a consistent basis throughout Ionis' operations and shall not include inter-company profits among Ionis and its Affiliates.

"Future In-License Agreement" means an agreement entered into by Ionis or Akcea after the Effective Date pursuant to which a Third Party grants to Ionis or Akcea a sublicensable license under any Patents or Know-How that is necessary or useful for the Development, Manufacture, or Commercialization of the Products.

"G&A Expenses" has the meaning set forth in Section 6 of Schedule 6.4.1.

"GAAP" means generally accepted accounting principles of the United States consistently applied, or for any non-US entity (a) international financial reporting standards (IFRS) consistently applied, or (b) for such non-US entity that does not use IFRS, the generally accepted accounting rules in its home jurisdiction for entities of a similar size in the same industry, consistently applied throughout its organization.

"GSK Agreement" means that certain Research, Development and License Agreement dated March 30, 201 between Glaxo Group Limited and Ionis, as amended.

"hATTR" has the meaning set forth in the recitals.

"Incremental Tax Cost" has the meaning set forth in Section 13.1.

"IND" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or any equivalent application for authorization to commence human clinical trials in other countries or regulatory jurisdictions.

"Indication" means a primary sickness or medical condition or any interruption, cessation, or disorder of a particular bodily function, system, or organ (each a "disease") requiring a separate NDA (or foreign equivalent filing) to obtain Approval to market and sell a Product for such disease.

"Initial 2018 Plans and Budgets" has the meaning set forth in Section 3.1.

"inotersen" means the compound having the following sequence and chemistry: 5-^{Me}U^{Me}C^{Me}U^{Me}UGGTTA^{Me}CATGAAA^{Me}U^{Me}C^{Me}C^{Me}C- 3. The underlined residues are 2'-O-(2-methoxyethyl) nucleosides (2'-MOE nucleosides). The residues are arranged so that there are five 2'-MOE nucleosides at the 5 and 3-ends of the molecule flanking a gap of ten 2-deoxynucleosides. The cytosine and uracil bases are methylated at the 5-position. ^{Me}U and T have the same nucleobase structure and the choice for the symbol depends on whether the sugar is 2′-deoxy-D-ribose or D-ribose. Each of the 19 internucleoside linkages is a phosphorothioate linkage. Inotersen does not include any product containing Conjugate Technology.

"Internal Expenses" has the meaning set forth in Section 6 of Schedule 6.4.1.

"Ionis" has the meaning set forth in the opening paragraph of this Agreement.

"Ionis Core Technology Know-How" means all Know-How Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term necessary to Develop or Commercialize a Product that relates generally to oligonucleotides including Conjugate Technology, other than Know-How specifically relating to a Product (including Ionis Product-Specific Know-How) or Know-How specifically relating to methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification.

"Ionis Core Technology Patents" means all Patents Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term necessary to Develop or Commercialize a Product claiming

subject matter generally applicable to oligonucleotides including Conjugate Technology, other than Ionis Product-Specific Patents or Patents that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification. The Ionis Core Technology Patents as of the Effective Date include the Patents set forth on Appendix 2.

"Ionis Indemnitee" has the meaning set forth in Section 11.1.1.

"Ionis Internal Oligonucleotide Safety Database" has the meaning set forth in Section 3.9.

"Ionis Know-How" means Ionis Core Technology Know-How and Ionis Product-Specific Know-How.

"Ionis Licensed Technology" means the (a) Ionis Patents, (b) Ionis Know-How, and (c) Ionis Manufacturing Technology.

"Ionis Manufacturing and Analytical Know-How" means Know-How that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification 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 Patents" means Patents that claim Ionis Manufacturing and Analytical Know-How. The Ionis Manufacturing Patents as of the Effective Date include the Patents set forth on Appendix 4 attached hereto. Ionis Manufacturing Patents do not include the Ionis Product-Specific Patents or the Ionis Core Technology Patents.

"Ionis Manufacturing Technology" means the (a) Ionis Manufacturing Patents, and (b) Ionis Manufacturing and Analytical Know-How.

"Ionis Patents" means the Ionis Core Technology Patents, Ionis Manufacturing Patents, and the Ionis Product-Specific Patents.

"Ionis Product-Specific Know-How" means all Know-How Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term necessary to Develop or Commercialize a Product or disclosed by Ionis to Akcea and specifically relating to (a) the composition of matter of a Product or (b) methods of using a Product as a prophylactic or therapeutic; *provided*, *however*, Know-How Controlled by Ionis or any of its Affiliates that (i) consists of subject matter applicable to oligonucleotide compounds or products in general or (ii) relates to an oligonucleotide compound that does not specifically modulate expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR, will not be considered Ionis Product-Specific Know-How, and in the case of (i) and (ii), such Know-How will be considered Ionis Core Technology Know-How.

"Ionis Product-Specific Patents" means all Patents Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term Covering (a) the composition of matter of a Product, (b) methods of using a Product, or (c) an oligonucleotide compound that specifically modulates expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR; *provided*, *however*, that Patents Controlled by Ionis or any of its Affiliates that include any claims that are directed to (i) subject matter applicable to oligonucleotide compounds or products in general or (ii) an oligonucleotide compound that does not specifically modulate expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR, will not be considered Ionis Product-Specific Patents, and in the case of (i) and (ii), such Patents will be considered Ionis Core Technology Patents. The Ionis Product-Specific Patents as of the Effective Date include the Patents set forth on Appendix 3.

"***IONIS-TTR-L***$_{Rx}$" means:

(i) the compound known as ION 682884 having the sequence and chemistry disclosed to Akcea via the electronic data room hosted in connection with the transactions contemplated hereunder; and/or

(ii) any oligonucleotide compound (other than inotersen and ION 682884) designed to modulate expression of TTR via the binding, partially or wholly, of such compound to the RNA that encodes TTR, that is determined after the Execution Date by Ionis' research management committee as ready to start the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND.

The Parties acknowledge that, if more than one of the foregoing compounds included in this definition are being simultaneously Developed or Commercialized under this Agreement, the Parties may create alternative designations for each such compound (e.g., IONIS-TTR-L-1_{Rx} or IONIS-TTR-L-2_{Rx}) in the Strategic Plan (and other related documentation) in order to avoid confusion and distinguish between the compounds, and in all cases such alternative designations will mean "*IONIS-TTR-*L_{Rx}" for all purposes of this Agreement.

"***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 Core Technology Patents***" means all Patents jointly invented by Ionis and Akcea at any time during the Agreement Term necessary to Develop or Commercialize a Product claiming subject matter generally applicable to oligonucleotides in a target-independent manner including Conjugate Technology, other than Akcea Product-Specific Patents, Ionis Product-Specific Patents, or Patents that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification.

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 9.1.

"***Joint Patents***" means, collectively, all Joint Product-Specific Patents and Joint Core Technology Patents.

"***Joint Product-Specific Patents***" means all Patents invented jointly by Ionis and Akcea at any time during the Agreement Term Covering (a) the composition of matter of a Product, or (b) methods of using a Product as a prophylactic or therapeutic; *provided however*, Patents jointly invented by Ionis and Akcea that include only claims that are directed to (i) subject matter applicable to oligonucleotide compounds or products in general in a target independent manner including Conjugate Technology or (ii) an oligonucleotide compound that does not specifically modulate expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR, will not be considered Joint Product-Specific Patents, and in the case of (i) and (ii), such Patents will be considered Joint Core Technology Patents.

"***Joint Profit Sharing Report***" has the meaning set forth in Section 4(c) of Schedule 6.4.1.

"***Joint Steering Committee***" or "***JSC***" has the meaning set forth in Section 3.4.1.

"***Know-How***" means any unpatented information or material, whether proprietary or not and whether patentable or not, including ideas, concepts, formulas, methods, procedures, designs, compositions, plans, documents, data, trade secrets, inventions, discoveries, compounds and biological materials.

"***Losses***" has the meaning set forth in Section 11.1.1.

"***MAA***" means a marketing authorization application filed with the EMA after completion of Clinical Trials to obtain Approval for a 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 the Approval of an MAA by (a) the EMA for a Product in any country in the EU, or (b) a Regulatory Authority in a European country in a Major Market.

"***Major Market***" means the United States of America, Germany, United Kingdom, France, Spain, Italy, Brazil, Canada, or Japan.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing or supply of API or Drug Product, including process development, formulation development, quality control development and testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical, clinical, or commercial purposes, of API or Drug Product.

"***Manufacturing Agreement***" has the meaning set forth in Section 3.8.2(b).

"***Material Change***" has the meaning set forth in Section 3.2.3.

"***Medical Affairs Activities***" means the performance of activities with respect to: continuing medical education; development, publication, and dissemination of publications; exhibiting and presenting at seminars and

conventions; conducting health economic studies; conducting health care professional and patient speakers programs; conducting appropriate activities involving opinion leaders; engaging medical science liaisons and conducting medical science liaison activities; conducting advisory board meetings or other consultant programs; and establishing clinical consumer and patient registries.

"***Medical Affairs Expenses***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Milestone Events***" has the meaning set forth in Section 6.3.4.

"***Milestone Payments***" has the meaning set forth in Section 6.3.4.

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Trials to obtain marketing approval for the applicable Product in the United States, or a foreign equivalent thereof.

"***NDA Approval***" means the Approval of an NDA by the FDA for a Product in the U.S.

"***NDA Transfer Date***" has the meaning set forth in Section 3.5.2.

"***Net Profit (or Loss)***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Net Revenue***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Net Sales***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Non-Breaching Party***" has the meaning set forth in Section 10.3.6.

"***Party***" or "***Parties***" has the meaning set forth in the opening paragraph of this Agreement.

"***Patents***" 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).

"***Payment Election Notice***" has the meaning set forth in Section 6.3.7(a).

"***Person***" means any individual, firm, corporation, partnership, limited liability company, trust, business trust, joint venture company, governmental authority, association, or other entity.

"***Phase 1 Clinical Trial***" means the initial clinical testing of a Product in humans (first-in-humans study) with the intention of gaining a preliminary assessment of the safety of such Product.

"***Phase 2 Clinical Trial***" means a human clinical trial of a Product, conducted in any country that is intended to explore a variety of doses, dose response and duration of effect to generate initial evidence of clinical safety and activity in a target patient population, that would satisfy the requirements of 21 CFR 312.21(b) (but does not provide data sufficient to file an NDA), or equivalent clinical trials required by a Regulatory Authority in a jurisdiction outside of the United States. A "*Phase 2 Clinical Trial*" includes any human clinical trial that has an efficacy endpoint.

"***Phase 3 Clinical Trial***" or "***Pivotal Study***" means a human clinical trial of a Product on a sufficient number of subjects that is designed to establish that such Product is safe and efficacious for its intended use and to determine warnings, precautions, and adverse reactions that are associated with such Product in the dosage range to be prescribed, which trial is intended to support Approval of such Product, as described in 21 C.F.R. 312.21(c) for the United States, or a similar Clinical Trial prescribed by the Regulatory Authorities in a foreign country.

"***PMDA***" means the Pharmaceutical and Medical Device Agency of Japan.

"***Post-Termination Transition Activities***" has the meaning set forth in Section 10.4.2(h).

"***Pre-Approval Akcea Development Activities***" means any Development activities that are allocated to Akcea by the JSC in the Strategic Plan and that are to be conducted for a Product in a country prior to receipt of Approval for such Product in such country.

"***Pre-Existing Competing Product***" has the meaning set forth in Section 5.1.3.

"***Prior Agreements***" means the agreements listed on Appendix 6.

"***Product***" means any pharmaceutical preparation that contains as an active pharmaceutical ingredient (a) inotersen, or (b) IONIS-TTR-L_{Rx}.

"***Product-Specific Patents***" mean, collectively, the Akcea Product-Specific Patents, Ionis Product-Specific Patents, and Joint Product-Specific Patents.

"***Profit/Loss Ratio***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Profit/Loss Share***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Profit Share Changeover Date***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Profit Share Payment***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Profit Share Start Date***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Prosecuting Party***" has the meaning set forth in Section 9.2.5.

"***R&D Support Expenses***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Receiving Party***" has the meaning set forth in Section 8.1.

"***Reconciliation Report***" has the meaning set forth in Section 4(d) of Schedule 6.4.1.

"***Regulatory Authority***" means any governmental authority 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, including FDA, EMA, or PMDA.

"***Regulatory Documentation***" means all applications, registrations, licenses, authorizations, and approvals (including all Approvals), all correspondence submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority), all supporting documents and all Clinical Trials and tests, including the manufacturing batch records, relating to a Product, and all data contained in any of the foregoing, including all regulatory drug lists, advertising and promotion documents, adverse event files, and complaint files.

"***Regulatory Expenses***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Regulatory Milestone Event***" means the regulatory milestone events set forth in Table 6.3.1 and Table6.3.2.

"***Regulatory Milestone Payment***" means the payments set forth in Table 6.3.1 and Table 6.3.2 to be made upon achievement of the corresponding Regulatory Milestone Event.

"***Regulatory Responsible Party***" has the meaning set forth in Section 3.5.1.

"***Regulatory Sub-Committee***" has the meaning set forth in Section 3.5.1.

"***Sales and Marketing Expenses***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Sales Milestone Event***" has the meaning set forth in Section 6.3.4.

"***Sales Milestone Payment***" has the meaning set forth in Section 6.3.4.

"***Senior Representatives***" has the meaning set forth in Section 13.4.1.

"***Services Agreement***" means the Services Agreement entered into by and between Ionis and Akcea dated December 17, 2015, as amended.

"***Significant Event***" has the meaning set forth in Section 7.1.1.

"***Stock Purchase Agreement***" means that certain Stock Purchase Agreement entered into between Ionis and Akcea of even date herewith.

"***Strategic Plan***" has the meaning set forth in Section 3.2.1.

"***Sublicense***" means an agreement pursuant to which Akcea or an Akcea Affiliate grants a Third Party the right to practice an Ionis Patent licensed to Akcea hereunder (whether by license or covenant not to sue) or an option to obtain such a right to Develop or Commercialize a Product.

"***Sublicense Revenue***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Sublicensee***" means any Third Party that enters into a Sublicense with Akcea or its Affiliate to Develop or Commercialize a Product.

"***Sublicensing Equity Threshold***" has the meaning set forth in Section 6 of Schedule 6.4.1.

"***Termination Transition Plan***" has the meaning set forth in Section 10.4.2(h).

"***Third Party***" means any Person other than Ionis or Akcea or their respective Affiliates.

"***Third Party Obligations***" means any financial, obligations, imposed by any Existing In-License Agreement or Future In-License Agreement, in each case, that relates to a Product, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transaction Documents***" means this Agreement and the Stock Purchase Agreement and the other documents and instruments to be executed and delivered in connection herewith and therewith.

"***Transthyretin***" or "***TTR***" means the gene target, transthyretin (GenBank accession # NM_000371; Gene ID: 7276), or any alternative splice variants, mutants, polymorphisms, and fragments thereof.

"***Valid Claim***" means a claim of a Patent that (a) in the case of any granted, unexpired United States Patent or foreign Patent, will not have been donated to the public, disclaimed, or held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (b) in the case of any United States or foreign patent application, is being prosecuted in good faith and will not have been permanently cancelled, withdrawn, or abandoned, *provided that* (i) no more than five years have passed since the earliest date of filing for such application in the United States (unless and until such claim is granted), and (ii) no more than eight years have passed since the earliest date of filing for such application outside of the United States (unless and until such claim is granted).

APPENDIX 2

IONIS CORE TECHNOLOGY PATENTS

Ionis Docket No.	Country	Patent/ Application No.	Grant Date	Title
ISPH-0333	United States	6,001,653	12/14/1999	HUMAN TYPE 2 RNASE H
ISIS-2003	United States	7,015,315	03/21/2006	GAPPED OLIGONUCLEOTIDES, DIRECTED TO: GAPMER AND HEMIMER COMPOUNDS WITH 2'-O-ALKYL MODIFICATIONS
ISIS-0710	United States	7,101,993	09/05/2006	OLIGONUCLEOTIDES CONTAINING 2'-OMODIFIED PURINES
CORE0115US	United States	9,127,276	09/08/2015	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115US.C1	United States	9,181,549	11/10/2015	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115US.C2	United States	14/744,539		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115AU	Australia	2014259750		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115BR	Brazil	112015027322-0		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115CA	Canada	2,921,162		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115CN	China	201480035635.3		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115EP	European Patent Office	14792010.2		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115HK	Hong Kong	16109545.3		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115IL	Israel	242127		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115IN	India	7302/CHENP/2015		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115JP	Japan	2016-512051		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115KR	Republic of Korea	10-2015-7033029		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115MX	Mexico	MX/a/2015/015220		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115NZ	New Zealand	712737		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
CORE0115RU	Russian Federation	2015151199		CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE
BIOL0248DZ	Algeria	150647		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248SG.D1	Singapore	10201801507R		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION

APPENDIX 3

IONIS PRODUCT-SPECIFIC PATENTS

Ionis Docket No.	Country	Patent/ Application No.	Filing Date	Grant Date	Title
BIOL0123AU.D1	Australia	2016203300	4/29/2011	7/27/2017	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123BR	Brazil	112012027547-0	4/29/2011		MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123CA	Canada	2,797,792	4/29/2011	2/27/2018	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123CA.D1	Canada	TBD	4/29/2011		MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123CN	China	ZL201180021445.2	4/29/2011	7/21/2017	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123EP	European Patent Office (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, SV, TR)	2563920	4/29/2011	3/15/2017	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123HK	Hong Kong	13107130.1	4/29/2011		MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123IL	Israel	222697	4/29/2011	8/30/2017	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123IN	India	9956/CHEN/2012	4/29/2011		MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123JP	Japan	5896175	4/29/2011	3/11/2016	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123KR	Korea	10-2012-7031119	4/29/2011		MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123MX	Mexico	343559	4/29/2011	11/10/2016	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123NZ	New Zealand	603339	4/29/2011	5/1/2015	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123RU	Russia	2592669	4/29/2011	7/4/2016	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123US.C1	United States	8,697,860	7/17/2013	4/15/2014	DIAGNOSIS AND TREATMENT OF DISEASE
BIOL0123US.C2	United States	9,816,092	6/23/2016	11/14/2017	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123US.C3	United States	15/729,860	10/11/2017		MODULATION OF TRANSTHYRETIN EXPRESSION

Ionis Docket No.	Country	Patent/ Application No.	Filing Date	Grant Date	Title
BIOL0123US.D1	United States	9,061,044	2/20/2014	6/23/2015	MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0123US.D2	United States	9,399,774	5/20/2015	7/26/2016	MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C1	United States	8,101,743	11/19/2008	1/24/2012	MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C7	United States	15/803,484	11/3/2017		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C8	United States	15/898,058	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C9	United States	15/898,057	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C10	United States	15/898,153	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C11	United States	15/898,128	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C12	United States	15/898,142	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C13	United States	15/898,061	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C14	United States	15/898,117	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C15	United States	15/898,073	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C16	United States	15/898,070	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
RTS-0531US.C17	United States	15/898,111	2/15/2018		MODULATION OF TRANSTHYRETIN EXPRESSION
BIOL0305US2	United States	15/605,114	5/25/2017		COMPOSITIONS AND THERAPEUTIC DOSES AND METHODS THEREOF
BIOL0248AU.D1	Australia	2017200950	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248CL.D1	Chile	2016-02262	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248CO.D1	Colombia	NC2016/0003763	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING

Ionis Docket No.	Country	Patent/ Application No.	Filing Date	Grant Date	Title
					HBV AND TTR EXPRESSION
BIOL0248DO.D1	Dominican Republic	P2016-0287	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248EG.D1	Egypt	D1/1741/2015	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248ID.D1	Indonesia	P-00201605718	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248MX.D1	Mexico	MX/a/2016/012654	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248NZ.D1	New Zealand	728517	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248PE.D1	Peru	001724-2016-DIN	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248US.C3	United States	15/687,306	8/25/2017		COMPOSITIONS AND METHODS FOR MODULATING TTR EXPRESSION
BIOL0248ZA.D1	South Africa	2016/00076	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION
BIOL0248WO[i]	Patent Cooperation Treaty	PCT/US14/036463	5/1/2014		COMPOSITIONS AND METHODS FOR MODULATING HBV AND TTR EXPRESSION

i National Applications containing TTR subject matter pending in the following jurisdictions: Brazil, Canada, China, Costa Rica, Eurasian Patent Office, European Patent Office, Hong Kong, Israel, India, Japan, Korea, Morocco, Malaysia, Nigeria, Philippines, Russia, Thailand, Trinidad and Tobago, Ukraine, and Vietnam. We may file divisional applications claiming IONIS-TTR-LRx at the appropriate time, in the desired jurisdictions.

APPENDIX 4

IONIS MANUFACTURING PATENTS

Technology	Ionis Docket Number	Country/Treaty	Application /Patent Number	Filing Date	Title
"Wet" ACN	ISIS-3294	United States	6,069,243	10/6/1999	PROCESS FOR OLIGONUCLEOTIDE SYNTHESIS
	ISIS-4216 (BE, CH, DE, GB, SE)	European Patent Convention	1119578	10/1/1999	PROCESS FOR OLIGONUCLEOTIDE SYNTHESIS
Alternative Solvents for Oligo Synthesis	DVCM0003US	United States	7,276,599	6/2/2004	OLIGONUCLEOTIDE SYNTHESIS WITH ALTERNATIVE SOLVENTS
	DVCM0003CA	Canada	2,540,692	6/2/2004	OLIGONUCLEOTIDE SYNTHESIS WITH ALTERNATIVE SOLVENTS
PADS	ISIS-2585	United States	6,114,519	10/15/1997	IMPROVED SYNTHESIS OF SULFURIZED OLIGONUCLEOTIDES
	ISIS-3245 (BE, CH, DE, ES, FR, GB, IE, IT, PT)	European Patent Convention	1023310	10/13/1998	IMPROVED SYNTHESIS OF SULFURIZED OLIGONUCLEOTIDES
	ISIS-4314	United States	6,242,591	01/11/2000	SYNTHESIS OF SULFURIZED 2'-SUBSTITUTED OLIGONUCLEOTIDES
	ISIS-4709	United States	7,227,015	12/12/2002	SYNTHESIS OF SULFURIZED OLIGONUCLEOTIDES
	ISIS-5479	United States	7,378,516	05/17/2004	SYNTHESIS OF SULFURIZED OLIGONUCLEOTIDES
	ISIS-5479US.C1	United States	7,723,511	4/21/2008	SYNTHESIS OF SULFURIZED OLIGONUCLEOTIDES
DMT Removal	ISIS-3349	United States	6,399,765	03/17/1999	METHODS FOR REMOVING DIMETHOXYTRITYL GROUPS FROM OLIGONUCLEOTIDES
Oligonucleotide Precipitation	ISIS-4728	United States	6,632,938	06/07/2001	PROCESSES FOR PURIFYING OLIGONUCLEOTIDES
	ISIS-5330	Canada	2,449,552	06/05/2002	PROCESSES FOR PURIFYING OLIGONUCLEOTIDES
	ISIS-5332 (CH, DE, FR, GB)	European Patent Convention	1399457	06/05/2002	PROCESSES FOR PURIFYING OLIGONUCLEOTIDES
CNET Avoidance	ISIS-3381(BE, CH, DE, ES, FR, GB, IE, IT)	European Patent Convention	1028124	9/6/1999	IMPROVED PROCESS FOR THE SYNTHESIS OF OLIGOMERIC COMPOUNDS

Technology	Ionis Docket Number	Country/Treaty	Application /Patent Number	Filing Date	Title
	ISIS-5080	United States	6,858,715	8/30/2002	IMPROVED PROCESS FOR THE SYNTHESIS OF OLIGOMERIC COMPOUNDS
	ISIS-5422	United States	7,041,816	1/20/2004	IMPROVED PROCESS FOR THE SYNTHESIS OF OLIGOMERIC COMPOUNDS
	ISIS-5488	United States	7,199,236	9/14/2004	IMPROVED PROCESS FOR THE SYNTHESIS OF OLIGOMERIC COMPOUNDS
	ISIS-5584	United States	7,186,822	12/28/2004	IMPROVED PROCESS FOR THE SYNTHESIS OF OLIGOMERIC COMPOUNDS
	ISIS-5585	United States	7,227,016	12/28/2004	PROCESS FOR THE SYNTHESIS OF OLIGOMERIC COMPOUNDS
Chloral-Free DCA	ISIS-5190	United States	7,169,916	3/31/2003	CHLORAL-FREE DCA IN OLIGONUCLEOTIDE SYNTHESIS
	ISIS-5190US.C1	United States	7,759,480	1/29/2007	CHLORAL-FREE DCA IN OLIGONUCLEOTIDE SYNTHESIS
	ISIS-5021	United States	6,645,716	1/29/2002	METHODS FOR DETECTION OF CHLORAL HYDRATE IN DICHLOROACETIC ACID
	ISIS-5245	United States	7,173,123	10/6/2003	METHODS FOR DETECTION OF CHLORAL HYDRATE IN DICHLOROACETIC ACID
	ISIS-5245US.C1	United States	7,446,193	2/1/2007	METHODS FOR DETECTION OF CHLORAL HYDRATE IN DICHLOROACETIC ACID
	ISIS-5216 (DE, ES, FR, GB, IT)	European Patent Convention	1356115	1/29/2002	METHODS FOR DETECTION OF CHLORAL HYDRATE IN DICHLOROACETIC ACID
Unylinker	DVCM0010EP (CH, DE, DK, ES, FR, GB, IE, IT)	European Patent Convention	1692139	11/15/2004	SUPPORTS FOR OLIGOMER SYNTHESIS
	DVCM0010EP.D1 (CH, DE, DK, ES, FR, GB, IE, IT)	European Patent Convention	2708541	11/15/2004	5,6-DIHYDROOXY-ISOINDOLE DERIVATIVES AS LINKERS FOR OLIGOMER SOLID PHASE SYNTHESIS
	DVCM0023US.P1	United States	7,202,264	11/15/2004	SUPPORTS FOR OLIGOMER SYNTHESIS
	DVCM0023US.C1	United States	7,576,119	1/11/2007	SUPPORTS FOR OLIGOMER SYNTHESIS
	DVCM0023US.C2	United States	7,718,810	7/17/2008	SUPPORTS FOR OLIGOMER SYNTHESIS
	DVCM0023US.C3	United States	8,153,725	03/19/2010	SUPPORTS FOR OLIGOMER SYNTHESIS

Technology	Ionis Docket Number	Country/Treaty	Application /Patent Number	Filing Date	Title
	DVCM0023US.D1	United States	8,541,599	03/07/2012	SUPPORTS FOR OLIGOMER SYNTHESIS
DCA/Toluene	ISIS-2710	United States	7,273,933	2/26/1998	METHODS FOR SYNTHESIS OF OLIGONUCLEOTIDES

APPENDIX 5

IN-LICENSE AGREEMENTS

1. Amended & Restated Licensing Agreement between Integrated DNA Technologies, Inc. and Ionis dated December 4, 2001 [IDT's core antisense oligonucleotide patents and patent applications]
2. Non-Exclusive Patent Cross License Agreement between Novartis Pharma AG and Ionis dated June 3, 1996 [Core methoxyethoxy (2'-MOE) oligonucleotide chemical modifications]
3. Collaboration and License Agreement between Hybridon, Inc. (Now Idera Pharmaceuticals) and Ionis dated May 24, 2001 [Hybridon's core antisense oligonucleotide patent portfolio]
4. Second Amended and Restated Strategic Collaboration and License Agreement between Alnylam Pharmaceuticals, Inc. and Ionis dated January 8, 2015
5. Settlement and Non-Exclusive License Agreement among Ionis, F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc., Roche Innovation Center Copenhagen A/S (formerly Santaris Pharma A/S), and Santaris Pharma A/S Corp. dated March 19, 2015
6. Non-Exclusive Patent License Agreement between Ionis and Molecular Biosystems, Inc. dated September 14, 1992, as amended March 27, 2001
7. Research and License Agreement between Ionis and McGill University dated January 1, 1994

In each case, only if (and to the extent) a Product under this Agreement incorporates technology that is in-licensed by Ionis under such agreement.

APPENDIX 6

PRIOR AGREEMENTS

1. Amended & Restated Licensing Agreement between Integrated DNA Technologies, Inc. and Ionis dated December 4, 2001 [IDT's core antisense oligonucleotide patents and patent applications]

2. Non-Exclusive Patent Cross License Agreement between Novartis Pharma AG and Ionis dated June 3, 1996 [Core methoxyethoxy (2'-MOE) oligonucleotide chemical modifications]

3. Collaboration and License Agreement between Hybridon, Inc. (Now Idera Pharmaceuticals) and Ionis dated May 24, 2001 [Hybridon's core antisense oligonucleotide patent portfolio]

4. Second Amended and Restated Strategic Collaboration and License Agreement between Alnylam Pharmaceuticals, Inc. and Ionis dated January 8, 2015 [Strategic collaboration and license for dsRNAi and ssRNAi]

5. Settlement and Non-Exclusive License Agreement among Ionis, F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc., Roche Innovation Center Copenhagen A/S (formerly Santaris Pharma A/S), and Santaris Pharma A/S Corp. dated March 19, 2015

6. Non-Exclusive Patent License Agreement between Ionis and Molecular Biosystems, Inc. dated September 14, 1992, as amended March 27, 2001

7. Research and License Agreement between Ionis and McGill University dated January 1, 1994

8. License Agreement between Ionis and Agilent Technologies Inc. dated March 10, 2009

9. License Agreement between Ionis and Avecia Biotechnology, Inc. dated October 15, 2009

10. Non-Exclusive Patent License between Ionis and BioSpring GMBH dated January 8, 2014

11. License Agreement between Ionis and Girindus America dated September 15, 2008

12. License Agreement between Ionis and Sanofi-Aventis Deutschland GMBH dated June 5, 2015

13. License Agreement between Ionis and ST Pharm Co., Ltd dated March 21, 2012

14. Research, Development and License Agreement dated March 30, 2010 between Glaxo Group Limited and Ionis, as amended

SCHEDULE 3.2.1

Strategic Plan Content Examples

The following are examples of items that may be included in the Strategic Plan, as appropriate, based on the stage of Development or Commercialization of the applicable Product.

i. Indications that will be pursued for each Product (which indications will be added to or refined over time) and the on-going pre-clinical Development, including registries and natural history studies, in support of such indications;

ii. Timing and launch sequence of initial and subsequent indications for each Product;

iii. Clinical Trials that the Parties will conduct for each Product, including patient populations, study designs, primary and secondary endpoints, length and size of study, associated timelines and budgets;

iv. Safety data delivery procedures governing the collection, investigation, reporting, and delivery of information between the Parties concerning any adverse experiences, and any product quality and product complaints involving adverse experiences related to, or class effects that could impact, the Products, sufficient to enable the Parties to comply with its legal and regulatory obligations and internal processes, as applicable;

v. Global regulatory strategy, including timing and key implementation items to support each targeted indication;

vi. Timing, budget, and design of all nonclinical and pre-clinical studies supporting the Development or Commercialization of the Products;

vii. Upcoming scientific, development, or commercial events of Akcea or competitors that may impact the Products;

viii. Publication plan (including scientific publications and presentations at medical meetings) and key messaging for Products on a rolling 12-month basis;

ix. Key elements of the manufacturing planning and strategy, including raw material supply, manufacturing scale-up, process validation, and inventory build plan to support Development, Product Approvals, and Commercialization; and

x. Key elements of the global Commercialization strategy for each Product, including, for example, high level pricing and reimbursement plans, market access strategy, Product positioning, sales forecasts (with supportive core assumptions), launch sequence, and other key Commercialization plans and goals.

SCHEDULE 3.8.1

IONIS' FULLY ABSORBED COST OF GOODS METHODOLOGY

Cost Estimate of API Cost per Kilogram

(in OOO's)

Direct Material:

Based on actual costs for raw materials.

Direct Labor:

Identify the number of dedicated FTEs required to support the manufacture of budgeted production volume. Divide fully burdened salaries for these FTEs by the budgeted production volume.

Manufacturing Equipment Support:

These are the costs associated with supporting our manufacturing equipment such as calibration, service contracts, environmental monitoring, water testing, and cleaning. Divide the total costs in this category by the budgeted production volume.

Depreciation:

This category includes the depreciation expense for the facilities and equipment in both manufacturing suites. The total costs in this category are divided by the total budgeted production volume. Because these costs are fixed in nature, the per unit cost will decline as our production volume increases.

Building Lease:

Costs in this category include rent expense and landlord pass-through costs for our manufacturing facility. The total costs in this category are divided by the total production volume.

Occupancy Costs:

Costs in this category include utilities, repairs, maintenance, security, property taxes, and insurance. The total costs in this category are divided by the total production volume.

Infrastructure Support:

The costs in this category are primarily costs of personnel needed to support manufacturing. The departments included in this category are information technology, purchasing, receiving, facilities, patents, health and safety (including hazardous waste costs), finance, HR, QA, ADQC, document control. We ask each department manager for an estimate of the percentage his/her department spends supporting manufacturing and we apply that percentage to the department's budget on a department by department basis.

Estimated Total API Cost per Kilogram

*Ionis' Fully Absorbed Cost of Goods does not include import duties, VAT or other taxes, which Akcea will be responsible for paying in addition to Ionis' Fully Absorbed Cost of Goods.

CMO: If Ionis uses a Third Party CMO, as permitted by this Agreement, Fully Absorbed Cost of Goods will mean the amounts paid to the CMO.

SCHEDULE 6.4.1

Profit Sharing Provisions

This Schedule 6.4.1 contains the terms governing the Parties' sharing of Net Profits or Losses (as applicable) for each Product, including the accounting policies and procedures the Parties will use to account for Net Revenues, Expenses, and Net Profits (or Losses).

1) Accounting.

a) Accounting. The Parties will account for all amounts required to be determined under this Schedule6.4.1 (including Net Revenues, Expenses, Net Profits (or Losses), and all elements of any of the foregoing) in accordance with GAAP, consistently applied. Where more than one accounting treatment is possible consistent with the terms and conditions of this Agreement and GAAP, each Party will account for amounts in a manner that is consistent with the manner in which such Party accounts for similar amounts for the purposes of its publicly reported financial statements; *provided*, *however*, that during any period in which (i) Ionis' independent auditors advise Ionis that Ionis should consolidate Akcea's financial statements with Ionis' financial statements, or (ii) Akcea is using Ionis' financial systems, Akcea will use the same accounting treatment used by Ionis. In the event a Party does not have similar transactions, procedures, or policies, the Parties will mutually agree on the appropriate accounting treatment.

b) Consistency with Accounting Treatment. The Parties acknowledge and agree that revenues or expenses will not be reflected in Net Profits (or Losses) unless and until such revenues or expenses are recognized by such Party in its financial statements in accordance with GAAP consistently applied by such Party with respect to the transaction(s) in question.

2) General Allocation Principles. All Expenses that relate to multiple products (including inotersen, IONIS-TTR-L_{Rx}, and non-Products (*e.g.*, volanesorsen and other Akcea products or Ionis products) will be allocated and accounted for in accordance with this Section 2 (General Allocation Principles). Such costs will be allocated according to the allocation methods agreed by the Parties for each Calendar Year unless there is a material change in which case, the Parties will update the allocation methods in accordance with the procedures outlined in this Schedule 6.4.1. Once agreed, the Parties will record in the JSC minutes the allocation methodology, allocations, and the schedule of monthly and quarterly reporting and reconciling.

a) Personnel Expenses

i) Where personnel are split across multiple products (including inotersen, IONIS-TTR-L_{Rx}, and non-Products (*e.g.*, volanesorsen and other Akcea products or Ionis products), the general presumption is that the cost should be evenly split on a *pro-rata* basis based on the number of products for which such personnel perform activities (*e.g.*, 50/50 for two products, or 1/3 for three products).

ii) If there is evidence that such a *pro-rata* split would not be reflective of the effort, then the allocation of personnel cost for a manager or a department will be presumed to be best measured based on the percentage of headcount that reports to that manager or department head (*e.g.*, inotersen dedicated headcount reporting to a country General Manager divided by the total headcount reporting to a country General Manager who are dedicated to any product or IONIS-TTR-L_{Rx} dedicated headcount reporting to the Vice President of Biostatistics divided by the total headcount reporting to the Vice President of Biostatistics).

iii) For Internal Expenses, if headcount is determined to not be a reasonable allocation basis, then a rational basis (preferably a measurable and activity-based measure) for allocation of a department head should be determined unless the result of such an alternative allocation for such department head would not be different by more than $50,000 on an annual basis from the split achieved using a *pro-rata* allocation based on the number of products as set forth under Section 2(a)(i) above, in which case such *pro-rata* allocation based on the number of products should be employed.

b) External Expenses

i) It is expected that the majority of external expenses incurred by or on behalf of a Party will be

incurred specifically for either a Product or the Party's other products, including volanesorsen if the Party is Akcea. These expenses will be coded to the appropriate product as they are incurred. The amounts under this section that are specifically related to a Product will be directly charged as Expenses.

ii) To the extent external expenses apply to multiple products (including inotersen, IONIS-TTR-L_{Rx}, and non-Products (*e.g.*, volanesorsen and other Akcea products or Ionis products), the general presumption is that the cost should be evenly split on a *pro-rata* basis based on the number of products for which such expense is incurred (*e.g.*, 50/50 for two products, or 1/3 for three products). If a per product *pro rata* split is determined to not be a reasonable allocation basis, then a rational basis for allocation should be determined using the general principles described in Section 2(a) above.

c) **G&A, R&D Support, and Overhead Expenses**. Unless otherwise agreed by the Parties, G&A Expenses, R&D Support Expenses, and overhead expenses will not be considered Expenses for purposes of determining Net Profit (or Loss), except for Compliance Expenses or when included in Fully Absorbed Cost of Goods as described in Schedule 3.8.1 of the Agreement.

d) **Method for Allocating Expenses.** For the 2018 Calendar Year, Akcea's Chief Financial Officer and Ionis' Chief Financial Officer will agree by the Effective Date on both an allocation methodology for identifying, allocating, and charging an appropriate portion of each Party's respective Expenses and on the allocations for inotersen and IONIS-TTR-L_{Rx} based on the 2018 budget. Promptly after the two CFO's have agreed on the allocation methodologies and allocations, they will present these to the JSC for review and approval.

For all following Calendar Years, Akcea's Chief Financial Officer and Ionis' Chief Financial Officer will agree during the budgeting process on both an allocation methodology for identifying, allocating, and charging an appropriate portion of each Party's respective Expenses and on the allocation for inotersen and IONIS-TTR-L_{Rx} based on the budget for the upcoming Calendar Year. The allocation methodology and allocations will be reviewed and approved by the JSC prior to November 15th of each year for the following year. If the Chief Financial Officers or the JSC cannot agree on an allocation methodology or allocations, then the Parties will promptly escalate to the Chair of each Party's audit committee for resolution, each acting in good faith.

e) **Net Revenue Sharing.** Ionis and Akcea will share Net Revenue related to each Product according to the Profit/Loss Ratio for such Product. Beginning on the Profit Share Start Date, Net Revenue for inotersen will be included in the Profit/Loss Share for inotersen. Akcea will keep 100% of inotersen Net Sales it earns prior to the Profit Share Start Date. If Akcea earns Sublicense Revenue with respect to inotersen prior to the Profit Share Start Date, then Akcea will pay to Ionis 60% of such Sublicense Revenue within 45 days after the end of the Calendar Quarter in which Akcea earns such Sublicense Revenue. Such payment will be accompanied by a written report detailing the amount of Sublicense Revenue earned and the calculation used by Akcea to determine Ionis' share of such Sublicense Revenue. Beginning on January 1, 2018, the Parties will share Net Revenue for IONIS-TTR-L_{Rx} on a 50/50 basis.

All Net Revenue (or any elements of Net Revenue) will be accompanied by a written report detailing the amount of Net Revenue (and details regarding any Net Sales) earned and the calculation used by Akcea to determine Ionis' share of such Net Revenue. In those situations in which Net Revenue is included in the Profit/Loss Share, the written report will be included as part of the monthly or quarterly report to Ionis under Section 4(c) and (d) of this Schedule 6.4.1, as applicable.

To the extent that a payment not explicitly tied to a Product is made under a Sublicense that grants rights both to a Product and one or more other products or to more than one Product (*e.g.*, an upfront payment), then, in either case, Akcea's board of directors will in good faith determine a *pro rata* portion of such payment that will be considered Sublicense Revenue with respect to each Product, which *pro rata* portion will be calculated based on the value of each of the products with respect to which rights are granted under such a Sublicense. If Ionis disagrees with such allocation, then such matter will be resolved by Expedited Arbitration.

If Akcea enters into a series of agreements with the same Sublicensee pursuant to which Akcea grants such Sublicensee a Sublicense under at least one of such agreements, then such agreements will be aggregated together and treated as a single Sublicense for purposes of calculating Sublicense Revenue under this Agreement.

3) Expense Sharing.

a) Inotersen.

i) Inotersen Expenses - Prior to Profit Share Start Date. Ionis will be responsible for all expenses incurred by the Parties associated with inotersen accrued prior to April 1, 2018, including the cost of inotersen-specific employees or consultants hired or engaged by Akcea prior to April 1, 2018, and $400,000 for that portion of any Akcea employees specifically allocated to inotersen activities. Akcea will be responsible for all expenses associated with inotersen accrued during the period commencing on April 1, 2018 and ending on the day before the Profit Share Start Date.

ii) Inotersen Expenses - After Profit Share Start Date. Beginning on the Profit Share Start Date, Ionis and Akcea will share Expenses from the Development and Commercialization of inotersen using the process set forth in this Schedule 6.4.1 in accordance with the applicable Profit/Loss Ratio.

iii) Inotersen Development Expenses and Regulatory Expenses. Prior to the Profit Share Start Date, the Parties will share Development Expenses and Regulatory Expenses as set forth in Section 3(a)(i) of this Schedule 6.4.1. From and after the Profit Share Start Date, all Development Expenses and Regulatory Expenses for inotersen will be calculated according to the License Agreement, paid for by the Parties using the process and payment terms set forth in the Services Agreement and will be considered "*Expenses*" for purposes of the Profit/Loss Share.

iv) Inotersen Cost of Goods. From the Effective Date up to the day before the day inotersen is approved, if Akcea buys inotersen API or Drug Product from Ionis or from a Third Party, the Parties will share the Cost of Goods on a 60/40 basis (60% to Ionis and 40% to Akcea). Beginning on the day inotersen is approved, inotersen Cost of Goods will be considered "*Expenses*" under Section 6(e)(iv) of this Schedule 6.4.1 for purposes of the Profit/Loss Share.

b) IONIS-TTR-L_{Rx}. Ionis will be responsible for all expenses associated with IONIS-TTR-L_{Rx} accrued prior to January 1, 2018. Commencing on January 1, 2018 the Parties will share equally (*i.e.*, 50/50) all Expenses for IONIS-TTR-L_{Rx}, including Ionis Development Expenses and Regulatory Expenses (Development and Regulatory Expenses for IONIS-TTR-L_{Rx} will be calculated according to the License Agreement), which will be considered "Expenses" for purposes of the Profit/Loss Share for IONIS-TTR-L_{Rx}.

4) Monthly Reporting and Quarterly Reconciliations.

a) Books and Records. The Parties agree to maintain books and records for inotersen and IONIS-TTR-L_{Rx} that will allow each Party to provide the other Party with Net Revenues, Expenses (including each cost category included in the definition of Expenses, Net Profits (or Losses), and all elements of any of the foregoing) for each Product. The Parties will prepare separate P&L statements for each Product on a monthly and quarterly basis using actual results. The Parties will also prepare separate budgeted and forecasted P&L statements as needed to comply with the provisions of this schedule.

b) Schedule for Delivery of Monthly and Quarterly Reports. For the 2018 Calendar Year, Akcea's Chief Financial Officer and Ionis' Chief Financial Officer will agree on the format of and a schedule for delivery of the reports described in this Section 4 on or before the Effective Date. For all following Calendar Years, Akcea's Chief Financial Officer and Ionis' Chief Financial Officer will agree before the end of each Calendar Year on the format of and a schedule for delivery of the reports described in this Section 4 for the upcoming year. If the CFOs cannot so agree, then the Parties will escalate to the Chair of each Party's audit committee to resolve the dispute, each acting in good faith.

c) Monthly Reports. In accordance with the delivery schedule determined pursuant to Section 4(b) above, each Party will provide the other Party with a statement of its Net Revenue, Net Sales, and Expenses

for the previous Calendar Month for each of inotersen and IONIS-TTR-L_{Rx} in sufficient detail to allow the other Party to understand how each category included in the definition of Net Revenue and each cost category included in the definition of Expenses compares to the approved budgeted P&L statement (as applicable) (the "***Joint Profit Sharing Report***") as well as details of any adjustments pertaining to the previous Calendar Month.

d) **Quarterly Reconciliation**. In accordance with the delivery schedule determined pursuant to Section 4(b) above, Akcea will provide Ionis with a written report (the "***Reconciliation Report***") for each of inotersen and IONIS-TTR-L_{Rx}. Each Reconciliation Report will set forth in a format to be agreed-upon by the Parties, the calculations of any Net Profit (or Loss) and each Party's share of such Net Profit (or Loss), in each case, for inotersen and for IONIS-TTR-L_{Rx}. Such Reconciliation Report will include for the applicable Product the (i) total Net Revenue, (ii) total Net Sales (including in reasonable detail the deductions and allowances allowed in the calculation of Net Sales), (iii) the Expenses incurred by each Party, broken down by each cost category included in the definition of Expenses, (iv) total Net Profit (or Loss), and (v) the net payment due from one Party to the other Party such that the Parties share the Net Profit (or Loss) for the applicable Product in accordance with the then-applicable Profit/Loss Ratio. For clarity, in the event any expense falls within more than one expense category within the definition of Expenses, such expense will only be counted once in the calculation of Expenses and Net Profit (or Loss) in the manner each Party records expenses on its own books according to GAAP.

e) **Reconciliation Payment.** The Party owing a net payment to the other Party will pay any undisputed amounts within 30 days following such reconciliation. Notwithstanding the foregoing, if a Party disputes an amount provided in a Reconciliation Report, then the JSC will promptly review such disputed amount and agree upon a resolution. If the JSC cannot agree on a resolution, then such matter will be escalated to the chair of each Party's audit committee for resolution, each acting in good faith. If requested by a Party, the Party incurring the applicable expense will promptly provide to the requesting Party any invoices or other supporting documentation for any payments related to inotersen or IONIS-TTR-L_{Rx} to a Third Party that individually exceed $100,000.

f) **Allowable Overages for Expenses.** If in any Calendar Year a Party incurs Expenses that, in the aggregate, exceed the amount budgeted as Expenses to be incurred by such Party in such Calendar Year in the then-current budgeted P&L statement *plus* an overage percentage approved by the JSC for the applicable Calendar Year (for each Calendar Year, the "***Allowable Overage"***), then such Party will itself bear 100% of such excess Expenses and the amount of such excess will not be deducted in the calculation of Net Profit (or Loss). To the extent that the Party that incurred such excess Expense has already been reimbursed for such excess Expense pursuant to the Agreement or has already included the amount of such excess Expense in the calculation of Net Profit (or Loss) and made a reconciliation payment based thereon, then such Party will reimburse the other Party for such excess Expenses.

5) **Forecasts.**

a) At the time each Party provides the other Party its Joint Profit Sharing Report for the previous Calendar Month, each Party will also provide a forecast of Net Revenue, Net Sales, Expenses, and Net Profit (or Loss) for each applicable Product for the remainder of the Calendar Quarter. At the end of each Calendar Quarter, each Party will provide the other Party a forecast of Net Revenue, Net Sales, Expenses, and Net Profit (or Loss) for the remainder of the current Calendar Year.

b) If Expenses are forecasted to exceed the then-current budget for Expenses by more than 10% for the current Calendar Year, the forecast must be approved by the JSC before the incremental Expenses can be included in future Expenses for purposes of Net Profit (or Loss) sharing.

c) The Parties recognize that the forecasts to be provided pursuant to this section will be estimates only and the Party providing such forecasts will have no liability to the other Party based thereon.

6) **Definitions.**

a) "***Compliance Expenses***" means those Internal Expenses and External Expenses incurred by a Party

allocable to compliance activities associated with a healthcare compliance program designed to meet the requirements of the Department of Health and Human Services' Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers (or any foreign equivalent).

b) "***Cost of Goods***" means:

i) In the case of supplies of a Product (including API and Drug Product) provided by a Third Party directly to Akcea, payments made by Akcea to such Third Party for such supply of such Product, *plus* the following Internal Expenses and External Expenses actually incurred by Akcea in connection with the supply thereof, in accordance with Akcea's consistently applied accounting policy across its operations:

(1) non-refundable or non-creditable indirect taxes;

(2) reasonable and customary brokerage fees;

(3) quality control and quality assurance costs; and

(4) any other cost incurred with supplying such Product and capitalizable to inventory under GAAP;

Where costs (1) to (4) are Internal Expenses to Akcea, these shall be calculated using an allocation methodology consistent with the principles outlined in Section 2(a) above.

or

ii) In the case of Product (including API and Drug Product) supplied by Ionis, Cost of Goods for such Product will be Ionis' Fully Absorbed Cost of Goods as described in Schedule 3.8.1.

iii) In the case of Product Manufactured by Akcea, Costs of Goods for such Product will be calculated in accordance with GAAP consistently applied in a manner that is consistent in the manner in which Akcea accounts for similar amounts for the purpose of its publicly reported financial statements.

Notwithstanding the foregoing, Cost of Goods for a Product will not include expenses included in the definition of Distribution Expenses for such Product.

c) "***Development Expenses***" means those Internal Expenses and External Expenses incurred by a Party that are reasonably or directly allocable to the performance of Development activities in accordance with the Strategic Plan and the Development Budget, other than Regulatory Expenses, including (i) the costs of non-clinical and preclinical studies, Clinical Trials, expanded access programs, post-Approval clinical studies, investigator grants, laboratory services, clinical PK assays, carcinogenicity studies, CMC studies, CRO services and pass-throughs, pharmacovigilance and risk management activities, packaging, distribution and reconciliation (including labels and translations, inventory control, IVRS, off-site storage and destruction), data management (including EDC), clinical study reports, investigator meetings, monitoring, SAB costs, DSMB costs, key opinion leader costs, program specific travel, metabolomics assays, courier services and clinical trial liability insurance costs, quality assurance costs for auditing clinical trial activities and preclinical studies support (report reviews), (ii) expenses of any comparator drug used in Clinical Trials or any post-Approval clinical studies, and (iii) expenses incurred by either Party directly or reasonably allocable to the performance of (or preparation for performance of) Medical Affairs activities. Development Expenses for a Product will not include any expenses included in the definition of Cost of Goods or Distribution Expenses for such Product.

d) "***Distribution Expenses***" means those Internal Expenses and External Expenses incurred by a Party that are directly or reasonably allocable to the distribution of a Product, including: (i) invoice, freight, postage, shipping, insurance, handling, and other transportation charges to fulfill orders and not otherwise accounted for as deductions under Net Sales, (ii) customer services, including order entry, billing, and adjustments, inquiry and credit and collection with respect to a Product, (iii) collection of data about sales to hospitals, prescribers, and end users, including costs of data aggregators and 3PL providers, (iv) reasonable and customary fees and other amounts payable to distributors, (v) costs to store Products, and (vi) duties and other monies paid to Third Parties.

e) "***Expenses***" means, during the relevant period, actual Internal Expenses and External Expenses (including accruals under GAAP) incurred by either Party in the conduct of activities under the Strategic Plan for inotersen and IONIS-TTR-L_{Rx}, including those listed below:

i) Sales and Marketing Expenses;

ii) Development Expenses;

iii) Regulatory Expenses;

iv) Cost of Goods as accounted for upon the sale or other use of a Product;

v) Distribution Expenses;

vi) Compliance Expenses;

vii) all payments made as Third Party Obligations;

viii) Losses incurred by a Party or its Affiliates with respect to a Third Party Claim to the extent such Losses may be included in Expenses in accordance with Section 11.2 (Losses as Expenses);

ix) expenses incurred in challenging Patents owned by Third Parties that potentially could be infringed by the making, using, selling, importing, exporting, or other exploitation of a Product;

x) expenses incurred in defending, settling, or satisfying any claim brought by a Third Party alleging that the exploitation of a Product infringes such Third Party's Patent (any such claim, a "***Third Party Infringement Claim***"); *provided, however*, with respect to any Third Party Infringement Claim filed by a Third Party within 18 months after the First Commercial Sale of a Product, 89% of any damages awarded as a final judgment by a court of competent jurisdiction will be treated as "*Expenses*" hereunder and the remaining 11% will be paid solely by Ionis as provided in Section 11.2;

xi) expenses incurred in enforcing Product-Specific Patents and Ionis Core Technology Patents against Third Parties with respect to Competitive Infringement in accordance with Section 9.3 or enforcing any Akcea intellectual property against any Third Party that is developing, manufacturing, or commercializing a Competing Product;

xii) expenses relating to the filing, prosecution, maintenance, and enforcement of Product-Specific Patents;

xiii) expenses of insurance (including any product liability insurance or accrual for self-insurance) directly attributable to the Development or Commercialization of a Product;

xiv) real estate expenses related to Akcea's Carlsbad, CA office location for so long as such facility is primarily used by Akcea personnel who are dedicated to Commercialization of the Products; and

xv) equipment depreciation for fixed assets that can be specifically identified as in use to support the Development or Commercialization of Products and is considered a reasonably allocable expense, but not corporate overhead excluded pursuant to Section 2(c) of this Schedule 6.4.1.

The following expenses will not be considered Expenses:

1) G&A Expenses, other than Compliance Expenses;

2) R&D Support Expenses;

3) overhead expenses, except as included in Fully Absorbed Cost of Goods;

4) the up-front fee payable by Akcea to Ionis pursuant to Section 6.1;

5) the Milestone Payments payable by Akcea to Ionis pursuant to Section 6.3;

6) expenses associated with stock-based compensation expenses or other *pro forma* adjustments to either Party's financials determined in accordance with GAAP; and

7) except as expressly included in Expenses (or a category of expenses included therein) and unless otherwise mutually agreed by the Parties:

(A) amortization and depreciation expenses, deductions, credits, interest expense, expenses including taxes and extraordinary or nonrecurring losses customarily deducted by a Party in calculating and reporting consolidated net income, manufacturing facility capital expenses, and capital expenditures, including purchases of facilities, property, or equipment; and

(B) property taxes and any other taxes not related to the Development, Manufacture, or Commercialization of a Product, including income based taxes.

In addition, in no event will any amounts deducted from gross sales for the purpose of calculating Net Sales be counted in the definition of Expenses.

Each of the following received in a period will be credited against Expenses in the period in which such amounts are received:

i) to the extent provided in Section 9.3.5 (Recovery), amounts recovered from an infringer of the Ionis Product-Specific Patents;

ii) amounts received as insurance payments for damages, losses, or expenses previously included in the calculation of Expenses; and

iii) tax refunds received to the extent they are not otherwise counted in Net Sales and relate to tax payments previously deducted from Net Sales or Expenses.

For clarity, in the event any expense falls within more than one expense category within this definition of Expenses, such expense will only be counted once in the calculation of Expenses and Net Profit (or Loss) in the manner each Party records expenses on its own books according to GAAP.

f) "***External Expenses***" means those expenses that are not Internal Expenses.

g) "***G&A Expenses***" means the Internal Expenses and External Expenses associated with performing the types of services set forth in the definition of G&A Services in the Services Agreement (regardless of which Party incurs the expense).

h) "***Internal Expenses***"means base salary *plus* a factor for current period reasonable and customary employee benefits and payroll taxes for the relevant employees. As pertains to the sales force and sales force management, internal expenses include expenses related to salaries, commissions, current period reasonable and customary employee benefits and payroll taxes, sales incentive payments, sales training expenses, and travel expense.

h) "***Medical Affairs Expenses***" means the Internal Expenses and External Expenses incurred by a Party directly or reasonably allocable to activities designed to ensure or improve appropriate medical use of, conduct medical education of, or further research regarding, a Product, including (i) activities of medical scientific liaisons; (ii) service-based medical activities including providing input and assistance with consultancy meetings and advisory board meetings, recommending investigators for clinical trials and providing input in the design of such trials and other research related activities, delivering non-promotional communications and conducting non-promotional activities including responding to unsolicited inquiries of medical professionals, presenting new clinical trial and other scientific information, conducting health economic studies, exhibiting and presenting at seminars and conventions, conducting speakers programs, conducting appropriate activities involving opinion leaders, providing disease education to health care professionals and consumers and establishing clinical consumer and patient registries; (iii) grants to support continuing medical education, symposia, or Third Party research related to a Product; (iv) development, publication and dissemination of publications relating to a Product, and (v) medical information services provided in response to inquiries communicated via sales representatives or received by letter, phone call, or email.

i) "***Net Profit (or Loss)***" means, with respect to a Product for a given time period (of no less than one-month increments), Net Revenues during such period less Expenses incurred during such time period. To the extent Net Revenues exceed Expenses for such Product for the relevant period, the

amount of such difference will be deemed "Net Profits," and, to the extent Expenses for a Product exceed Net Revenues for such Product for the relevant period, the amount of such difference will be deemed "Net Losses." For sake of clarity, Net Profit (or Loss) will be determined prior to application of any income taxes.

j) "***Net Revenue***" means, during the relevant period for a Product, the sum of (i) Net Sales, if any, of such Product during such period, *plus* (ii) Sublicense Revenue for such Product.

k) "***Net Sales***" means, with respect to any Product, the gross amount billed or invoiced by Akcea or its Affiliates for sales of such Product in arm's length transactions to Third Parties, less deductions (if not already deducted in the amount invoiced) and allowances as determined in accordance with GAAP.

Net Sales and any applicable deductions and allowances from the gross invoiced sales prices of Product will be determined in accordance with, as applicable, Akcea's or its Affiliates' standard accounting procedures and GAAP. If Akcea or its Affiliates make any adjustments to such deductions and allowances after the associated Net Sales have been reported pursuant to this Schedule 6.4.1, then the adjustments will be reported and reconciled with the next report and payment.

l) "***Profit/Loss Changeover Date***" means the first day of the Calendar Quarter immediately following the Calendar Quarter in which the First Commercial Sale of IONIS-TTR- L_{Rx} occurs in any country in the world.

m) "***Profit/Loss Ratio***" means, (a) prior to the Profit Share Changeover Date, 60/40 (60% to Ionis and 40% to Akcea) with respect to inotersen and 50/50 with respect to IONIS-TTR-L_{Rx}, and (b) from and after the Profit Share Changeover Date, 50/50 with respect to both Products.

n) "***Profit/Loss Share***" means, with respect to each Product, the sharing of Net Revenues, Expenses and Net Profit (or Loss) for such Product between the Parties as contemplated under this Agreement.

o) "***Profit Share Start Date***" means the earlier of (i) the first day of the Calendar Quarter after receipt of Approval of inotersen in the United States, or (ii) January 1, 2019.

p) "***R&D Support Expenses***" means the Internal Expenses and External Expenses associated with performing the types of services set forth in the definition of R&D Support Services in the Services Agreement (regardless of which Party incurs the expense).

q) "***Regulatory Expenses***" means Internal Expenses and External Expenses incurred by a Party that are directly or reasonably allocable to prepare Product regulatory submissions to obtain, support, or maintain Approval and to comply with post-Approval requirements of a Regulatory Authority, including FDA user and other fees, reporting and regulatory affairs activities, and recalls and withdrawals for Products (other than expenses for Products that are deductible from Net Revenue).

r) "***Sales and Marketing Expenses***" means those Internal Expenses and External Expenses incurred by a Party that are directly or reasonably allocable to sales, promotion, and marketing of a Product, including expenses related to performing market research, non-clinical marketing studies advertising, producing promotional literature, sponsoring seminars and symposia, sales training meetings and seminars, originating sales, providing reimbursement support, and other similar sales, marketing, and patient support services. For clarity, Sales and Marketing Expenses include expenses described in the foregoing sentence incurred prior to Approval of a Product in preparation for the commencement of sales, promotion, and marketing activities.

s) "***Sublicense Revenue***" means any fees, payments, or other consideration Akcea or its Affiliate receives from a Sublicensee under a Sublicense, including license fees, up-front payments, milestone payments (including development, regulatory, and sales-based milestones), royalty pre-payments, cancellation or forgiveness of debt, or license maintenance fees, and payments made by a Sublicensee in consideration of equity or debt securities of Akcea or an Akcea Affiliate above the then-fair market value but excluding: payments made in consideration of equity or convertible debt securities of Akcea or its Affiliates at fair market value (*provided that* any premium over fair market value that is paid for such equity or debt securities will be Sublicense Revenue). If Akcea or its Affiliate receives any non-cash Sublicense Revenue (excluding in-kind commitments by the applicable Sublicensee to Develop and Commercialize a Product), then Akcea will pay Ionis, at Akcea's election, either (i) a cash payment

equal to the fair market value of Ionis' portion of the Sublicense Revenue, or (ii) the in-kind portion, if practicable, of the Sublicense Revenue, *provided that* if such in-kind Sublicense Revenue is in the form of equity securities of a Third Party and does not exceed the Sublicensing Equity Threshold. If the in-kind portion of the Sublicense Revenue in the form of Third Party equity securities exceeds the Sublicensing Equity Threshold, then Akcea will pay Ionis the remainder of such payment in cash. Consideration paid under a series of agreements related to a Product will be aggregated and treated as one Sublicense.

t) "***Sublicensing Equity Threshold***" means the threshold amount of equity securities in a Third Party equal to 18.5% of such Third Party's issued and outstanding shares (i) transferred to Ionis by Akcea or (ii) Ionis' and Akcea's combined ownership interest, so long as Ionis and Akcea are consolidating for financial reporting purposes.

SCHEDULE 6.4.2

Alternative Royalty Provisions

If Ionis provides written notice to Akcea within 90 days following a Change of Control of Akcea terminating the Profit/Loss Share under Section 6.4.1 of the Agreement, then such Profit/Loss Share will be replaced with the alternative royalty provisions set forth on this Schedule 6.4.2, which will thereafter apply to all Products:

***Section 13.20*Royalty Payments for Products Sold by Akcea and its Affiliates**.

13.20.1 Royalty Payments by Akcea. On a country-by-country basis, during the Royalty Term for a Product in a country, Akcea will pay Ionis royalties on Annual Worldwide Net Sales of Products sold by Akcea, its Affiliates, and its Sublicensees (notwithstanding anything to the contrary set forth in the definition of Net Sales) in accordance with Table X below. Akcea will no longer make payments to Ionis with respect to Products sold by its Sublicensees as Sublicense Revenue under SCHEDULE 6.4.1 of the Agreement.

Table X

Royalty Tier	Annual Worldwide Net Sales of Products	Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $250,000,000	x-2%
2	For the portion of Annual Worldwide Net Sales > $250,000,000 but < $500,000,000	x%
3	For the portion of Annual Worldwide Net Sales > $500,000,000 but < $750,000,000	x+2%
4	For the portion of Annual Worldwide Net Sales > $750,000,000	x+4%

At the time of such Change of Control, the base royalty on Annual Worldwide Net Sales of Products, defined as "*x*" in Table X above, will be equal to 50% of Akcea's net profit margin on sales of Products, excluding any one-time extraordinary expenses. Net profit margin will be calculated using Akcea's audited financial statements for the three Calendar Years prior to such Change of Control, if available.

If it is reasonably expected that the net profit margin on sales of Products will be materially different in the two Calendar Years following such Change of Control, defined as greater than a 25% change in net profit margin on sales of Products, then the royalty will instead be calculated based on the average of two Calendar Years of forward looking statements and one Calendar Year of historical statements. Notwithstanding the foregoing, in no event will "*x*" in Table X be lower than 27%.

Akcea will pay Ionis royalties on Annual Worldwide Net Sales of Products sold by Akcea or its Affiliates arising from named patient and other similar programs under Applicable Laws, and Akcea will provide reports and payments to Ionis consistent with the provisions of Section 6.6, *mutatis mutandis*.

13.20.2 Royalty Term. Akcea's obligation to pay Ionis the royalties described in Section 13.20.1 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 Ionis Licensed Patents Covering such Product in the country in which such Product is made, used, or sold, (b) 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 12th anniversary of the First Commercial Sale of such Product in such country (such period, the "Royalty Term").

13.20.3 Changes to Definition of Net Sales. Ionis and Akcea agree that any reasonable definition of "*net sales*" customarily used in drug discovery, development, or commercialization licensing or collaboration contracts that is agreed to by a Party (or a Third Party acquirer or assignee) and a Sublicensee with respect to amounts payable to such Party from such Sublicensee in an arms-length transaction under a particular Sublicense will replace the definition of Net Sales in this Agreement and will be used in calculating the payment to the other Party on sales of Products sold pursuant to such Sublicense and due under this Agreement, for so long as the same definition of net sales is used to calculate the amount payable from the applicable Sublicensee to such Party.

SCHEDULE 10.4.2(H)

Post-Termination Transition Activities

Commercial; Patient Continuity

- Continued performance of activities necessary to fill existing or new prescriptions for Products in all countries where the Product is sold until transitioned to Ionis or terminated at Ionis' request.
- Facilitation of the transition of commercial responsibilities to Ionis.
- Until agreed upon transition date, continue to handle all call/contact center activities, including adverse event reporting, product quality complaints, medical information, and reimbursement support for existing and new patients until transitioned to Ionis.

Medical Affairs

- Until an agreed upon transition date, continue to handle medical information inquiries from physicians.
- Provide a Medical Information point of contact during transition and up to 6 months post transition date to serve as a resource for questions from the Ionis Medical Information team.

Government and Managed Care Contracts

- Coordinate with Ionis to process government and managed care contracts, including rebates/chargebacks, reporting and transition to Ionis' labeler code and government contracts.

Supply Chain/Manufacturing

- Work with Supply Chain teams to utilize existing Drug Product with Akcea trade dress in coordinated fashion, and transition over time to Ionis trade dress.
- Sale to Ionis of any API or Drug Product in Akcea's possession at a price equal to Akcea's cost at the time of manufacture.
- If Akcea is the sole qualified site for producing Drug Product, then Akcea may conduct an additional campaign to manufacture Drug Product in a quantity to meet the expected demand for the applicable Product for the next 48 months. Ionis will reimburse Akcea for its Cost of Goods of such supply.
- Cooperate with Ionis to facilitate a transfer of (or replication of) Akcea's Manufacturing Agreement with CMOs and supply chain vendors for the applicable Product.

Quality

- Akcea will continue stability testing on API and Drug Product.
- Akcea will assist in transferring stability testing on API and Drug Product to Ionis.
- Transition/Coordinate with Ionis regulatory personnel for annual report generation and change control submissions.

Regulatory

- Take actions necessary to transfer regulatory responsibilities and information to Ionis.
- Manage regulatory responsibilities (including REMs if applicable) until the applicable marketing authorization is transferred.
- Coordinate all regulatory communications and submissions with Ionis and consider Ionis' comments in good faith until transition of the applicable Approval to Ionis.

Pharmacovigilance/Global Safety Database

- Transfer the Global Safety Database for the Product to Ionis.

- Be responsible for and manage the Global Safety Database until transitioned to Ionis. Subject to the applicable Safety Data Exchange Agreement (if any), continue to receive, process, and submit all adverse drug experience reports to the FDA, EMA, or other relevant health authorities as required by the relevant country regulations until transitioned to Ionis.

Post-Approval Studies and Commitments

- Continue to conduct any Akcea Non-Commercial Activities, and Akcea will maintain vendors for such studies/commitments until transitioned to Ionis.
- Work with Ionis to transition compliance with such commitments, which may include assigning the relevant vendor contracts at Ionis' election and to the extent assignable, or authorizing the transfer of data and materials to a vendor of Ionis' choosing to replicate Akcea's compliance with such commitments.

Ionis Designee

Ionis may designate a third-party designee to exercise Ionis' rights under the Post-Termination Transition Activities.

Exhibit 10.3

Execution Version

AMENDED AND RESTATED SERVICES AGREEMENT

AMENDED AND RESTATED SERVICES AGREEMENT

This AMENDED AND RESTATED SERVICES AGREEMENT (this "***Services Agreement"***) is made as of March 14, 2018 (the "***Execution Date"***) by and among, **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, with its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Ionis"***) and **AKCEA THERAPEUTICS, INC.**, a Delaware corporation, with its principal place of business at 55 Cambridge Parkway, Suite 100, Cambridge, MA 02142 ("***Akcea"***). As of the Effective Date, this Services Agreement, amends, updates and replaces in its entirety the December 18, 2015 Services Agreement between Ionis and Akcea (the "***2015 Services Agreement"***). All capitalized terms not defined herein will have the meanings set forth in the Development Commercialization and License Agreement, dated December 18, 2015 (the "***2015 License Agreement"***), and the Development, Commercialization, Collaboration, and License Agreement, dated as of the Execution Date, by and between Ionis and Akcea (as it may be amended from time to time, the "***2018 License Agreement"*** and together with the 2015 License Agreement, the "***License Agreements"***). Ionis and Akcea each may be referred to herein individually as a "***Party,"*** or collectively as the "***Parties."***

RECITALS

WHEREAS, on December 18, 2015, (i) Ionis Pharmaceuticals, Inc. formed Akcea, a Delaware corporation, as a wholly-owned subsidiary for the initial purpose of serving as the development and commercialization entity for the following lipid-modulating antisense drugs: IONIS-APOCIII$_{Rx}$ (IONIS304801), IONIS-APOCIII-L$_{Rx}$ (IONIS678354), IONIS-APO(a)$_{Rx}$ (IONIS494372), IONIS-APO(a)-L$_{Rx}$ (IONIS681257), IONIS-ANGPTL3$_{Rx}$(IONIS563580) and IONIS-ANGPTL3-L$_{Rx}$ (IONIS703802) (the "***Lipid Drugs"***); (ii) entered into the 2015 License Agreement to develop, manufacture and commercialize the Lipid Drugs; and (iii) entered into the 2015 Services Agreement to provide certain general and administrative services in support of Akcea's business;

WHEREAS, on the Execution Date, Ionis and Akcea entered into the 2018 License Agreement to develop, commercialize, collaborate on and manufacture the following antisense drugs: inotersen and IONIS-TTR-L$_{Rx}$ (the "***TTR Drugs"***);

WHEREAS, Akcea continues to need certain services related to general and administrative services in support of its business; and

WHEREAS, Ionis wishes to provide such Services;

WHEREAS, through this Services Agreement, the Parties now wish to amend and restate the 2015 Services Agreement to expand the Services to include both the Lipid Drugs and the TTR Drugs (collectively the "***Supported Drugs"***).

AGREEMENT

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants contained herein, and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, Ionis and Akcea each agree as follows:

1. **Services**. On an annual basis as part of the Parties' annual budgeting process the Parties will agree on which of the following services set forth in this Article 1 Ionis will provide to Akcea during the upcoming year; *provided that* if Ionis desires to cease providing or Akcea desires to cease receiving one or more services previously provided to Akcea by Ionis, then such Party will notify the other Party of such cessation in advance of the applicable annual budgeting process as necessary to allow Akcea to transition in an orderly and rational manner to performing such services internally or obtaining replacement services.

1.1 **General and Administrative Services.** The general and administrative support services provided to Akcea under this Services Agreement of the type described below will be referred to herein as the "***G&A Services."***

1.1.1 **Investor Relations Services.** Ionis will provide to Akcea investor relations services regarding matters of fair and accurate disclosure and compliance with Ionis' disclosure policy and applicable Law, including, without limitation, compliance with the Sarbanes-Oxley Act of 2002. Such services will include drafting; processing for review and issuing press releases; conference call scripts and presentations; managing conference and medical meeting attendance; managing media and public relations activities; and facilitating interactions with investors and analysts.

1.1.2 **Pre-Commercial and Competitive Intelligence Services.** Ionis will provide to Akcea services related to pre-commercial activities and related to competitive intelligence services for all of the Supported Drugs as appropriate.

1.1.3 **Accounting and Payroll Services.** Ionis will provide to Akcea bookkeeping and accounting services, including maintaining the books and records of Akcea's financial operations, preparing financial statements (including quarterly and annual financial statements), billings, accounts payable, stock option accounting services, internal audit support services, financial budgeting and forecasting as needed, review of compliance with financial and accounting procedures and government accounting functions (*e.g.*, preparing budgets and setting rates), in each case, in accordance with GAAP, and government regulations as applicable. In addition, Ionis will administer Akcea's employee payroll, including withholding and remitting employee and employer payroll taxes.

1.1.4 **Personnel Services.** Ionis will provide personnel services to Akcea, including maintaining general employee insurance obligations, establishing and managing of an employee benefits program, advising on employee relations and related issues, and managing of Akcea's retirement plans, including the Ionis Pharmaceuticals, Inc. 401(k) Retirement Plan. However, the Parties expect Akcea to develop its own stock administration capabilities in the near future.

1.1.5 **Legal Services.** Ionis will provide Akcea with legal services, including legal services from Ionis' General Counsel and other legal counsel with respect to: labor and personnel matters; management of Akcea's employee equity incentive plans and programs; compliance with applicable securities laws and regulations; compliance with other applicable laws and regulations; litigation management; contract negotiation and preparation; commercial sales agreements; mergers and acquisitions; tax issues; preventive counseling; and all matters relating to corporate governance of Akcea. Notwithstanding the foregoing, if, with the advice of counsel, Akcea reasonably believes an actual or potential conflict of interest is likely to arise between the interests of Ionis' stockholders and Akcea's stockholders, then Akcea may retain its own counsel at its own expense for such matters.

1.1.6 **Risk Management; Insurance.** Ionis will provide Akcea centralized insurance purchasing for liability, property, casualty and other normal business insurance and the handling of claims.

1.1.7 **Tax Related Services.** Ionis will assist Akcea in the preparation of ex-U.S. and U.S. federal, state and local income tax returns, tax research and planning and assistance on tax audits or other tax-related matters.

1.1.8 **Corporate Record Keeping Services.** Ionis will maintain, on behalf of Akcea, corporate records, including minutes of meetings of the board of directors and stockholders of Akcea, supervision of transfer agent and registration functions, maintenance of stock records, including the tracking of stock issuances and stock reservations.

1.1.9 **Financial Services.** Ionis will provide to Akcea the following financial services: (i) banking services administration, including bank account administration, loan administration, covenant compliance administration, maintenance of cash collection and disbursement systems and arrangement of letters of credit, foreign currency exchanges or conversion calculations and cash transfers; (ii) financial management and information services, including centralized cash management, leasing, customer financing, financial analysis on foreign currency issues, risk assessment and hedging strategies; (iii) investment banking services, including managing Ionis' and Akcea's relationships with debt rating agencies. In connection with such services, Ionis is authorized to invest the funds deposited by Akcea with Ionis in taxable, tax-exempt or tax-preferred instruments of short or longer term duration based upon Ionis' assessment of Akcea's tax considerations and Akcea's cash needs and consistent with Akcea's investment policy and guidelines. Ionis will advise Akcea on a quarterly basis as to the earnings that Akcea may expect on its cash deposits during the following quarter.

1.1.10 **Credit Services.** Ionis will assist Akcea in identifying and obtaining cost-effective sources of financing consistent with the needs of Ionis and its affiliated companies.

1.1.11 **COO, CFO and CBO Oversight Services.** The Parties acknowledge and agree that Ionis' COO, CFO and CBO do and will supervise the employees performing the Services hereunder, and in consideration for such supervisory services, a portion of the COO's, CFO's and CBO's salary will be allocated to and paid by Akcea using the allocation methodology set forth in **APPENDIX A** (Allocation Methodologies).

1.2 **R&D Support Services.** The research and development support services provided to Akcea under this Services Agreement of the type described below will be referred to herein as the "***R&D Support Services.***"

1.2.1 **Information Technology Services.** Ionis will provide information technology and telephone services to Akcea, including but not limited to: intercompany network services and database management services between Ionis and Akcea; information technology planning services; centralized procurement of hardware and software; support for initial set up or relocation of Akcea facilities; email services; phone services; and mobile device services. Ionis may provide additional information technology services that are mutually agreed between Ionis and Akcea. In addition, Ionis will allow Akcea to access, display and use software systems and programs owned by or licensed to Ionis, except to the extent that Ionis is precluded by its licenses from providing such access, display or use.

1.2.2 **Purchasing Services.** Ionis will provide services to Akcea related to purchasing, including purchase order management, vendor selection, payment terms, negotiating preferred pricing and negotiating supplier agreements.

1.2.3 **Facilities and Office Services.** To the extent necessary, Ionis will provide Akcea office and facility services, primarily the appropriate personnel to support Akcea's office and facility infrastructure.

1.2.4 **Intellectual Property Support Services.** Ionis will provide intellectual property support services to Akcea, including but not limited to filing, prosecuting, maintaining, enforcing, and defending the Ionis Product-Specific Patents licensed to Akcea, trademarks and copyrights, patent due diligence to support partnership transactions and advice regarding intellectual property strategy (collectively, the "***IP Support Services***"). In the event that a Third Party challenges one of the Ionis Core Technology Patents licensed to Akcea under a License Agreement, then the Parties will discuss and agree to a percentage of the expense to defend such challenge for which Akcea will reimburse Ionis.

1.3 **Specialty Services.** If, from time to time, Akcea wishes Ionis to perform specific projects that go beyond the services already specified in Section 1.1 or Section 1.2 to perform specific projects, Akcea and Ionis will execute a work order that will be governed by the terms of this Services Agreement and will specify the projects Ionis will perform for Akcea and the payment Akcea will make to Ionis for such project. The Parties will execute a work order prior to initiating such work (collectively, the "***Specialty Services***"). An email from Akcea's Chief Executive Officer, President, Chief Operating Officer, or Chief Financial Officer referencing this Services Agreement and authorizing Ionis to perform specific Specialty Services will be considered a work order for purposes of this Section 1.3. Ionis will not be reimbursed for performing work that goes beyond the scope of any Specialty Services without an agreed and executed work order. Examples of a Specialty Service under this Section 1.3 are business development services relating to corporate partnering transactions and other services related to a corporate partnership or financing.

1.4 **Development, Regulatory and Manufacturing Services.** Ionis will provide services related to Development (including regulatory affairs) and Manufacturing in support of the Lipid Drugs pursuant to the terms of the 2015 License Agreement. Ionis will provide services related to Development (including regulatory affairs) and Manufacturing in support of the TTR Drugs pursuant to the terms of the 2018 License Agreement. Ionis will be reimbursed by Akcea for such services for each of the Lipid Drugs and TTR Drugs using the same methodology the Parties use under the 2015 License Agreement.

2. **Performance of Services.**

2.1 **Performance.** All services described in Article 1 of this Services Agreement are collectively referred to as the "***Services.***" Ionis will provide all Services (i) on an ongoing basis during the Term, as reasonably required or requested by Akcea, (ii) promptly, (iii) in accordance with the terms of this Services Agreement, (iv) in accordance with the standards and practices for the performance of similar services by Ionis in the conduct of its own business and (v) in a manner consistent with Law applicable to Ionis and Akcea.

2.2 **Authority.** Consistent with Ionis' signature policy and established procedures and, to the extent of the scope of the Services such Ionis employee is performing for Akcea, Ionis personnel have the authority to act on Akcea's behalf.

3. **Compensation.**

3.1 **Charge for Services.** Akcea will pay Ionis fees for the Services as specified in **APPENDIX A** (Allocation Methodologies) attached hereto, which provides details regarding how to calculate such fees (except Specialty Service fees). These Allocation Methodologies will generally be determined from a good faith estimate by Ionis of a percentage of each Ionis functional area detailed in Section 1 of this Agreement dedicated to providing the Services hereunder. From time to time, the Parties may mutually agree to update **APPENDIX A** (Allocation Methodologies) as needed, including in the event of a change of circumstances of one or more of the Parties. At a minimum, on an annual basis as part of Ionis' annual budgeting process, the Parties will review **APPENDIX A** (Allocation Methodologies) in good faith to ensure the allocations set forth therein are fair and commercially reasonable.

3.2 **Specialty Services Fee.** Akcea will pay Ionis for Specialty Services rendered based upon a good faith estimate of the time burden required of Ionis personnel to perform the Specialty Services based upon the statement of work provided by Akcea. If there is a material change in the statement of work, in scope or budget, Ionis will prepare a revised estimate for Akcea's approval.

3.3 **Direct Out-of-Pocket Expenses.** Akcea will be responsible for paying and will bear the cost of all out-of-pocket expenses for which Akcea is the primary beneficiary, including but not limited to (i) legal services provided to Akcea by outside counsel; (ii) insurance policies and claims that relate specifically to Akcea; (iii) accounting, auditing and tax related services provided to Akcea by external accountants and tax advisors; (iv) filing fees and other costs (*e.g.*, translation costs) charged by Third Parties in connection with filing, prosecuting and maintaining Akcea's patents, trademarks and copyrights; and (v) travel costs associated with providing any of the Services contemplated by this Services Agreement (collectively the "***Direct Expenses***"). Akcea and Ionis will use commercially reasonable efforts to have the applicable Third Parties bill Akcea directly for any Direct Expenses. For any out-of-pocket expenses that benefit both Ionis and Akcea but are not Direct Expenses, such expenses will be allocated to Akcea in the same manner as the fees above and depending on whether such expense is in connection with G&A Services, R&D Support Services, IP Support Services, or Specialty Services.

3.4 **Payment Terms.** Ionis will invoice Akcea within fifteen (15) days following the end of each Quarter for all amounts due related to the provision of Services under this Services Agreement. Invoices will contain such detail as Akcea may reasonably require and will be payable in U.S. Dollars. All undisputed amounts will be paid by Akcea within 30 days of its receipt of an invoice. Ionis will provide Akcea with W-9s or other forms as may be reasonably requested by Akcea in order to process such payments.

4. **Personnel.** Ionis will assign employees ("***Ionis Personnel***") in sufficient numbers, and with the proper skill, training and experience, to provide the Services. Ionis will be solely responsible for paying its Ionis Personnel and providing any employee benefits that they are owed. Before providing Services, all Ionis Personnel must have agreed in writing to (i) confidentiality obligations consistent with the terms of this Services Agreement and (ii) assign all right, title and interest in any intellectual property created by such Ionis Personnel, in performance of the Services to Ionis. The Parties intend for there to be additional Ionis Personnel who are not 100% dedicated to the provision of Services who will instead provide Services as needed.

5. Covenants of Akcea.

5.1 Cooperation. Akcea will fully cooperate with Ionis to permit Ionis to perform Ionis' duties and obligations under this Services Agreement in a timely manner. Akcea will direct its officers, directors, employees and agents ("***Representatives"***) to (i) properly and timely respond to requests by Ionis for information and (ii) if requested by Ionis, meet with or consult with the service provider and its professional advisors regarding any matter related to the Services. Akcea will also promptly provide Ionis with copies of any agreements, instruments or documents in possession of Akcea as are reasonably requested by Ionis, and promptly provide Ionis with any notices or other communications that Akcea may receive that may have any effect on Ionis' performance of the Services.

5.2 Accuracy of Information. Akcea will be responsible for the completeness and accuracy of all information furnished to Ionis by Akcea and Representatives of Akcea in connection with Ionis' performance of the Services. Ionis may rely upon such information in its performance of Services under this Agreement.

5.3 Policies and Procedures.

5.3.1 During any period in which Ionis is required to consolidate the results of Akcea for purposes of reporting its results under U.S. GAAP, Akcea and its employees will comply with the policies and procedures of Ionis that Ionis, in Ionis' good faith reasonable judgment, determines that Akcea should comply with to ensure that Ionis can satisfy its reporting obligations as a public company with a class of securities registered under the Securities Exchange Act. These policies include, but are not limited to (i) Ionis' Code of Ethics, (ii) Ionis' Disclosure Policies and Procedures, (iii) Ionis' Signature Policy, (iv) Ionis' Publication Clearance Policy, (v) Ionis' Policies and Procedures Manual and (vi) Ionis' Internal Control Procedures as set forth in the Amended and Restated Investor Rights Agreement entered into between Ionis and Akcea on the Execution Date (the "***2018 Investor Rights Agreement"***); provided, on a policy by policy basis, Akcea may replace a policy with a reasonably comparable policy that has been expressly approved by Ionis' Chief Financial Officer and General Counsel and Akcea's governance committee of its Board of Directors.

5.3.2 During any period in which Ionis is no longer required to consolidate the results of Akcea for purposes of reporting its results under U.S. GAAP but is required to record its share of Akcea's income or losses pursuant to U.S. GAAP, Akcea will provide Ionis with a reconciliation between Akcea's accounting policies as applied and Ionis' accounting policies as applied. Akcea will provide this reconciliation in a timely manner. In order to execute the reconciliation in an accurate fashion, Ionis and Akcea will be required to provide each other with their accounting policies in sufficient detail to facilitate such reconciliation and verify that all differences that been identified. Akcea will perform the reconciliation to a level of detail that ensures that Ionis has the ability to assert its financial statements are materially correct. Neither Party will be required to provide the other with information to a lower level of detail, but either Party may do so upon the other Party's request. In addition, Akcea will permit Ionis' auditors to have access to Akcea results as necessary to perform procedures on Akcea's financial information solely for the purposes of preparing Ionis' publicly filed financial statements.

6. Financial Records; Audit Right. Ionis will maintain accurate financial records relating to its provision of the Services hereunder for a period of three (3) years, or longer as required by applicable Law. The terms set forth in **APPENDIX B** will govern each Party's rights and obligations with respect to the auditing of such financial records.

7. **Confidential Information.** The terms regarding confidentiality and non-use set forth in the 2018 Investor Rights Agreement and ARTICLE 8 of the 2018 License Agreement will govern each Party's rights and obligations concerning disclosure, non-use, and/or publication of the terms of this Services Agreement and/or any information exchanged or arising under this Services Agreement.

8. **Indemnification; Insurance.** The terms of ARTICLE 11 of the 2015 License Agreement will govern each Party's indemnification and insurance obligations, respectively, with respect to this Services Agreement in relation to the Lipid Drugs and the terms of ARTICLE 11 of the 2018 License Agreement will govern each Party's indemnification and insurance obligations, respectively, with respect to this Services Agreement in relation to the TTR Drugs.

9. **Taxes.** Notwithstanding anything to the contrary in this Services Agreement, for so long as Ionis and Akcea file consolidated federal and/or state tax returns, Ionis will retain all Akcea-generated tax attributes generated by Akcea's activities for the relevant federal and/or state tax return. Following deconsolidation of federal and/or state tax returns, Akcea will file its own federal and/or state taxes as a separate entity and Akcea will retain such Akcea-generated tax attributes for the relevant federal and/or state tax return.

10. **Disclaimer; Limitation of Liability.**

10.1 **Disclaimer**. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN SECTION 2 ABOVE, NO PARTY MAKES ANY REPRESENTATIONS OR EXTENDS ANY WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, WARRANTIES OF MERCHANTABILITY, QUALITY, FITNESS FOR A PARTICULAR PURPOSE, NONINFRINGEMENT, OR VALIDITY OF PATENT CLAIMS, WHETHER ISSUED OR PENDING.

10.2 **Limitation of Liability**.

10.2.1 Akcea acknowledges that Ionis is not in the business of providing Services and that Services are being provided pursuant to this Agreement as an accommodation to Akcea. Akcea's sole and exclusive remedy and Ionis' sole and exclusive liability for any breach of Section 1 or Section 2, and for any damages of Akcea suffered or incurred directly or indirectly in connection with the provision of Services (whether any claim related to such damages arises in contract, in tort, by statute or otherwise), will be the re-performance by Ionis of Services at such Ionis' expense.

10.2.2 OTHER THAN (A) A PARTY'S INDEMNIFICATION OBLIGATIONS SET FORTH UNDER SECTION 8, (B) AS A RESULT OF A PARTY'S WILLFUL MISCONDUCT OR A PARTY'S BREACH OF SECTION 7, NO PARTY WILL BE LIABLE TO THE OTHER PARTY OR ITS AFFILIATES FOR SPECIAL, INCIDENTAL, CONSEQUENTIAL, EXEMPLARY, PUNITIVE, MULTIPLE OR OTHER INDIRECT DAMAGES ARISING OUT OF THIS SERVICES AGREEMENT OR THE EXERCISE OF RIGHTS HEREUNDER, OR FOR LOSS OF PROFITS, LOSS OF DATA, LOSS OF REVENUE, OR LOSS OF USE DAMAGES ARISING FROM OR RELATING TO ANY BREACH OF THIS SERVICES AGREEMENT, WHETHER BASED UPON WARRANTY, CONTRACT, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, REGARDLESS OF ANY NOTICE OF SUCH DAMAGES.

11. **Effectiveness; Term.** This Agreement will take effect automatically without further action of either Party upon the date on which the closing of the Stock Purchase Agreement dated as of the Execution Date by and between the Parties occurs (the "***Effective Date"***). The initial term of this Services Agreement will commence on the Effective Date and will expire on December 31, 2020 (the "***Initial Term"***). Following such Initial Term, this Services Agreement will automatically renew on an annual basis for periods of 12 months each (each, an "***Additional Term"***) unless one Party provides the other Party written notice that it does not wish to renew this Services Agreement at least 180 days in advance of the date of the expiration of the Initial Term or the then-current Additional Term, as applicable (the period commencing on the Effective Date and ending on latest to expire of the Initial Term or any Additional Term, the "***Term"***).

12. Term and Termination.

12.1 **Termination Prior to the Effective Date.** Notwithstanding anything to the contrary set forth in this Agreement, this Services Agreement may be terminated and the transactions contemplated herein be abandoned at any time prior to the Effective Date (in which case the 2015 Services Agreement will continue in full force and effect in accordance with its terms):

(a) by mutual written consent of Akcea and Ionis;

(b) by either Akcea or Ionis:

(i) if the Effective Date shall not have occurred on or prior to June 30, 2018; or

(ii) if any governmental authority having jurisdiction over Akcea or Ionis shall have enacted, issued, promulgated, enforced, or entered any Applicable Law or taken any other material action that has the effect of making the transactions contemplated by the Transaction Documents illegal or otherwise restraining or prohibiting the consummation of such transactions.

12.2 **Termination of License Agreements.** This Services Agreement will automatically terminate upon the termination or expiration of both the License Agreements.

12.3 **Termination by Akcea for Breach by Ionis.** At any time following the Effective Date, if Ionis breaches any material term of this Services Agreement, and such material breach is not cured by Ionis within sixty (60) days of notice therefor (or cannot be cured), then Akcea may terminate this Services Agreement.

12.4 **Termination by Ionis for Breach by Akcea.** At any time following the Effective Date, if Akcea breaches any material term of this Services Agreement, and such material breach is not cured by Akcea within sixty (60) days of notice therefor (or cannot be cured), then Ionis may stop performing Services hereunder until such breach is cured.

12.5 **Effect of Termination or Expiration.** Upon termination or expiration of this Services Agreement after the Effective Date, neither Ionis nor Akcea will have any further obligations under this Services Agreement, except that (unless otherwise agreed by the Parties or as set forth in the 2018 Investor Rights Agreement or the applicable License Agreement):

12.5.1 Ionis will terminate all its Services in progress in an orderly manner as soon as practical and in accordance with a schedule agreed to by the Parties;

12.5.2 Ionis will deliver to Akcea or, at Akcea's option, dispose of any Akcea Confidential Information developed through termination or expiration;

12.5.3 Akcea will pay Ionis any undisputed monies due and owing, up to the time of termination or expiration, for Services properly performed and all expenses actually incurred;

12.5.4 Ionis will promptly return to Akcea all Confidential Information and copies thereof provided to Ionis under this Services Agreement, except for one (1) copy which Ionis may retain solely to monitor Ionis' surviving obligations; and

12.5.5 the provisions set forth in Section 5.3, Sections 6 through 10, this 12.5 and 13 will survive any such termination or expiration in accordance with its terms.

13. Miscellaneous.

13.1 **Assignment.** Neither this Services Agreement nor any of the rights or obligations hereunder may be assigned by a Party without the prior written consent of the other Party, except that each Party may assign this Services Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its business or assets to which this Services Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if Akcea or any of its Affiliates or Sublicensees transfers or assigns this

Services Agreement or a Sublicense to one of its Affiliates that is incorporated in a jurisdiction that does not have a Bilateral Income Tax Treaty with the United States or in a jurisdiction where a Bilateral Income Tax Treaty requires withholding taxes on any payment described in this Services Agreement, then Akcea (or such Affiliate or Sublicensee), will increase (i.e., "gross up") any payment due Ionis under Article 6 of the 2015 License Agreement or the 2018 License Agreement, as applicable, for the Incremental Tax Cost such that Ionis receives the amount Ionis would have otherwise received under Article 6 of the 2015 License Agreement or the 2018 License Agreement, as applicable, but for such transfer or assignment. In addition, Ionis may assign or transfer its rights to receive payments under this Agreement (but, subject to any right that Akcea may have under applicable Law), without Akcea's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any assignment not in accordance with the foregoing will be void. This Services Agreement will be binding upon, and will inure to the benefit of, all permitted successors and assigns.

13.2 **Force Majeure.** No Party will be held liable or responsible to any other Party nor be deemed to have defaulted under or breached this Services Agreement for failure or reasonable delay in fulfilling or performing any term of this Services Agreement (except any payment obligation) when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party, which may include, without limitation, embargoes, acts of war (whether war be declared or not), insurrections, riots, civil commotions, acts of terrorism, strikes, lockouts or other labor disturbances, or acts of God. The affected Party will notify the other Parties of such force majeure circumstances as soon as reasonably practical and will make every reasonable effort to mitigate the effects of such force majeure circumstances.

13.3 **Notices.** Except where otherwise specifically provided in this Services Agreement, all notices, requests, consents, approvals and statements will be in writing and will be deemed to have been properly given by (i) personal delivery, (ii) electronic facsimile transmission, (iii) electronic mail or by (iv) nationally recognized overnight courier service, addressed in each case, to the intended recipient as set forth below:

To Akcea:	Akcea Therapeutics Inc. 55 Cambridge Parkway, Suite 100 Cambridge, MA 02142 Attention: Chief Executive Officer
With a copy to:	Akcea Therapeutics Inc. 55 Cambridge Parkway, Suite 100 Cambridge, MA 02142 Attention: Vice President, Legal Email: legalnotices@akceatx.com
To Ionis:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, California 92010 Attention: Chief Financial Officer
With a copy to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, California 92010 Attn: General Counsel Email: legalnotices@ionisph.com

Such notice, request, demand, claim or other communication will be deemed to have been duly given on (a) the date of personal delivery, (b) the date actually received if by facsimile or electronic mail or (c) on the next Business Day after delivery to a nationally recognized overnight courier service, as the case may be. Any Party may change the address to which notices, requests, demands, claims and other communications hereunder are to be delivered by giving the other Party notice in the manner herein set forth.

13.4 **Relationship of the Parties.** It is expressly agreed that the Parties will be independent contractors hereunder and that the relationship among the Parties under this Services Agreement will not constitute a partnership, joint venture or agency. No Party will have the authority under this Services Agreement to make any statements, representations or commitments of any kind or to take any action that will be binding on any other Party, without the prior consent of such other Party.

13.5 **Governing Law.** This Services Agreement will in all respects be governed by and construed in accordance with the substantive laws of the State of New York, without regard to its choice of law rules.

13.6 **Dispute Resolution.** Any dispute arising under this Services Agreement will be resolved in accordance with the terms of Section 13.4 of the 2018 License Agreement.

13.7 **Severability.** If one or more provisions of this Services Agreement are held by a proper court or arbitral tribunal to be unenforceable under applicable law, the unenforceable portions of such provisions, or such provisions in their entirety, to the extent necessary and permitted by law, will be severed herefrom, and the balance of this Services Agreement will be enforceable in accordance with its terms.

13.8 **Entire Agreement.** Except as otherwise expressly set forth in this Services Agreement, this Services Agreement, the 2018 Investor Rights Agreement and the License Agreements constitute the entire agreement among the Parties with respect to the subject matter herein and supersede all previous agreements whether written or oral, with respect to such subject matter. Unless otherwise expressly indicated, references herein to sections, subsections, paragraphs and the like are to such items within this Services Agreement. The Parties acknowledge that this Services Agreement is being executed and delivered concurrently with the execution and delivery by the Parties and/or their Affiliates of the 2018 Investor Rights Agreement and the 2018 License Agreement. In the event of any conflict, discrepancy or inconsistency between this Services Agreement and either the applicable License Agreement or the 2018 Investor Rights Agreement, the terms of the License Agreement or the 2018 Investor Rights Agreement, as the case may be, will control.

13.9 **Amendment and Waiver.** This Services Agreement may not be amended, nor any rights hereunder waived, except in a writing signed by the properly authorized representatives of each Party.

13.10 **No Implied Waivers.** The waiver by a Party of a breach or default of any provision of this Services Agreement by any other Party will not be construed as a waiver of any succeeding breach of the same or any other provision, nor will any delay or omission on the part of a Party to exercise or avail itself of any right, power or privilege that it has or may have hereunder operate as a waiver of any right, power or privilege by such Party.

13.11 **Counterparts.** This Services Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument, and will become effective when there exist copies hereof which, when taken together, bear the authorized signatures of each of the Parties hereto. Only one such counterpart signed by the Party against whom enforceability is sought needs to be produced to evidence the existence of this Services Agreement.

IN WITNESS WHEREOF, the Parties hereby execute this Services Agreement as of the Effective Date.

AKCEA THERAPEUTICS INC.

By:	/s/ Paula Soteropoulos
Print Name:	Paula Soteropoulos
Title:	Chief Executive Officer

IONIS PHARMACEUTICALS, INC.

By:	/s/ Stanley T. Crooke
Print Name:	Stanley T. Crooke
Title:	Chief Executive Officer

APPENDIX A

ALLOCATION METHODOLOGY

Akcea Support Services Assumptions

1. **G&A**
    a. **CEO**
        i. Assumes no costs allocated to Akcea
    b. **COO**
        i. % of effort – 5%
        ii. Akcea pre-commercialization expenses and Goldman Sachs consulting excluded from allocations
    c. **CBO**
        i. % of effort – 6%
            1. % of effort calculated using weighted average of salaries of individuals within this department based on time spent on Akcea activities
            2. CBO – 3%
            3. Patient Advocacy – 5%
            4. Alex (25%) & Alissa (5%) – 20% - Competitive and Market Analysis
    d. **Corporate Communications**
        i. % of effort – 10%
        ii. Costs associated with press releases, presentation development, website maintenance and update included within allocation cost base
        iii. Initial website design is not included
        iv. Cost associated with the Isis annual report, annual meeting, IR conference calls & webcasts, Thomson Reuters service and media consulting and investor targeting, Peter Steinerman, excluded from the allocation cost base ($613k)
    e. **Finance**
        i. % of effort – 10%
            1. % of effort based on estimated number of FTE's across all finance functions
            2. Payroll – 0.2 FTE
            3. General accounting 0.3 FTE
            4. Tax, insurance and stock based comp – 0.1 FTE
            5. Treasury services and other misc – 0.1 FTE
            6. Controller – 0.15 FTE
            7. FP&A – 0.5 FTE
            8. CFO – 0.1 FTE
            9. Costs associated with PCAOB, filing fees for 10K & Q's, convertible debt, tax studies and tax returns excluded from the allocation cost base ($162k)
    f. **Human Resources**
        i. % of effort – 3%

ii. Based on overall headcount – assumed average 10 Akcea headcount for 2015

iii. 10 / 415 = 2.4% X 7 employees = 0.17 FTE

iv. Rounded to 0.2 FTE as will require slightly more effort as Akcea headcount are all new hires rather than just ongoing support

v. Costs associated with Isis board and executive compensation (Barney & Barney), employee events and certain office supplies excluded from allocation cost base ($390k)

g. Legal

i. % of effort – 10%

ii. Work includes clinical trial support & initial forming of company

iii. Costs associated with proxy advisors and proxy printing excluded from allocation cost base ($27k)

h. Occupancy costs

i. % of effort – 8%

ii. Based of FTE's to support Akcea vs overall G&A headcount

iii. Cost base based on Gazelle Ct costs, including property taxes and insurance, with allocation to G&A based on square footage occupied

iv. Added 30% to office/cube space to allow for allocation of common space

v. Costs specifically related to Labs excluded from occupancy cost base (Nitrogen supplies, lab equipment service contracts, specialized lab janitorial services)

R&D Support

a. R&D Allocations

i. % of effort – 5%

ii. Based on FTE's to support Akcea vs overall R&D Support headcount

iii. Cost base includes D&O insurance

iv. Costs excluded relate to equity adjustments and promotions becuase they pertain to 2014, amortization of non-Akcea related license fees, property taxes and property insurance (allocated as part of occupancy cost) ($4.2M)

b. Information technology

i. % of effort - 2%

ii. Includes support services and help desk support only

iii. Costs excluded from allocation cost base relate to Carlsbad phone and internet services ($165k)

c. Alliane Management

i. Assumes no costs allocated to Akcea

d. Business Development

i. % of effort – 3%

ii. % of effort includes work on initial partner discussions, term sheets, agreement negotiations, due diligence, presentations, CDA's

iii. Costs for data rooms, consulting and in-licensing excluded from allocation cost base ($137k)

e. Graphics

i. Assumes no costs allocated to Akcea

f. Purchasing

i. % of effort – 5%

ii. Work performed includes contract negotiations, set up purchasing contracts, clinical ops purchasing involvement

iii. All shipping and receiving costs excluded from allocation cost base ($239k)

g. Facilities

i. Assumes no costs allocated to Akcea

h. Patents

i. % of effort – 10%

ii. Excluded costs include patent write-off's and patent amortization for non-lipid drugs ($1.9M)

i. Health & Safety

i. Assumes no cost allocation to Akcea

j. MBO Accrual – Other R&D

i. Costs excluded as relate to other departments

k. Occupancy Costs

i. % of effort – 4%

ii. Based on FTE's to support Akcea vs overall R&D Support headcount

iii. Cost base based on Gazelle Ct costs, including property taxes and insurances, with allocation to R&D Support based on square footage occupied

iv. Added 30% to office/cube space to allow for allocation of common space

v. Costs specifically related to Labs excluded from occupancy cost base (Nitrogen supplies, lab equipment service contracts, specialized lab janitorial services)

APPENDIX B

AUDIT RIGHTS AND PROCEDURES

During the Agreement Term and for a period of 36 months thereafter, at the request and expense of Akcea, Ionis will permit an independent certified public accountant of nationally recognized standing appointed by Ionis and agreed to by Akcea (such agreement not to be unreasonably withheld), at reasonable times and upon reasonable notice, but not more than once per Calendar Year, to examine such records as are necessary to verify the calculation and reporting of out-of-pocket expenses and the correctness of any invoice submitted to Akcea for payment for Services under this Agreement. As a condition to examining any records of Ionis, such auditor will sign a nondisclosure agreement reasonably acceptable to Ionis. Any records of Ionis examined by such accountant will be deemed Ionis' Confidential Information. Upon completion of the audit, the accounting firm will provide both Parties with a written report disclosing whether the amounts invoiced by Ionis for payment by Akcea are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If the Audit Report shows that Ionis' invoices under this Agreement were more than the amount that should have been invoiced, then Ionis will reimburse Akcea the difference between such amounts to eliminate any discrepancy revealed by said inspection within 30 days of receiving the Audit Report, with interest calculated under Section 6. If the Audit Report shows that Ionis' invoiced amounts under this Agreement were less than the amount that should have been invoiced, then Akcea will reimburse Ionis equal to the difference between the amounts which should have been invoiced and the actual invoiced amount. Akcea will pay for such audit, except that if Ionis is found to have incorrectly invoiced Akcea by more than 5% of the amount that should have been invoiced, Ionis will reimburse Akcea's reasonable costs of the audit.

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: May 4, 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: May 4, 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 March 31, 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: May 4, 2018

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D. Chief Executive Officer	Elizabeth L. Hougen Chief Financial Officer

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