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, 2017

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, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

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

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

Common Stock, $.001 Par Value

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, or a smaller reporting company. See definition of "large accelerated filer," "accelerated filer" and "smaller reporting 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 ☐

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 May 2, 2017 was 123,965,560.

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TRADEMARKS

Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc.

Akcea Therapeutics™ is a trademark of Ionis Pharmaceuticals, Inc.

Regulus Therapeutics® is a registered trademark of Regulus Therapeutics Inc.

SPINRAZA™ is a trademark of Biogen, Inc.

KYNAMRO® is a registered trademark of Kastle Therapeutics LLC

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

	March 31, 2017 (Unaudited)	December 31, 2016
ASSETS		
Current assets:		
Cash and cash equivalents	$ 114,221	$ 84,685
Short-term investments	746,060	580,538
Contracts receivable	69,357	108,043
Inventories	6,801	7,489
Other current assets	25,933	17,177
Total current assets	962,372	797,932
Property, plant and equipment, net	95,439	92,845
Patents, net	21,175	20,365
Deposits and other assets	5,010	1,325
Total assets	$ 1,083,996	$ 912,467
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 23,237	$ 21,120
Accrued compensation	8,267	24,186
Accrued liabilities	30,870	36,013
Current portion of long-term obligations	56	1,185
Current portion of deferred contract revenue	108,150	51,280
Total current liabilities	170,580	133,784
Long-term deferred contract revenue	115,759	91,198
1 percent convertible senior notes	508,411	500,511
Long-term obligations, less current portion	15,043	15,050
Long-term financing liability for leased facility	72,397	72,359
Total liabilities	882,190	812,902
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 123,880,559 and 120,351,480 shares issued and outstanding at March 31, 2017 and December 31, 2016, respectively	124	122
Additional paid-in capital	1,410,102	1,311,229
Accumulated other comprehensive loss	(30,460)	(30,358)
Accumulated deficit	(1,177,960)	(1,181,428)
Total stockholders' equity	201,806	99,565
Total liabilities and stockholders' equity	$ 1,083,996	$ 912,467

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	
	2017	**2016**
Revenue:		
Commercial Revenue:		
SPINRAZA royalties	$ 5,211	$ —
Licensing and other royalty revenue	3,547	1,660
Total commercial revenue	8,758	1,660
Research and development revenue under collaborative agreements	101,546	35,214
Total revenue	110,304	36,874
Expenses:		
Research, development and patent	82,638	80,964
Selling, general and administrative	13,677	10,562
Total operating expenses	96,315	91,526
Income (loss) from operations	13,989	(54,652)
Other income (expense):		
Investment income	2,280	1,457
Interest expense	(11,363)	(9,490)
Other expense	(1,438)	—
Income (loss) before income tax expense	3,468	(62,685)
Income tax expense	—	(232)
Net income (loss)	$ 3,468	$ (62,917)
Basic net income (loss) per share	$ 0.03	$ (0.52)
Shares used in computing basic net income (loss) per share	122,861	120,598
Diluted net income (loss) per share	$ 0.03	(0.52)
Shares used in computing diluted net income (loss) per share	124,972	120,598

See accompanying notes.

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

	Three Months Ended March 31,	
	2017	**2016**
Net income (loss)	$ 3,468	$ (62,917)
Unrealized gains (losses) on securities, net of tax	266	(2,550)
Reclassification adjustment for realized gains included in net income (loss)	(374)	—
Currency translation adjustment	(6)	—
Comprehensive income (loss)	$ 3,354	$ (65,467)

See accompanying notes.

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

	Three Months Ended March 31,	
	2017	**2016**
Operating activities:		
Net income (loss)	$ 3,468	$ (62,917)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:		
Depreciation	1,980	1,841
Amortization of patents	393	377
Amortization of premium on investments, net	1,608	2,039
Amortization of debt issuance costs	396	298
Amortization of convertible senior notes discount	7,506	5,795
Amortization of long-term financing liability for leased facility	1,675	1,672
Stock-based compensation expense	20,912	20,103
Gain on investment in Regulus Therapeutics, Inc.	(374)	—
Non-cash losses related to patents, licensing and property, plant and equipment	93	396
Changes in operating assets and liabilities:		
Contracts receivable	38,686	(5,124)
Inventories	688	379
Other current and long-term assets	(14,077)	(2,747)
Accounts payable	472	(11,417)
Accrued compensation	(15,919)	(9,728)
Accrued liabilities and deferred rent	(6,273)	(1,886)
Deferred contract revenue	81,431	(14,849)
Net cash provided by (used in) operating activities	122,665	(75,768)
Investing activities:		
Purchases of short-term investments	(266,185)	(41,366)
Proceeds from the sale of short-term investments	99,223	81,805
Purchases of property, plant and equipment	(3,237)	(628)
Acquisition of licenses and other assets, net	(983)	(382)
Proceeds from the sale of Regulus Therapeutics	2,507	—
Net cash (used in) provided by investing activities	(168,675)	39,429
Financing activities:		
Proceeds from equity awards	6,324	2,736
Proceeds from sale of stock to Novartis	71,640	—
Offering costs paid	(778)	—
Principal payments on debt and capital lease obligations	(1,640)	(1,857)
Net cash provided by financing activities	75,546	879
Net increase (decrease) in cash and cash equivalents	29,536	(35,460)
Cash and cash equivalents at beginning of period	84,685	128,797
Cash and cash equivalents at end of period	$ 114,221	$ 93,337
Supplemental disclosures of cash flow information:		
Interest paid	$ 106	$ 31
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,648	$ 2,524
Unpaid deferred offering costs	$ 319	$ —

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three months ended March 31, 2017 and 2016 on the same basis as the audited financial statements for the year ended December 31, 2016. 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, 2016 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 our wholly owned subsidiary, Akcea Therapeutics, Inc., which we formed in December 2014 and its wholly owned subsidiaries, Akcea Therapeutics UK Ltd, which Akcea formed in August 2016 and Akcea Intl Ltd., which Akcea formed in February 2017. Unless the context requires otherwise, “Ionis”, “Company,” “we,” “our,” and “us” refers to Ionis Pharmaceuticals, Inc. and its wholly owned subsidiary, Akcea Therapeutics, Inc.

2. Significant Accounting Policies

Revenue Recognition

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 consolidated condensed balance sheet.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We often enter into agreements to license and sell our proprietary patent rights on an exclusive or non-exclusive basis in exchange for upfront fees, milestone payments and/or royalties. We generally recognize as revenue immediately license payments with stand-alone value when the license is delivered and for which we are reasonably assured of collecting the resulting receivable. We recognize royalty revenue in the period in which the counterparty sells the related product, unless we are unable to obtain information to estimate the royalty. For example, for the first quarter of 2017 we recorded SPINRAZA royalty revenue of $5.2 million.

Research and development revenue under collaborative agreements

Arrangements with multiple deliverables

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services, and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable.

Amendments to agreements

From time to time we amend our collaboration agreements. For these agreements, before we identify our deliverables and allocate consideration to each unit of accounting, we must determine if the amendment should be accounted for as a separate agreement, or if the amendment and any undelivered elements for the original agreement should be accounted for as a single new arrangement.

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 $100 million upfront payment in the second quarter of 2015. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis and for providing an initial supply of active pharmaceutical ingredient, or 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 $75 million, which we received in April 2017. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$.

We concluded that the February 2017 amendment should be evaluated with the undelivered elements of the original agreement as a single new arrangement. Under the amendment, there was a substantial increase in the consideration we are eligible to receive and it included a significant change in the deliverables we will provide. As a result, we evaluated our original and 2017 amended agreements with Bayer together to determine our deliverables. We concluded that the 2017 amendment did not impact the items we already delivered to Bayer.

Identifying deliverables and units of accounting

We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a stand-alone basis. For example, our 2017 amended agreement with Bayer has multiple elements. We evaluated the deliverables in this arrangement when we entered into the 2017 amended agreement and determined that certain deliverables have stand-alone value. Below is a list of the three units of accounting under our 2017 amended agreement:

- The exclusive license we granted to Bayer to develop and commercialize IONIS-FXI-L_{Rx} for the treatment of thrombosis;
- The development services we agreed to perform for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx}; and
- The remaining undelivered IONIS-FXI_{Rx} API that was part of the original agreement.

We determined that each of these three units of accounting have stand-alone value. The license we granted to Bayer has stand-alone value because it gives Bayer the exclusive right to develop IONIS-FXI-L_{Rx} or to sublicense its rights. The development services and the remaining undelivered supply of API each have stand-alone value because Bayer or another third party could provide these items without our assistance.

Measurement and allocation of arrangement consideration

Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees and royalties on product sales. We initially allocate the amount of consideration that is fixed and determinable at the time the agreement is entered into and exclude contingent consideration. We allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

We determined that the allocable arrangement consideration for the 2017 amended Bayer collaboration was $76.3 million, comprised of the $75 million we received as part of the amendment and the remaining amount of the $100 million upfront payment we had not yet recognized into revenue, related to the undelivered API. We allocated the consideration based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation specialist to assist us with determining BESP. We estimated the selling price of the license granted for IONIS-FXI-L_{Rx} by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for IONIS-FXI-L_{Rx}. We then discounted the projected income to present value. The significant inputs we used to determine the projected income of the license included:

- 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 estimated the selling price of the development 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 development services. The significant inputs we used to determine the selling price of the development services included:

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

For purposes of determining BESP of the services we will perform and the API we will deliver in our 2017 amended Bayer transaction, accounting guidance required us to include a markup for a reasonable profit margin.

Based on the units of accounting under the 2017 amended agreement, we allocated the $76.3 million of allocable consideration as follows:

- $64.9 million to the IONIS-FXI-L_{Rx} exclusive license;
- $11.0 million for development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx}; and
- $0.4 million for the remaining delivery of IONIS-FXI_{Rx} API.

Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the IONIS-FXI-L_{Rx} license, we determined that the revenue we would have allocated to the IONIS-FXI-L_{Rx} license would change by approximately one percent, or $0.7 million, from the amount we recorded.

Timing of revenue recognition

We recognize revenue as we deliver each item under the arrangement and the related revenue is realizable and earned. For example, we recognized revenue for the exclusive license we granted Bayer for IONIS-FX-L_{Rx} in the first quarter of 2017 because that was when we delivered the license. We also recognize revenue over time as we provide services. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We estimate our period of performance at the inception of the agreement when the agreements we enter into do not clearly define such information. We then recognize revenue from development services ratably over such period. In certain instances, the period of performance may change as the development plans for our drugs progress. If our estimates and judgments change over the course of our collaboration agreements, it may affect the timing and amount of revenue that we recognize in future periods. Any changes in estimates are recognized on a prospective basis.

The following are the periods over which we are recognizing revenue for each of our units of accounting under our 2017 amended Bayer agreement:

- We recognized the portion of the consideration attributed to the IONIS-FXI-L_{Rx} license in the first quarter of 2017 because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx} over the period of time we are performing the services; and
- We are recognizing the amount attributed to the remaining API supply as we deliver it to Bayer.

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 they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, in the first quarter of 2017, we and our wholly owned subsidiary, Akcea, entered into two separate agreements with Novartis at the same time: a collaboration agreement and a stock purchase agreement, or SPA.

Akcea entered into a collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Akcea received a $75 million upfront payment. For each drug, Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and delivering API. Under the collaboration agreement, Novartis has an exclusive option to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. If Novartis exercises an option for one of these drugs, Novartis will pay us a license fee and will assume all further global development, regulatory and commercialization activities for the licensed drug. Akcea is also eligible to receive a development milestone payment, milestone payments if Novartis achieves pre-specified regulatory milestones, commercial milestones and tiered royalties on net sales from each drug under the collaboration.

Under the SPA, Novartis purchased 1.6 million shares of Ionis' common stock for $100 million in the first quarter of 2017 and paid a premium over the weighted average trading price at the time of purchase. Additionally, the SPA requires Novartis to purchase an additional $50 million of common stock in the future.

We evaluated the Novartis agreements to determine whether we should treat the agreements separately or as a single arrangement. We considered that the agreements were negotiated concurrently and in contemplation of one another. Additionally, the same individuals were involved in the negotiations of both agreements. Based on these facts and circumstances, we concluded that we should treat both agreements as a single arrangement and 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.

Milestone payments

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and/ or commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraphs.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

During the first step of the development stage, we or our partners study our drugs in Investigational New Drug, or IND,-enabling studies, which are animal studies intended to support an IND application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate.

The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing authorization from the Food and Drug Administration, or FDA, and/or foreign equivalents. The Phase 3 studies typically involve larger numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing authorization. This stage of the drug's life-cycle is the regulatory stage.

If a drug achieves marketing authorization, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the partnered drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow us or our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to marketing authorization and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing authorization such as a New Drug Application, or NDA, in the United States or a Marketing Authorization Application, or MAA, in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Marketing authorization in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain authorization from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment immediately. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or in part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements*.

Option to license

In several of our collaboration agreements, we provide our partner with an option to obtain a license to one or more of our drugs. When we have a multiple element arrangement that includes an option to obtain a license, we evaluate if the option is a deliverable at the inception of the arrangement. We do not consider the option to be a deliverable if we conclude that it is substantive and not priced at a significant and incremental discount. We consider an option substantive if, at the inception of the arrangement, we are at risk as to whether our collaborative partner will choose to exercise its option to obtain the license. In those circumstances, we do not include the associated license fee in the allocable consideration at the inception of the agreement. Rather, we account for the license fee when our partner exercises its option. For example, during 2016, we earned license fee revenue when three of our partners, AstraZeneca, Biogen and Janssen, exercised their option to license three of our drugs, which under the respective agreements we concluded to be substantive options at inception. As a result, in 2016 we recognized the related revenue immediately in research and development revenue under collaborative agreements on our statement of operations as these amounts relate to drugs in development under research and collaboration arrangements.

Cash, cash equivalents and short-term 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 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 have equity investments in privately and publicly held biotechnology companies that we have received as part of a technology license or partner agreement. At March 31, 2017, we held ownership interests of less than 20 percent in each of the respective companies.

We account for our equity investments in publicly held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock of these publicly-held companies as a separate component of comprehensive income (loss). At March 31, 2017, we held equity investments in one publicly held company, Antisense Therapeutics Limited. We account for equity investments in privately held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. At March 31, 2017, we held cost method investments in three companies, Atlantic Pharmaceuticals Limited, Kastle Therapeutics and Dynacure SAS. Realization of our equity position in these private companies is uncertain. When realization of our investment is uncertain, we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

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 deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. 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, 2017 and 2016. Total inventory was $6.8 million and $7.5 million as of March 31, 2017 and December 31, 2016, 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 condensed consolidated balance sheet and we expense them as the services are provided.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the 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 net income or loss by the weighted-average number of common shares outstanding during the period. 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
Income available to common shareholders	$ 3,468	122,861	$ 0.03
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 common shareholders, plus assumed conversions	$ 3,468	124,972	$ 0.03

For the three months ended March 31, 2017, the calculation excludes the 1 percent and 2¾ percent notes because the effect on diluted earnings per share was anti-dilutive.

For the three months ended March 31, 2016, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

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

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, 2017 and 2016 (in thousands):

	Three Months Ended March 31,	
	2017	2016
Beginning balance accumulated other comprehensive loss	$ (30,358)	$ (13,565)
Unrealized losses on securities, net of tax (1)	266	(2,550)
Amounts reclassified from accumulated other comprehensive income (2)	(374)	—
Currency translation adjustment	6	—
Net current period other comprehensive loss	(102)	(2,550)
Ending balance accumulated other comprehensive loss	$ (30,460)	$ (16,115)

(1) There was no tax benefit for other comprehensive loss for the three months ended March 31, 2017 and 2016.

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

Convertible debt

We account for convertible debt instruments, including our 1 percent and 2¾ percent notes, 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, which includes the operations of our wholly owned subsidiary, Akcea Therapeutics, Inc. We formed Akcea to develop and commercialize drugs for patients with serious cardiometabolic diseases caused by lipid disorders. 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 use judgments and estimates in determining the allocation of shared expenses to the two segments.

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, 2017 and 2016, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2017	**2016**
Risk-free interest rate	1.8%	1.5%
Dividend yield	0.0%	0.0%
Volatility	66.3%	57.9%
Expected life	4.5 years	4.5 years

ESPP:

	Three Months Ended March 31,	
	2017	**2016**
Risk-free interest rate	0.7%	0.5%
Dividend yield	0.0%	0.0%
Volatility	66.5%	69.4%
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, 2017 was $48.09 per share.

We did not grant stock options or RSUs to our Board of Directors during the three months ended March 31, 2017 and 2016.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2017 and 2016 (in thousands). Our consolidated non-cash stock-based compensation expense includes $3.2 million of stock-based compensation expense for Akcea employees for each of the three months ended March 31, 2017 and 2016.

	Three Months Ended March 31,	
	2017	**2016**
Research, development and patent	$ 16,122	$ 14,770
Selling, general and administrative	4,790	5,333
Total	$ 20,912	$ 20,103

As of March 31, 2017, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $91.8 million and $25.6 million, respectively. We will adjust total unrecognized compensation cost for future forfeitures. We expect to recognize the cost of non-cash stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.5 years and 1.8 years, respectively.

Impact of recently issued accounting standards

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. Under the current accounting guidance, we recognize revenue from milestone payments we earn under the milestone method. Under the new guidance, the milestone method of revenue recognition is eliminated. This new guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance as originally issued is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. In July 2015, the FASB issued updated accounting guidance to allow for an optional one year deferral from the original effective date. As a result, we will adopt this guidance beginning on January 1, 2018. The guidance allows us to select one of two methods of adoption, either the full retrospective approach, meaning the guidance would be applied to all periods presented, or modified retrospective approach, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to our opening accumulated deficit balance. As we have a significant number of collaborations that span several years with associated revenue, we are currently evaluating which adoption method we will use and assessing the impact the adoption will have on our consolidated financial statements and disclosures.

In January 2016, the FASB issued 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 net income (loss), instead of recognizing unrealized gains and losses through accumulated other comprehensive income, as we currently do under the existing guidance. The amended guidance also changes several disclosure requirements for financial instruments, including the methods and significant assumptions we use to estimate fair value. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2017. We will adopt this guidance on January 1, 2018 and we will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. We are currently determining the effects the adoption will have on our consolidated financial statements and disclosures.

In February 2016, the FASB issued amended accounting guidance related to lease accounting, which requires 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, similar to current accounting guidance. We will record expense for operating type leases on a straight-line basis as an operating expense and we will record expense for finance type leases as interest expense. 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 consolidated balance sheet for the earliest comparative period presented. We are currently assessing the timing of adoption as well as the effects it 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 are currently assessing the timing of adoption as well as the effects it will have on our consolidated financial statements and disclosures.

3. Investments

As of March 31, 2017, we had primarily invested our excess cash 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, 2017:

One year or less	64%
After one year but within two years	24%
After two years but within three and a half years	12%
Total	100%

As illustrated above, at March 31, 2017, 88 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, 2017, we had an ownership interest of less than 20 percent in three private companies and one public company with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Kastle and Dynacure and the publicly-traded company is Antisense Therapeutics Limited. We account for equity investments in the privately-held companies under the cost method of accounting and we account for equity investments in the publicly-traded company at fair value. 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.

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

		Gross Unrealized		
March 31, 2017	**Cost** (1)	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities:				
Corporate debt securities (2)	$ 341,043	$ 18	$ (405)	$ 340,656
Debt securities issued by U.S. government agencies	64,784	2	(72)	64,714
Debt securities issued by the U.S. Treasury (2)	23,297	—	(19)	23,278
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	55,828	2	(116)	55,714
Total securities with a maturity of one year or less	484,952	22	(612)	484,362
Corporate debt securities	189,152	49	(833)	188,368
Debt securities issued by U.S. government agencies	25,670	—	(124)	25,546
Debt securities issued by the U.S. Treasury	3,497	—	(1)	3,496
Debt securities issued by states of the U.S. and political subdivisions of the states	55,101	16	(291)	54,826
Total securities with a maturity of more than one year	273,420	65	(1,249)	272,236
Total available-for-sale securities	$ 758,372	$ 87	$ (1,861)	$ 756,598

		Gross Unrealized		
December 31, 2016	**Cost** (1)	**Gains**	**Losses**	**Estimated Fair Value**
Available-for-sale securities:				
Corporate debt securities	$ 195,087	$ 25	$ (161)	$ 194,951
Debt securities issued by U.S. government agencies	26,548	—	(10)	26,538
Debt securities issued by the U.S. Treasury	29,298	2	(14)	29,286
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	72,775	2	(134)	72,643
Total securities with a maturity of one year or less	323,708	29	(319)	323,418
Corporate debt securities	202,408	36	(1,174)	201,270
Debt securities issued by U.S. government agencies	28,807	1	(167)	28,641
Debt securities issued by states of the U.S. and political subdivisions of the states	36,816	1	(349)	36,468
Total securities with a maturity of more than one year	268,031	38	(1,690)	266,379
Total available-for-sale securities	$ 591,739	$ 67	$ (2,009)	$ 589,797
Equity securities:				
Regulus Therapeutics Inc.	$ 2,133	$ 281	$ —	$ 2,414
Total equity securities	$ 2,133	$ 281	$ —	$ 2,414
Total available-for-sale and equity securities	$ 593,872	$ 348	$ (2,009)	$ 592,211

(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, 2017 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	354	$ 421,288	$ (1,180)	$ 22,387	$ (58)	$ 443,675	$ (1,238)
Debt securities issued by U.S. government agencies	41	84,017	(196)	—	—	84,017	(196)
Debt securities issued by the U.S. Treasury	4	25,773	(20)	—	—	25,773	(20)
Debt securities issued by states of the U.S. and political subdivisions of the states	97	90,816	(336)	4,916	(71)	95,732	(407)
Total temporarily impaired securities	496	$ 621,894	$ (1,732)	$ 27,303	$ (129)	$ 649,197	$ (1,861)

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, 2017, 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, 2017 and December 31, 2016 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, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 100,318	$ 100,318	$ —
Corporate debt securities (2)	529,024	—	529,024
Debt securities issued by U.S. government agencies (3)	90,260	—	90,260
Debt securities issued by the U.S. Treasury (4)	26,774	26,774	—
Debt securities issued by states of the U.S. and political subdivisions of the states (5)	110,540	—	110,540
Total	$ 856,916	$ 127,092	$ 729,824

	At December 31, 2016	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 54,137	$ 54,137	$ —
Corporate debt securities (3)	396,221	—	396,221
Debt securities issued by U.S. government agencies (3)	55,179	—	55,179
Debt securities issued by the U.S. Treasury (3)	29,286	29,286	—
Debt securities issued by states of the U.S. and political subdivisions of the states (5)	109,111	—	109,111
Investment in Regulus Therapeutics Inc.	2,414	2,414	—
Total	$ 646,348	$ 85,837	$ 560,511

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

(2) At March 31, 2017, $6.8 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 March 31, 2017, $1.0 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.

(5) At March 31, 2017 and December 31, 2016, $2.7 million and $9.3 million, respectively, were 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 is required to purchase $50 million of common stock in the future. Novartis will make this purchase either in Akcea's common stock at the IPO price if an IPO occurs under certain conditions, in our common stock at a premium if an IPO does not occur by April 2018, or in a combination of both of these under certain conditions. If an IPO does not occur within the required timeframe, Novartis is required to purchase our common stock at a premium calculated in the same manner as Novartis' initial investment. Therefore, at the inception of the SPA, we recorded a $5.0 million asset representing the fair value of the potential future premium we will receive if Novartis purchases 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 will issue unregistered shares to Novartis if they purchase our common stock. We measured this asset using Level 3 inputs and recorded it in other assets on our condensed consolidated balance sheet. At the end of each period prior to an Akcea IPO or the purchase by Novartis of our common stock, we will remeasure the fair value of this asset and record an adjustment to other income/expense on our condensed consolidated statement of operations for the change in value.

The following is a reconciliation of the potential premium we may receive 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 asset (at December 31, 2016)	$ —
Value of the potential premium we will receive from Novartis at inception of the SPA (January 2017)	5,035
Recurring fair value adjustment at March 31, 2017	(1,438)
Ending balance of Level 3 asset (at March 31, 2017)	$ 3,597

At December 31, 2016 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 $661.9 million at March 31, 2017. 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. 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, 2017 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.

6. Collaborative Arrangements and Licensing Agreements

Below, we have included our collaborations with substantive changes during the first three months of 2017 from those included in Note 6 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2016.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved drug to treat pediatric and adult patients with SMA. Additionally, we and Biogen are currently developing four other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$, IONIS-MAPT$_{Rx}$ (formerly IONIS-BIIB4$_{Rx}$) and two drugs to treat undisclosed neurodegenerative diseases, IONIS-BIIB5$_{Rx}$ and IONIS-BIIB6$_{Rx}$. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. From inception through March 2017, we have received over $550 million from our Biogen collaborations.

During the three months ended March 31, 2017, we earned revenue of $20.4 million from our relationship with Biogen, including $5 million we earned in the first quarter of 2017 for validation of an undisclosed neurological disease target and SPINRAZA royalties. Our revenue from Biogen represented 18 percent of our total revenue for the three months ended March 31, 2017. In comparison, we earned revenue of $21.3 million for the same period in 2016, which represented 58 percent of our total revenue for that period. Our condensed consolidated balance sheet at March 31, 2017 included deferred revenue of $57.7 million 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 patients 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. We recorded revenue of $91.2 million related to the license for IONIS-FXI$_{Rx}$ in June 2015 and we recognized the majority of the remaining amount related to development activities for IONIS-FXI$_{Rx}$ through November 2016.

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 in April 2017. We recorded revenue of $64.9 million related to the license for IONIS-FXI-L$_{Rx}$ in February 2017 and we are recognizing the remaining amount over the period we are performing the ongoing development activities for IONIS-FXI-L$_{Rx}$ and IONIS-FXI$_{Rx}$ through May 2019. We plan to conduct a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in patients with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to rapidly 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 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, substantive 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. We will earn the next milestone payment of $10 million if we advance a program under this collaboration.

During the three months ended March 31, 2017, we earned revenue of $65.5 million from our relationship with Bayer, which represented 59 percent of our total revenue for that period. In comparison, we earned revenue of $1.3 million for the same period in 2016, which represented three percent of our total revenue for that period. Our condensed consolidated balance sheet at March 31, 2017 included no deferred revenue related to our relationship with Bayer because we received the $75 million payment in April 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 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 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 commercialization activities for such drug.

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it will retain $60 million and will pay 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 substantive 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 substantive 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 plans to co-commercialize any licensed drug commercialized by Novartis in selected markets, under terms and conditions that it plans to negotiate with Novartis in the future, through the specialized sales force Akcea is building to commercialize volanesorsen. Following Novartis' exercise of its option for either drug, Akcea will earn the next milestone payment of $25 million if Novartis advances the Phase 3 study for either drug. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee.

The agreement with Novartis will continue until the earlier of the date that all of Novartis' options to obtain the exclusive licenses under the agreement expire unexercised or, if Novartis exercises its options, until the expiration of all payment obligations under the agreement. In addition, the agreement as a whole or with respect to any drug under the agreement, may terminate early under the following situations:

- Novartis may terminate the agreement as a whole or with respect to any drug at any time by providing written notice to us;
- Either we or Novartis may terminate the agreement with respect to any drug by providing written notice to the other party in good faith that we or Novartis has determined that the continued development or commercialization of the drug presents safety concerns that pose an unacceptable risk or threat of harm in humans or would violate any applicable law, ethical principles, or principles of scientific integrity;

- Either we or Novartis may terminate the agreement for a drug by providing written notice to the other party upon the other party's uncured failure to perform a material obligation related to the drug under the agreement, or the entire agreement if the other party becomes insolvent; and
- We may terminate the agreement if Novartis disputes or assists a third party to dispute the validity of any of our patents.

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. Additionally, the SPA requires Novartis to purchase an additional $50 million of common stock in the future. Subject to the terms of the SPA, Novartis will make this purchase either in Akcea's common stock at the IPO price if an IPO occurs under certain conditions, in our common stock at a premium if an IPO does not occur by April 2018, or in a combination of both of these under certain conditions. If an IPO does not occur within the required timeframe, Novartis is required to purchase our common stock at a premium calculated in the same manner as Novartis' initial investment.

To determine the amount of revenue to recognize under our agreements with Novartis, we first concluded that we would account for the collaboration and SPA agreements as a single multiple element arrangement. We next identified four separate units of accounting under the arrangement, each with stand-alone value.:

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

We then determined the total consideration under the arrangement was $180.0 million, which included the following:

- $75 million from the upfront payment;
- $100 million our common stock Novartis purchased under the SPA, including $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 will pay if they purchase our common stock in the future.

We first allocated $71.6 million of the consideration to equity based on the fair value of our common stock Novartis purchased. Next, we allocated the remaining consideration of $108.4 million based on the relative stand-alone selling price of each unit of accounting as follows:

- $64.0 million for the development services for AKCEA-APO(a)-L_{Rx};
- $40.1 million for the development 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 the amount attributed to the development services for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} over the period of time we are performing the services, currently estimated to be through August 2018 and May 2019, respectively. We will recognize the amount attributed to the API supply as we deliver it to Novartis. We determined at the inception that all milestones under its Novartis collaboration are substantive milestones and we will recognize any future exercise of an option to license a drug under the Novartis agreement in full in the period the option is exercised. 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, the sublicense fees are eliminated.

During the three months ended March 31, 2017, we earned revenue of $9.6 million from our relationship with Novartis. Our condensed consolidated balance sheet at March 31, 2017 included deferred revenue of $98.8 million related to our relationship with Novartis.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics, our wholly owned subsidiary. 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.

We formed Akcea to develop and commercialize drugs for patients with serious cardiometabolic diseases caused by lipid disorders. Moving our lipid drugs into a company that we own ensures that our core focus at Ionis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs.

The following table shows our segment revenue and loss from operations for the three months ended March 31, 2017 and March 31, 2016 (in thousands), respectively.

March 31, 2017	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	5,211	—	—	5,211
Licensing and other royalty revenue	3,547	—	—	3,547
Total commercial revenue	8,758	—	—	8,758
R&D revenue under collaborative agreements	$ 143,425	$ 9,597	$ (51,476)	$ 101,546
Total segment revenue	$ 152,183	$ 9,597	$ (51,476)	$ 110,304
Income (loss) from operations	$ 73,832	$ (59,873)	$ 30	$ 13,989

March 31, 2016	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
R&D revenue under collaborative agreements	$ 35,214	$ —	$ —	$ 35,214
Licensing and other royalty revenue	1,660	—	—	1,660
Total segment revenue	$ 36,874	$ —	$ —	$ 36,874
Loss from operations	$ (38,567)	$ (16,049)	$ (36)	$ (54,652)

The following table shows our total assets by segment at March 31, 2017 and December 31, 2016 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
March 31, 2017	$ 1,202,164	$ 132,982	$ (251,150)	$ 1,083,996
December 31, 2016	$ 1,067,770	$ 10,684	$ (165,987)	$ 912,467

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,	
	2017	2016
Partner A	59 %	3 %
Partner B	18 %	58 %
Partner C	4 %	14 %

Contracts receivables from one significant partner comprised approximately 92 percent of our contracts receivables at March 31, 2017. Contracts receivables from two significant partners comprised approximately 92 percent of our contracts receivables at December 31, 2016.

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

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

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our financial position and outlook, our business, the business of Akcea Therapeutics, Inc., a wholly owned subsidiary of Ionis Pharmaceuticals, and the therapeutic and commercial potential of our technologies and products in development, including SPINRAZA, IONIS-TTR$_{Rx}$ and volanesorsen. 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, 2016, which is on file with the U.S. Securities and Exchange Commission and are available from us, and those identified within this Item in the section entitled "Risk Factors" beginning on page 30 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. 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. The recent U.S. approval and commercial launch of SPINRAZA for pediatric and adult patients with SMA highlights our progress toward this goal. Our pipeline also contains two near-term potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential, volanesorsen and IONIS-TTR$_{Rx}$. In the first quarter of 2017, we reported positive Phase 3 data in patients with familial chylomicronemia, or FCS. As a result, in the third quarter of 2017, we plan to file for marketing authorization for volanesorsen to treat patients with FCS. We also plan to report data from our Phase 3 study of IONIS-TTR$_{Rx}$ in patients with FAP in the second quarter of 2017.

With FDA approval in December 2016, SPINRAZA injection became the first and only approved drug to treat pediatric and adult patients with SMA. SMA is a leading genetic cause of death in infants and toddlers that is marked by progressive, debilitating muscle weakness. In the first quarter, we earned $5.2 million in commercial revenue from SPINRAZA royalties. We anticipate that this revenue will grow as the U.S. launch progresses and Biogen obtains marketing approvals in additional countries. Biogen has filed for marketing authorization in the EU, Japan, Australia and Canada, and plans to file in other countries this year. The European Medicines Agency, or EMA, is reviewing the SPINRAZA marketing application under accelerated assessment. In April 2017, Biogen received a positive CHMP opinion for SPINRAZA recommending marketing approval with a broad indication in the EU. Biogen estimates that there are approximately 20,000 patients with SMA in the U.S., EU and Japan, with a large percentage in the United States.

Akcea Therapeutics, Inc. is our subsidiary focused on developing and commercializing volanesorsen and three other clinical-stage drugs for serious cardiometabolic diseases caused by lipid disorders, AKCEA-APO(a)-L$_{Rx}$, AKCEA-ANGPTL3-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. Each of these four drugs could potentially treat multiple patient populations. Moving these drugs into a company that we own allows us to retain substantial value from them and ensures our core focus remains on innovation. In March 2017, we and Akcea filed a registration statement with the intention of completing an initial public offering, or IPO. Akcea plans to use proceeds from an IPO to further advance its drugs and commercialization efforts. Akcea is continuing to assemble the global infrastructure to continue developing the drugs in its pipeline, to commercialize them with a focus on lipid specialists as the primary call point and to provide the specialized patient and physician support required to address rare disease patient populations.

We and Akcea are developing volanesorsen to treat two severe and rare, genetically defined diseases, 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. The clinical development program for volanesorsen 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 what we believe is a favorable risk benefit profile supported by data from both APPROACH and COMPASS, we and Akcea are actively preparing for marketing authorization in the U.S., Europe and Canada in the third quarter of 2017. We estimate that FCS and FPL each affect 3,000 to 5,000 patients globally. If approved, we plan to commercialize volanesorsen for both FCS and FPL through Akcea.

IONIS-TTR$_{Rx}$ is potentially a first-in-class and best-in-class drug for the treatment of all forms of transthyretin, or TTR, amyloidosis, a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body. We are evaluating IONIS-TTR$_{Rx}$ in an ongoing Phase 3 study, NEURO-TTR, in patients with FAP. More than half of these patients also have TTR amyloid cardiomyopathy. As part of our Phase 3 study, we are evaluating cardiomyopathy in this subset of patients by cardiac imaging and biomarkers which will provide data on cardiovascular endpoints. Together the polyneuropathy and cardiomyopathy forms of TTR amyloidosis represent a large commercial opportunity for IONIS-TTR$_{Rx}$. We plan to report data from the NEURO-TTR study in the second quarter of 2017. We and GSK, our partner for IONIS-TTR$_{Rx}$, are preparing to file for marketing authorization. GSK is preparing to commercialize IONIS-TTR$_{Rx}$.

In addition to our Phase 3 programs, we have a pipeline of drugs with the potential to be first-in-class and/or best-in-class drugs to treat patients with diseases that have inadequate treatment options. We are addressing a broad spectrum of diseases from common diseases affecting millions, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease, to rare diseases, such as amyotrophic lateral sclerosis and Huntington's disease. Our pipeline has over a dozen drugs in Phase 2 development, many of which we believe have the potential to be significant commercial opportunities. In particular, IONIS-FXI$_{Rx}$ and AKCEA-APO(a)-L$_{Rx}$ represent the value we have created. IONIS-FXI$_{Rx}$ is the first antithrombotic drug in development that has shown it can decrease the risk of blood vessel obstruction caused by a blood clot without increasing bleeding risk. 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. AKCEA-APO(a)-L$_{Rx}$ is the first and only drug in clinical development designed to selectively and robustly lower Lp(a), a key driver of cardiovascular disease. We believe that addressing Lp(a) is the next important horizon in lipid-focused cardiovascular disease treatment. In March 2017, Akcea initiated a Phase 2b study of AKCEA-APO(a)-L$_{Rx}$ in patients with elevated Lp(a).

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 for which our partners can provide expertise, tools and resources to complement our drug discovery efforts. 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 each partnership. We also form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas. Lastly, we also work with a consortium of companies that can exploit our drugs and 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 potential R&D revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. We have the potential to earn nearly $13 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 arrangements. With the approval of SPINRAZA in the U.S., we added 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 as the launch progresses and if SPINRAZA is approved in additional countries. We also have the potential to further increase our commercial revenue with volanesorsen sales and IONIS-TTR_{Rx} royalties. We believe we have the key elements in place to achieve sustained long-term financial growth, including multiple drivers of revenue; a mature, broad and rapidly-advancing clinical pipeline; a partnership strategy that leverages partner resources; and an innovative drug technology 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,	
	2017	**2016**
Total revenue	$ 110,304	$ 36,874
Total operating expenses	$ 96,315	$ 91,526
Income (loss) from operations	$ 13,989	$ (54,652)
Net income (loss)	$ 3,468	$ (62,917)

For the first three months of 2017 we earned net income of $3.5 million, compared to a net loss of $62.9 million for the same period in 2016. Our net income was driven by the substantial revenue we earned. In the first quarter of 2017, we added $5.2 million of commercial revenue from SPINRAZA royalties to our strong base of R&D revenue of over $100 million.

Our operating expenses were relatively flat year over year. As this year progresses, we expect a shift between categories. We anticipate R&D expenses to decrease as our Phase 3 programs wind down. We expect selling, general and administrative expenses to increase as Akcea continues to prepare to launch volanesorsen. Because of the efficiency of our technology, even with our projected declining R&D expenses this year, we will continue to advance our earlier stage drugs and add new drugs to our pipeline.

Recent Events

Our Corporate and Drug Development Highlights *(Q1 2017 and subsequent activities)*

Recent SPINRAZA Accomplishments:

- Biogen reported $47 million from sales of SPINRAZA in the first quarter.
- Biogen received a positive CHMP opinion for SPINRAZA, recommending marketing approval with a broad indication in the EU.
- We and Biogen reported positive data at AAN from the CHERISH and NURTURE studies as well as encore data from the ENDEAR study.
  - CHERISH data from an end of study analysis in non-ambulatory patients with later-onset SMA (consistent with Type 2) demonstrated:
    - A highly statistically significant and clinically meaningful improvement in motor function scores in SPINRAZA-treated patients compared to untreated patients.
    - Attainment of new motor milestones and upper limb motor function consistently in favor of SPINRAZA-treated patients.
    - A favorable safety profile with no discontinuations due to adverse events.
  - Data from an interim analysis of the NURTURE study in pre-symptomatic infants with genetically diagnosed SMA demonstrated that at the time of the interim analysis:
    - All infants were alive without the need for permanent ventilation.
    - Most infants achieved new motor milestones on essentially the same timeline as would be expected of a healthy infant.
    - No infants discontinued or withdrew from the study due to adverse events, and no new safety concerns were identified.

Recent Corporate and Pipeline Accomplishments:

- We received more than $290 million in cash from partners in the first quarter of 2017.
- In April, we received $75 million from Bayer to advance both IONIS-FXI_{Rx} and its LICA follow on, IONIS-FXI-L_{Rx}.
- GSK initiated Phase 2 studies of IONIS-HBV_{Rx} and the LICA follow on, IONIS-HBV-L_{Rx}.
- We initiated a Phase 1 study of IONIS-AGT-L_{Rx}, a wholly owned generation 2.0+ LICA drug, in patients with treatment resistant hypertension.
- We published papers in *Nature Biotechnology* on the mechanism of action for antisense drugs that significantly expand therapeutic opportunities for the technology.
- We published a paper in *Nucleic Acid Therapeutics* on the analysis of its Integrated Safety Database, which demonstrated no class generic effect of 2'-O-methoxyethyl-modified antisense oligonucleotides on platelet numbers and function.
- Our CEO, Dr. Stanley Crooke, received the E. B. Hershberg Award from the American Chemical Society

Recent Akcea Accomplishments:

- We and Akcea reported that volanesorsen achieved its primary endpoint in the Phase 3 APPROACH study, demonstrating robust reductions in triglycerides and reduced incidence of pancreatitis attacks and reduced frequency and severity of abdominal pain.
- We and Akcea initiated a strategic collaboration with Novartis worth up to more than $1 billion plus royalties for the development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}.
- Akcea initiated a Phase 2b study of AKCEA-APO(a)-L_{Rx} in patients with elevated Lp(a).
- Akcea filed a registration statement with the intention of completing an initial public offering.
- Top-line data from the Phase 3 APPROACH study of volanesorsen were presented at the 2017 European Atherosclerosis Society congress.
- Akcea published interim data in *Expert Review of Cardiovascular Therapy* from the IN-FOCUS survey that was commissioned to quantify the burden of FCS on patients and the healthcare system.

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 and other equity investments;
- Determining the appropriate cost estimates for unbilled preclinical and clinical development activities; and
- Estimating our net deferred income tax asset valuation allowance.

These critical accounting policies and estimates are included in our Annual Report on Form 10-K for the year ended December 31, 2016 in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations”. There have been no material changes to these critical accounting policies and estimates.

For the first quarter of 2017, we have the following additional critical accounting policy:

- Valuing of premiums under our and Akcea’s Novartis collaboration.

During the first quarter of 2017, we valued the premiums under the SPA agreement with Novartis. These premiums included the premium Novartis paid related to the $100 million purchase of our stock in the first quarter of 2017 and the premium we may receive related to Novartis’ potential purchase of our stock in the future. These valuations required us to use level 3 inputs, which we consider to be a critical accounting policy for our results in the first quarter of 2017.

For valuation purposes, 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; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions.

We determined the fair value of the premium we received and future premium we may receive by calculating the value based on the stated premium in the SPA. We also included a lack of marketability discount when we determined the fair value of the premiums because we initially issued unregistered shares as part of the $100 million purchase and we expect to issue unregistered shares to Novartis if they purchase our common stock in the future. Additionally, for the future potential stock purchase, we estimated the probability of an Akcea IPO. We concluded the following fair values:

- $28.4 million for the premium paid by Novartis for its purchase of our common stock in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis will pay if they purchase our common stock in the future at a premium.

See further discussion about our valuation of the potential premium in Note 4, *Fair Value Measurements*, in the Notes to the Consolidated Financial Statements.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2017 was $110.3 million, compared to $36.9 million for same period in 2016. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees.

Commercial Revenue

SPINRAZA Royalties

The first quarter of 2017 was the first full quarter in which we earned commercial revenue from SPINRAZA royalties. Commercial revenue from SPINRAZA royalties for the three months ended March 31, 2017 was $5.2 million.

Licensing and Other Royalty Revenue

Our revenue from licensing activities and other royalties for the three months ended March 31, 2017 was $3.5 million, compared to $1.7 million for 2016.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three months ended March 31, 2017 was $101.5 million, compared to $35.2 million for the same period in 2016. The change in our R&D revenue was primarily due to revenue from the license fee from Bayer and Akcea's new collaboration with Novartis. Our R&D revenue for the first three months of 2017 primarily consisted of the following:

- $65.5 million from Bayer primarily for the license of IONIS-FXI-L_{Rx};
- $5 million milestone payment from Biogen for validating an undisclosed neurological disease target;
- $25.3 million from the amortization of upfront fees; and
- $5.7 million primarily from services we performed for our partners.

Operating Expenses

Operating expenses for the three months ended March 31, 2017 were $96.3 million, and were essentially flat compared to $91.5 million for the same period in 2016. As this year progresses, we expect our operating expenses to remain flat. We anticipate R&D expenses to decrease as our Phase 3 programs wind down. We expect selling, general and administrative expenses to increase as Akcea continues prepare to launch volanesorsen. Because of the efficiency of our technology, even with our projected declining R&D expenses this year, we will continue to advance our earlier stage drugs and add new drugs to our pipeline.

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

	Three Months Ended March 31,	
	2017	**2016**
Ionis Core	$ 60,620	$ 58,600
Akcea Therapeutics	66,290	12,859
Elimination of intercompany activity	(51,507)	(36)
Subtotal	75,403	71,423
Non-cash compensation expense related to equity awards	20,912	20,103
Total operating expenses	$ 96,315	$ 91,526

In order 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, 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,	
	2017	**2016**
Research, development and patent expenses	$ 66,516	$ 66,194
Non-cash compensation expense related to equity awards	16,122	14,770
Total research, development and patent expenses	$ 82,638	$ 80,964

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

	Three Months Ended March 31,	
	2017	2016
Ionis Core	$ 54,829	$ 55,270
Akcea Therapeutics	63,194	10,960
Elimination of intercompany activity	(51,507)	(36)
Subtotal	66,516	66,194
Non-cash compensation expense related to equity awards	16,122	14,770
Total research, development and patent expenses	$ 82,638	$ 80,964

For the three months ended March 31, 2017, our total research, development and patent expenses were $66.5 million, and were flat, compared to $66.2 million for the same period in 2016. 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. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs and contribute to the advancement of the science by funding core antisense technology research.

Our antisense drug discovery expenses were as follows (in thousands) and are part of our Ionis Core business segment:

	Three Months Ended March 31,	
	2017	2016
Antisense drug discovery expenses	$ 12,598	$ 11,597
Non-cash compensation expense related to equity awards	3,963	3,496
Total antisense drug discovery expenses	$ 16,561	$ 15,093

Antisense drug discovery expenses for the three months ended March 31, 2017 were $12.6 million, and, were slightly higher, compared to $11.6 million for the same period in 2016. Expenses were higher because we conducted more research activities to support our partnerships during the three months ended March 31, 2017 compared to same period in 2016. 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,	
	2017	2016
SPINRAZA	$ 5,648	$ 9,402
Volanesorsen	4,259	5,414
IONIS-TTR$_{Rx}$	6,786	4,488
Other antisense development projects	10,417	9,884
Development overhead expenses	11,203	10,383
Total antisense drug development, excluding non-cash compensation expense related to equity awards	38,313	39,571
Non-cash compensation expense related to equity awards	7,012	6,088
Total antisense drug development expenses	$ 45,325	$ 45,659

Antisense drug development expenses were $38.3 million for the three months ended March 31, 2017, compared to $39.6 million for the same period in 2016. Expenses for the three months ended March 31, 2017 were slightly lower compared to the same period in 2016 primarily because we are winding down two of our Phase 3 programs. Specifically, we have transitioned all further development of SPINRAZA to Biogen and we are closing out our Phase 3 volanesorsen trial in patients with FCS. We are still conducting our Phase 3 trial of IONIS-TTR$_{Rx}$, with data expected in the second quarter of 2017, and Akcea is conducting a Phase 3 trial of volanesorsen in patients with FPL. 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,	
	2017	2016
Ionis Core	$ 27,711	$ 29,257
Akcea Therapeutics	58,996	10,314
Elimination of intercompany activity	(48,394)	—
Subtotal	38,313	39,571
Non-cash compensation expense related to equity awards	7,012	6,088
Total antisense drug development expenses	$ 45,325	$ 45,659

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.

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, our Akcea subsidiary 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,	
	2017	2016
Manufacturing and operations expenses	$ 8,805	$ 7,996
Non-cash compensation expense related to equity awards	1,705	1,602
Total manufacturing and operations expenses	$ 10,510	$ 9,598

Manufacturing and operations expenses were $8.8 million for the three months ended March 31, 2017, compared to $8.0 million for the same period in 2016. 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,	
	2017	2016
Ionis Core	$ 8,104	$ 7,690
Akcea Therapeutics	3,784	306
Elimination of intercompany activity	(3,083)	—
Subtotal	8,805	7,996
Non-cash compensation expense related to equity awards	1,705	1,602
Total manufacturing and operations expenses	$ 10,510	$ 9,598

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,	
	2017	2016
Personnel costs	$ 2,852	$ 2,244
Occupancy	1,878	1,852
Patent expenses	499	758
Depreciation and amortization	67	57
Insurance	346	339
Other	1,158	1,780
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	6,800	7,030
Non-cash compensation expense related to equity awards	3,442	3,584
Total R&D support expenses	$ 10,242	$ 10,614

R&D support expenses for the three months ended March 31, 2017 were $6.8 million, and were essentially flat compared to $7.0 million for the same period in 2016. 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,	
	2017	2016
Ionis Core	$ 6,416	$ 6,726
Akcea Therapeutics	414	340
Elimination of intercompany activity	(30)	(36)
Subtotal	6,800	7,030
Non-cash compensation expense related to equity awards	3,442	3,584
Total R&D support expenses	$ 10,242	$ 10,614

Selling, General and Administrative Expenses

Selling, general and administrative expenses include costs associated with the pre-commercialization and commercialization activities for our drugs and costs to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of pre-commercialization, 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 nominal fees we owe under our in-licensing agreements related to SPINRAZA in these costs.

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

	Three Months Ended March 31,	
	2017	2016
Selling, general and administrative expenses	$ 8,887	$ 5,229
Non-cash compensation expense related to equity awards	4,790	5,333
Total selling, general and administrative expenses	$ 13,677	$ 10,562

Selling, general and administrative expenses were $8.9 million for the three months ended March 31, 2017, and increased compared to $5.2 million for the same period in 2016 due to Akcea continuing to build out its organization. Expenses for Akcea will increase as it continues to prepare to launch volanesorsen. Also contributing to the increase were nominal fees we owe under our in-licensing agreements related to SPINRAZA. 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,	
	2017	2016
Ionis Core	$ 5,791	$ 3,330
Akcea Therapeutics	3,096	1,899
Non-cash compensation expense related to equity awards	4,790	5,333
Total selling, general and administrative expenses	$ 13,677	$ 10,562

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,	
	2017	2016
Development and patent expenses	$ 63,194	$ 10,960
General and administrative expenses	3,096	1,899
Total operating expenses, excluding non-cash compensation expense related to equity awards	66,290	12,859
Non-cash compensation expense related to equity awards	3,180	3,190
Total Akcea Therapeutics operating expenses	$ 69,470	$ 16,049

Operating expenses for Akcea were $66.3 million for the three months ended March 31, 2017, and increased compared to $12.9 million for the same period in 2016. $48.4 million of the increase in Akcea's development expenses was for one-time sublicensing expenses related to entering into the Novartis collaboration. $33.4 million of these expenses were non-cash. Akcea will pay the remaining $15 million of sublicensing expenses to us. For future payments received under the Novartis collaboration, Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee. Additionally, Akcea is continuing to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen. During the first quarter of 2017, Akcea reported positive results from its Phase 3 study of volanesorsen in patients with FCS. Akcea is preparing to file for marketing approval in the U.S., EU and Canada in the third quarter of 2017. 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. Additionally, for each period presented, we allocated a portion of Ionis' general and administrative expenses, which are included in general and administrative expenses in the table above, to Akcea for work we performed on Akcea's behalf. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three months ended March 31, 2017 was $2.3 million, compared to $1.5 million for 2016. The increase in investment income was primarily due to a higher average cash balance, a gain on the sale of our stock in Regulus Therapeutics and an improvement in the market conditions during the three months ended March 31, 2017 compared to same period in 2016.

Interest Expense

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 for our primary facility and other miscellaneous debt.

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

	Three Months Ended March 31,	
	2017	2016
Convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 7,902	$ 6,093
Interest expense payable in cash	1,715	1,671
Non-cash interest expense for long-term financing liability	1,675	1,672
Other	71	54
Total interest expense	$ 11,363	$ 9,490

Interest expense for the three months ended March 31, 2017 was $11.4 million and increased compared to $9.5 million for the same period in 2016. The increase was primarily non-cash expense.

Net Income (Loss) and Net Income (Loss) per Share

Net income for the three months ended March 31, 2017 was $3.5 million, compared to a net loss of $62.9 million for the same period in 2016. Basic and diluted net income per share for the three months ended March 31, 2017 was $0.03. Basic and diluted net loss per share was $0.52 for the same period in 2016. We had net income for the three months ended March 31, 2017 compared to a net loss for the same period in 2016 primarily due to increased R&D revenue and the addition of commercial revenue from SPINRAZA royalties. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have recently added commercial royalty revenue from SPINRAZA royalties. Additionally, we earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through March 31, 2017, we have earned approximately $2.2 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through March 31, 2017, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities, and we have borrowed approximately $1.3 billion under long-term debt arrangements to finance a portion of our operations.

At March 31, 2017, we had cash, cash equivalents and short-term investments of $860.3 million and stockholders' equity of $201.8 million. In comparison, we had cash, cash equivalents and short-term investments of $665.2 million and stockholders' equity of $99.6 million at December 31, 2016. Our cash, cash equivalents and short-term investments increased in the first quarter of 2017 primarily from the $175 million we received from our new collaboration with Novartis and the more than $100 million that we earned in late 2016 and received in 2017. Our first quarter cash balance did not include the $75 million from Bayer for expanding our collaboration, which we received in April 2017.

At March 31, 2017, we had consolidated working capital of $791.8 million compared to $664.1 million at December 31, 2016. Working capital increased in 2017 primarily due to the increase in our cash, cash equivalents and short-term investments as a result of the substantial payments we received from partners during the first quarter of 2017.

As of March 31, 2017, our debt and other obligations totaled $773.1 million compared to $774.1 million at December 31, 2016.

The following table summarizes our contractual obligations as of March 31, 2017. 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)	$ 720.0	$ 6.9	$ 13.9	$ 699.2	$ —
Financing arrangements	13.3	0.3	13.0	—	—
Facility rent payments	117.3	6.6	14.0	14.8	81.9
Other obligations (principal and interest payable)	1.2	0.1	0.1	0.1	0.9
Operating leases	23.5	2.3	3.8	3.0	14.4
Total	$ 875.3	$ 16.2	$ 44.8	$ 717.1	$ 97.2

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility leases, equipment financing arrangements and other obligations.

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, 2017, 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, 2017 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 Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed constructed our primary R&D facility in Carlsbad, California. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under this lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the facility. Accounting rules required us to record the cost of the facility as a fixed asset with a corresponding liability. We are depreciating the building over its economic life and we apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2017 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.

As part of Akcea's formation, we made an initial cash investment of $100 million in the company to fund Akcea's operations. In January 2017, we provided Akcea with a convertible line of credit for up to $150 million, and as of March 31, 2017 Akcea had borrowed $91 million. As Akcea continues to progress we may seek additional capital to fund Akcea's future operating needs. As such, we may pursue various financing alternatives, like issuing shares of Ionis' or Akcea's stock in private or public financings, issuing Ionis or Akcea debt instruments, or securing lines of credit. We may also consider entering into collaborations specific to Akcea's pipeline with partners to provide for additional operating cash. For example, in January 2017, we and Akcea initiated a collaboration with Novartis and we received $175 million in payments.

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, 2016.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

If the market does not accept our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, we are not likely to generate revenues or become consistently profitable.*

Even if our drugs are authorized for marketing, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$, and Kynamro, 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, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, unaffordable.

The degree of market acceptance for our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, 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, we expect the product label for volanesorsen and IONIS-TTR$_{Rx}$ will require periodic platelet monitoring, which could negatively affect our ability to attract and retain patients for these drugs. Additionally, in the clinical setting, some patients discontinued treatment with volanesorsen, including five patients who discontinued participation in the APPROACH study due to platelet count declines. While we believe Akcea can better maintain patients on volanesorsen through Akcea's patient-centric commercial approach where it plans to have greater involvement with physicians and patients, if Akcea cannot effectively maintain patients on volanesorsen, we may not be able to generate substantial revenue from volanesorsen sales.

If we or our partners fail to compete effectively, our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, 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, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, 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, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro.

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 and in obtaining FDA and other regulatory authorizations of 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 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, RG7800, RG7916, and LMI070 could compete with SPINRAZA and metreleptin could compete with volanesorsen, patisiran, tafamadis, diflunisal, tolcapone and ALN-TTRsc02 could compete with IONIS-TTR$_{Rx}$ and lomitapide and evolocumab could compete with Kynamro.

Following approval, our drugs, including SPINRAZA, volanesorsen and IONIS-TTR$_{Rx}$ could be subject to regulatory limitations. Kynamro is 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, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro.

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. For example Kynamro is subject to a Boxed Warning and is only available through a Risk Evaluation and Mitigation Strategy.

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, volanesorsen, IONIS-TTR_{Rx}, and Kynamro.

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 additional funding and SPINRAZA's development and commercialization may be harmed or delayed.

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

If government or other third-party payors fail to provide adequate coverage and payment rates for our drugs, including SPINRAZA, IONIS-TTR_{Rx}, volanesorsen and Kynamro, 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 patients 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 recent 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 volanesorsen, IONIS-TTR_{Rx}, and additional approvals for SPINRAZA and Kynamro, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including volanesorsen and IONIS-TTR_{Rx}, will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA or Kynamro will be approved in additional markets outside the United States 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, volanesorsen and IONIS-TTR$_{Rx}$ for marketing or additional marketing authorizations for SPINRAZA or Kynamro. 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, volanesorsen and IONIS-TTR$_{Rx}$, 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 volanesorsen in a sufficient number of patients to demonstrate volanesorsen is safe and effective in patients with FCS or FPL to support an application for marketing authorization, especially since a small number of patients in the APPROACH FCS study experienced severe thrombocytopenia, a condition where the patient has severely low platelet levels. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays.

Failure to receive marketing authorization for our drugs, volanesorsen and IONIS-TTR$_{Rx}$, or additional authorizations for SPINRAZA or Kynamro, 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 volanesorsen and IONIS-TTR$_{Rx}$. If any of our drugs in clinical studies, including volanesorsen and IONIS-TTR$_{Rx}$, 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 studies for volanesorsen and IONIS-TTR$_{Rx}$. 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;
- patients 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, volanesorsen, IONIS-TTR$_{Rx}$, and Kynamro, 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 volanesorsen in patients with FPL and an ongoing open label extension study of volanesorsen in patients with FCS. Adverse events or results from these studies could negatively impact our planned marketing approval applications for volanesorsen in patients with FCS or the commercial opportunity for volanesorsen.

Any failure or delay in the clinical studies, including the Phase 3 studies for volanesorsen and IONIS-TTR$_{Rx}$, 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. 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, volanesorsen and IONIS-TTR_{Rx}, or result in enforcement action after authorization that could limit the commercial success of our drugs, including SPINRAZA, volanesorsen, IONIS-TTR_{Rx} and Kynamro.

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 volanesorsen and IONIS-TTR_{Rx}. 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 volanesorsen and IONIS-TTR_{Rx} or additional authorizations for SPINRAZA and Kynamro.

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, 2017, we had an accumulated deficit of approximately $1.2 billion and stockholders' equity of approximately $201.8 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 revenue has come from collaborative arrangements, with additional revenue 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.

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. In the past, based on the disappointing results of Phase 3 clinical studies, we had a partner discontinue its investment in one of our drugs.

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 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, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro.

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 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, volanesorsen and IONIS-TTR$_{Rx}$ 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 of 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, 2017, we had cash, cash equivalents and short-term investments equal to $860.3 million. If we do not meet our goals to successfully commercialize our drugs, including SPINRAZA, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro, 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:

- marketing approvals and successful commercial launch for SPINRAZA;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs, including volanesorsen and IONIS-TTR$_{Rx}$.

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, 2017, the market price of our common stock ranged from $19.59 to $65.34 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, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro. 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, products 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 these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

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

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

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 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 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, volanesorsen, IONIS-TTR$_{Rx}$ and Kynamro 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.

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 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, 2017. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2017.

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 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 change 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 has 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. Gilead cross-appealed on the issue of validity. The appeal is pending before the Court of Appeals for the Federal Circuit. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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 Collaboration, Option and License Agreement, dated January 5, 2017, between Akcea Therapeutics, Inc. and Novartis Pharma AG. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.2	Stock Purchase Agreement, dated January 5, 2017, between Akcea Therapeutics, Inc., Ionis Pharmaceuticals, Inc. and Novartis Pharma AG.
10.3	Amendment #1 dated February 10, 2017 between the Registrant and Bayer AG. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
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, 2017, 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).

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 9, 2017
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 9, 2017

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

EXHIBIT 10.1

STRATEGIC COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

AKCEA THERAPEUTICS, INC.

AND

NOVARTIS PHARMA AG

STRATEGIC COLLABORATION, OPTION AND LICENSE AGREEMENT

This STRATEGIC COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 5th day of January, 2017 (the "***Execution Date***") by and between **AKCEA THERAPEUTICS, INC.**, a Delaware corporation, having its principal place of business at 55 Cambridge Parkway, Cambridge, MA 02142 USA, together with each of Akcea's Affiliates ("***Akcea***"), and**NOVARTIS PHARMA AG**, a company organized under the laws of Switzerland, having its principal place of business at Lichtstrasse 35, 4002 Basel, Switzerland ("***Novartis***"). Novartis and Akcea each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1. All attached appendices and schedules are a part of this Agreement. As of the Effective Date, Akcea is a wholly-owned subsidiary of Ionis Pharmaceuticals, Inc. ("***Ionis***") and therefore Akcea and Ionis are Affiliates.

RECITALS

WHEREAS, Akcea has rights to and is developing the novel cardio-metabolic lipid drugs, AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, based on Akcea's and Ionis' knowledge, experience and intellectual property rights to both antisense technology and to AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx};

WHEREAS, Akcea seeks a partner with sufficient expertise in developing and commercializing human therapies to enable the further global development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx};

WHEREAS, Novartis has expertise in globally researching, developing and commercializing human therapeutics and, in particular, cardio-metabolic lipid drugs;

WHEREAS, Novartis and Akcea desire to enter into a strategic collaboration in cardio-metabolic lipid diseases under which Akcea will continue to develop in human clinical trials AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} through the completion of a Phase 2 dose-ranging study;

WHEREAS, Novartis desires to receive from Akcea, and Akcea desires to grant to Novartis, an exclusive option to obtain an exclusive worldwide license under this Agreement to research, develop, manufacture and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} respectively;

WHEREAS, simultaneously with the execution of this Agreement, Novartis, Ionis and Akcea are entering into the Stock Purchase Agreement;

WHEREAS, following Novartis' exercise of its Option for a Product, Novartis will research, develop, manufacture and commercialize such Product globally in accordance with this Agreement; and

WHEREAS, Akcea will have the right to Co-Commercialize in Major Markets such Products licensed to Novartis.

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

ARTICLE 1.
PRE-OPTION DEVELOPMENT OF AKCEA-APO(A)-L_{RX} AND AKCEA-APOCIII-L_{RX}

1.1. **Overview**. The intent of the (A) pre-Option Exercise Collaboration is (i) for Akcea to develop AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} through the completion of a Phase 2 Dose-Ranging Trial, (ii) for Akcea to provide Novartis with API in quantities sufficient for Novartis to conduct the Pre-Option Novartis Activities prior to Option exercise, (iii) for Novartis to initiate, prior to Option exercise, a manufacturing plan to manufacture AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} to supply the Phase 3 Cardiovascular Outcomes Trial (or "***CVOT***") for each Product, which CVOT Novartis will conduct following Option exercise for each such Product, and (iv) to provide Novartis an exclusive option to obtain an exclusive license to develop, manufacture and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, which options are exercisable after the End of Phase 2b Meeting for each of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, and (B) following Novartis' exercise of its Option for a Product (y) for Novartis to develop, manufacture and commercialize such Product globally in accordance with this Agreement, and (z) to provide Akcea the right to Co-Commercialize in selected markets such Product licensed to Novartis on terms and conditions to be agreed upon between the Parties. Prior to Option Exercise, the Collaboration will be conducted under the Pre-Option Development Plan and managed and overseen by the Collaboration Steering Committee (CSC). The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. This Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} Pre-Option Responsibilities**. Akcea will use Commercially Reasonable Efforts to develop each of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} through the completion of a Phase 2 Dose-Ranging Trial in accordance with the Pre-Option Development Plan attached hereto as APPENDIX 2. Subject to Section 2.1.3(a), any material changes to the Pre-Option Development Plan must be mutually agreed to by the CSC.

1.2.1. **Akcea's Activities Prior to Option Exercise on a Product-by-Product Basis**. On a Product-by-Product basis, Akcea shall use Commercially Reasonable Efforts to (i) conduct the Akcea Activities under the Pre-Option Development Plan for such Product in accordance with the timelines specified therein and (ii) complete the other activities Akcea agreed to conduct under this ARTICLE 1, until the earlier of the date (x) Novartis exercises the applicable Option for such Product under this Agreement; *provided*, *however*, if Novartis exercises its Option before Akcea completes the Akcea Activities, Akcea will complete such remaining uncompleted Akcea Activities, (y) the Option Period has expired with respect to such Product, or (z) the Parties mutually agree that, for scientific, medical or other reasons, continuing to conduct the Akcea Activities under the Pre-Option Development Plan for such Product is futile. Without limiting the foregoing, Akcea may discontinue an activity under the Pre-Option Development Plan if after having consulted, and having given good faith consideration to the recommendations of the CSC, Akcea in good faith believes that continuing such activity would (A) pose an unacceptable risk or threat of harm in humans, or (B) violate any Applicable Law, ethical principles, or principles of scientific integrity. If there are additional activities Novartis wishes Akcea to conduct under the Pre-Option Development Plan, the Parties will discuss and mutually agree on any such additional activities through the CSC, and Akcea will use Commercially Reasonable Efforts to conduct such agreed activities under the Pre-Option Development Plan (and such plan will be updated accordingly).

1.2.2. **Novartis' Activities prior to Option Exercise on a Product-by-Product Basis**. Prior to the Option Exercise, Novartis shall use Commercially Reasonable Efforts to conduct at risk the Pre-Option Novartis Activities attached hereto as SCHEDULE 1.3.2 so as to enable timely initiation of the CVOT for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} upon exercise by Novartis of the Option for such Product.

1.2.3. **Delivery of the Draft Study Report and Final Study Report**. On a Product-by-Product basis, no later than [***] months before the anticipated Completion of the Phase 2 Dose-Ranging Trial, the Parties shall define and agree on the format and substantive content of the Draft Study Report and the Final Study Report in accordance with the ICH E3 industry guidelines for Structure and Content of Clinical Study Report. Notwithstanding the foregoing, it is understood and agreed that the Draft Study Report will include all [***], as well as all [***], [***] and [***] and any information related thereto, [***] and [***] generated from the [***] in sufficient detail so as to reasonably demonstrate whether [***] has been achieved in accordance with [***] and whether any [***] further development of a Product.

Following Completion of the Phase 2 Dose-Ranging Trial, Akcea will use Commercially Reasonable Efforts to complete the Draft Study Report and Akcea shall deliver to Novartis such Draft Study Report within [***] ([***]) calendar days after the date on which such Draft Study Report becomes available (but no later than [***] months following Completion of such study). For a period of [***] ([***]) calendar days from and after the delivery of such Draft Study Report, Novartis shall have the right to request from Akcea such additional information then in the possession of or readily available to Akcea as Novartis may reasonably require regarding the Phase 2 Dose-Ranging Trial, and Akcea shall promptly provide or make available to Novartis any such additional information.

Akcea will use Commercially Reasonable Efforts to complete the Final Study Report once Akcea has the data and other information necessary for such Final Study Report. Akcea shall deliver to Novartis such Final Study Report within [***] ([***]) calendar days after the date on which such Final Study Report is completed. For a period of [***] ([***]) calendar days from and after the delivery of such Final Study Report, Novartis shall have the right to request from Akcea such additional information then in the possession of or readily available to Akcea as Novartis may reasonably require regarding the Phase 2 Dose-Ranging Trial, and Akcea shall promptly provide or make available to Novartis any such additional information that Akcea has not previously delivered to Novartis. Furthermore, Akcea shall make available to Novartis through due diligence, information, data, and documents requested by Novartis in the possession of or readily available to Akcea generated between the Effective Date and the Final Study Report, relevant for Novartis.

1.2.4. **Delivery of the Phase 2 Dose-Ranging Trial Information Package**. As promptly as practicable following Completion of the Phase 2 Dose-Ranging Trial for a Product (but no later than [***] calendar days following Completion of such study), Akcea will deliver to Novartis the Phase 2 Dose-Ranging Trial Information Package. During the period beginning on the date Novartis receives such Phase 2 Dose-Ranging Trial Information Package until the Option Deadline (which period will in no event be less than [***] calendar days from the date Novartis receives such Phase 2 Dose-Ranging Trial Information Package), Novartis shall have the right to request from Akcea such additional information relating to the Phase 2 Dose-Ranging Trial then in the possession of or readily available to Akcea as Novartis may reasonably require in order to make a scientific, legal, regulatory and business evaluation of the Development and Commercialization potential of the applicable Product, and Akcea shall promptly (but no later than [***] calendar days after Akcea's receipt of such request) provide or make available to Novartis any such additional information.

For purposes of this Agreement, "***Phase 2 Dose-Ranging Trial Data Package***" means, with respect to a Product, [***] for the Phase 2 Dose-Ranging Trial, [***] any updates to the Appendices and Schedules attached to this Agreement since the Effective Date (such original Appendices and Schedules attached as of the Effective Date, the "***Original Akcea Schedules***" and such updated Appendices and Schedules, the "***Updated Akcea Schedules***"), which Updated Akcea Schedules will be redlined to reflect any changes to the Original Akcea Schedules since the Effective Date, and (iv) written confirmation that Akcea's representations, warranties and covenants under Section 9.1 and Section 9.2 are true, valid and accurate as of the anticipated date of exercise of the Option on a Product-by-Product basis (together with a disclosure schedule if Akcea determines it is necessary to list any qualifications to such representations, warranties or covenants in order to make such representations, warranties and covenants true, valid and accurate as of the anticipated date of exercise of the Option on a Product-by-Product basis).

1.2.5. **End of Phase 2b Meeting**. Prior to, but no later than [***] months before the anticipated Completion of the Phase 2 Dose-Ranging Trial for a Product, in preparation for the End of Phase 2b Meeting, Novartis will deliver to Akcea drafts of all documents Novartis reasonably determines are necessary for the End of Phase 2b Meeting, including, at a minimum, a draft [***] for the CVOT and the Cardiovascular Risk Reduction (or "***CVRR***") Indication Novartis will pursue for such Product, draft [***] and [***]. The Parties will update such draft documents after the primary endpoint and key safety data generated based on the database lock under the statistical analysis plan for such study are available and, within [***] ([***]) calendar days after Completion of the Phase 2 Dose-Ranging Trial for such Product, will promptly convene a special meeting of the CSC for the CSC to mutually agree on the final contents of all such documents prior to Akcea requesting an End of Phase 2b Meeting. If the CSC cannot agree on final versions of such documents within such [***] ([***]) calendar day period, then (i) [***] will have the final decision-making authority regarding the final contents of all such documents to the extent such contents relate to [***] or its Affiliate's[***], or any information pertaining to[***] or its Affiliate's other [***] (collectively, "***[***] Information***"), and (ii) [***] will have the final decision-making authority regarding the final contents of all such documents to the extent such contents do not relate to [***] Information, and each Party will make such final decisions within [***] calendar days. Once such documents are finalized, Akcea will use Commercially Reasonable Efforts to schedule and conduct an End of Phase 2b Meeting. Akcea will invite Novartis to participate in any key internal Akcea meetings Akcea holds to prepare and discuss strategy for the first End of Phase 2b Meeting for such Product. The Parties will mutually agree on a plan and strategy (including key messages) for the conduct of the End of Phase 2b Meeting that reflects Akcea's role as IND-holder for such Product and facilitates Novartis' active participation as the Party potentially responsible for conducting the CVOT and IND and MAA/NDA-Holder in the event of Option exercise. Akcea will invite Novartis representatives to attend the End of Phase 2b Meeting and such representatives will participate in such meeting under the direction of Akcea.

1.2.6. **Other Regulatory Interactions before Option Exercise**. Any interactions Akcea has or plans to have with a Regulatory Authority for a Product before Option Exercise (other than the End of Phase 2b Meeting under Section 1.2.5), including any meetings, correspondence and submissions, shall be the sole responsibility of Akcea. Subject to Section 2.1.3(a), Akcea shall present to the CSC for the CSC's review and comment, Akcea's material planned interactions and material submissions to Regulatory Authorities in Major Markets in accordance with the principles set forth in ARTICLE 2.

1.2.7. **Disclosure of Results**. Akcea will promptly disclose to Novartis through the CSC the results of all work performed by Akcea under the Pre-Option Development Plan (including activities under SCHEDULE 1.3.2) in a reasonable manner as such results are obtained. Akcea will provide reports and analyses at each CSC meeting detailing the current status of each Product under the Pre-Option Development Plan together with a summary of the data generated by Akcea under such plan. Furthermore, during the Option Period, Akcea shall promptly notify Novartis of, and promptly provide to Novartis, all data and/or information in the possession of or readily available to Akcea relating to a Product that Akcea generates before the end of the Option Period that would be relevant for Novartis' decision concerning the exercise of the Option, as well as any such data and information specifically requested by Novartis during the Option Period.

Novartis shall provide [***] on the [***] at each [***] together with a [***]or other [***] generated by [***] from conducting such [***]. If reasonably requested [***], Novartis shall [***] that Novartis has not previously [***] under this Agreement.

The results, reports, analyses and other information regarding the Products disclosed by one Party to the other Party pursuant hereto may be used only in accordance with the rights granted and other terms and conditions under this Agreement. Any reports required under this Section 1.2.7 may take the form of and be recorded in minutes of the CSC that will contain copies of any slides relating to the results and presented to the CSC.

1.3. Manufacturing and Supply.

1.3.1. Manufacturing and Supply during the Option Period.

(a) **Akcea Activities**. [***], Akcea is responsible for supplying API sufficient to support the (i) [***], (ii) the [***] and [***], and (iii) the [***] activities for each Product, in each case as set forth in the Pre-Option Development Plan.

(b) **Pre-Option Novartis Activities**. In support of the Pre-Option Novartis Activities, [***], Akcea will supply or cause to be supplied to Novartis during the Option Period, API in the quantities, at the [***], and on such other terms and conditions as set forth on SCHEDULE 1.3.1. In addition, at Novartis' reasonable written request [***] calendar days in advance of [***], Akcea shall [***] to allow Novartis to conduct, [***], an audit of Akcea's or its Affiliates' (including CMO) manufacturing facility where such API was made, [***] for Novartis to complete its vendor qualification activities for such API.

If, during the Option Period, Novartis notifies Akcea that [***], the Parties will [***] through the CSC [***].

1.3.2. Product Manufacturing Transition Strategy.

(a) ***Manufacturing Transition Strategy, Plan and Activities***. Within [***] days from the Effective Date, the Parties will discuss and mutually agree through the CSC, on an initial manufacturing technology transition strategy to transition API and Finished Drug Product Manufacturing for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} to [***] as the case may be.

(b) Within [***] calendar days from the Effective Date, Akcea shall deliver the first quantity of API in accordance with SCHEDULE 1.3.1.

Upon written notice from Novartis, Akcea shall transfer the relevant analytical methods [***] for the Pre-Option Novartis Activities pertaining to the first lot of API, and Akcea shall reasonably cooperate with and provide reasonable assistance to Novartis or its designee at mutually agreed times, through documentation, consultation, training and face-to-face meetings, [***] to facilitate the transfer of analytical methods and initiation of the Pre-Option Novartis Activities. Such cooperation and assistance shall be [***] for a period of [***] ([***]) calendar days following the date Akcea transfers the relevant analytical methods.

(c) Prior to Option Exercise, through the CSC, the Parties will agree on a final manufacturing technology transition plan, and, upon Novartis' notification to Akcea (such notice, the "***Manufacturing Tech Transfer Notice***") that Novartis is ready to commence the manufacturing technology transfer under such plan, Akcea will, at a mutually agreed date and time as soon as practicable after such notice, transfer [***] the Akcea Manufacturing and Analytical Know-How necessary to manufacture API and Finished Drug Product Manufacturing for AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx, including relevant analytical methods, API batch records and the CMC sections of the IND for each Product.

As reasonably requested by Novartis during the Option Period, Akcea shall reasonably cooperate with and provide reasonable assistance to Novartis or its designee at mutually agreed times, through documentation, consultation, training and face-to-face meetings, to enable Novartis [***] in an efficient and timely manner to proceed with the Pre-Option Novartis Activities and manufacturing transfer strategy contemplated under Section 1.3.1 and this Section 1.3.2. Regarding site visits, Akcea will host Novartis [***] personnel at Akcea's Affiliate's manufacturing facility in Carlsbad, CA for up to [***] Business Days and at Akcea's designated CMO(s) for up to [***] Business Days, and Akcea's or its Affiliate's personnel will visit Novartis' [***] manufacturing facility for up to [***] Business Days. Such cooperation and assistance shall be [***] for a period of [***] ([***]) calendar days following the date Akcea initiates the manufacturing technology transfer.

Akcea shall assist Novartis with such manufacturing transition strategy and provide technical support to Novartis [***] reasonably sufficient to successfully implement the transfer strategy and enable manufacturing processes for such API and Finished Drug Product for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} [***].

Once every [***] during the Option Period at each CSC meeting, Novartis will provide progress updates regarding the progress of Novartis' activities under such plan and Akcea will provide a progress update regarding Akcea's activities to support such transfer strategy. Each Party's CMC teams will participate in such CSC meetings to discuss such progress updates. Beginning on the Effective Date, Novartis shall use Commercially Reasonable Efforts to conduct or have conducted the Pre-Option Novartis Activities under SCHEDULE 1.3.2 to ensure that such API and Finished Drug Product is manufactured and ready for use on time for the planned initiation of the CVOTs. As the development of AKCEA-APOCIII-L_{Rx} progresses, Novartis will update SCHEDULE 1.3.2 to include API and Finished Drug Product manufacturing activities to support the CVOT and Commercialization for AKCEA-APOCIII-L_{Rx}. Akcea shall support the manufacturing transition strategy for those activities listed in SCHEDULE 1.3.2 for which Akcea is responsible.

(d) ***Novartis' CMO Agreements***. In furtherance of such plan, the Parties agree that Novartis may enter into contractual arrangements (each, a "***CMO Agreement***") with one or more CMOs to manufacture clinical supplies for Phase 3 Trials and commercial supply of API and Finished Drug Product. Novartis will [***] executing such CMO Agreement. Novartis will have final decision-making authority with regard to the [***] and the [***]. In any such CMO Agreement, Novartis shall use Commercially Reasonable Efforts to include the [***] if this Agreement terminates with respect to a given Product or the Option for a given Product terminates or expires unexercised.

(e) ***Manufacturing License Grant to Novartis during the Option Period***. Subject to the terms and conditions of this Agreement, Akcea hereby grants Novartis, a worldwide, non-exclusive, sublicensable (but only by Novartis to a Novartis Affiliate or a CMO), royalty-free license under the Licensed Technology solely to conduct during the Option Period the manufacturing and manufacturing transition activities contemplated by this Section 1.3.2 to manufacture API and Finished Drug Product for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}.

(f) ***Manufacturing Transition Activities Costs***. Akcea's technology transfer activities under this Section 1.3.2 will be [***] until the [***] calendar day after the date Akcea initiates the manufacturing technology transfer. Thereafter, any technology transfer activities Akcea agrees to conduct will be under a mutually agreed scope of work (such agreement not to be unreasonably withheld, delayed or conditioned) and, after the [***] under such scope of work, [***] for any such technology transfer activities conducted by Akcea and its Affiliates.

1.3.3. After Option Exercise.

(a) Within [***] calendar days after Option Exercise for a Product, Akcea will provide Novartis with an inventory of any API, Finished Drug Product and packaged Clinical Study material for such Product in Akcea's possession (together with the price Akcea was charged by Ionis ([***] for such material). If, within [***] calendar days after Novartis' receipt of such inventory list, Novartis delivers a written request to Akcea to purchase any such material, then Akcea will sell such material to Novartis [***] ([***]) for such material calculated [***]. Promptly after Akcea receives such order from Novartis, Akcea will ship such material to Novartis and Novartis will pay Akcea within [***] ([***]) calendar days after Novartis' receipt of such material.

(b) If requested by Novartis and mutually agreed by Akcea (such agreement not to be unreasonably withheld, delayed or conditioned), after Option Exercise, Akcea shall continue to provide the manufacturing transition assistance with respect to any activities contemplated by Section 1.3.2 that were not completed during the Option Period. Novartis will compensate Akcea in accordance with Section 7.10 for Akcea's and its Affiliates' activities conducted under this Section 1.3.3(b).

(c) If, after Option Exercise, Novartis notifies Akcea that Novartis wishes to acquire additional API, the Parties will discuss in good faith and endeavor to mutually agree through the JDCC on the quantity and timelines for the supply of any such additional API on terms and conditions as set forth in SCHEDULE 1.3.1. If required, the Parties shall negotiate in good faith the terms and conditions of a Supply and Quality Agreement.

ARTICLE 2.
COLLABORATION MANAGEMENT AND COSTS

2.1. Development Management.

2.1.1. Collaboration Steering Committee during the Option Period. The Parties will establish a Collaboration Steering Committee ("***CSC***") initially comprising the individuals from each Party as set forth on SCHEDULE 2.1.1 with the powers, roles and responsibilities set forth in this Section 2.1.1 to provide strategic oversight for the Collaboration during the Option Period. The CSC will consist of three representatives appointed by Akcea and three representatives appointed by Novartis (which may include representative(s) from each Party's Affiliates), and each CSC member will be a senior executive of such Party (or its Affiliate). The CSC will be chaired by Akcea. The CSC will determine the CSC operating procedures at its first meeting, including the CSC's policies for replacing CSC members, policies for participation by additional representatives or consultants invited to attend CSC meetings, and the location of meetings, which will be codified in the written minutes of the first CSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending CSC meetings.

(a) **Role of the CSC**. Without limiting any of the foregoing, subject to Section 2.1.3, the CSC will perform the following functions, some or all of which may be addressed directly at any given CSC meeting:

(i) approve material amendments to the Pre-Option Development Plan, including approving any additional costs associated with any approved changes to the Akcea Activities;

(ii) review the Phase 2 Dose-Ranging Trial protocol;

(iii) discuss any additional activities Novartis wishes Akcea to conduct under the Pre-Option Development Plan as contemplated by Section 1.2.1;

(iv) mutually agree on the final contents of all documents for the End of Phase 2b Meeting as contemplated by Section 1.2.5;

(v) review Akcea's material planned interactions and material submissions to Regulatory Authorities in Major Markets as contemplated by Section 1.2.6;

(vi) review reports and analyses provided by Akcea detailing the current status of each Product under the Pre-Option Development Plan (including any summary of the data generated by Akcea under such plan) as contemplated by Section 1.2.7;

(vii) review updates provided by Novartis on the Pre-Option Novartis Activities (including a summary of relevant data or other information generated by Novartis from conducting such activities) as contemplated by Section 1.2.7;

(viii) discuss and mutually agree on a manufacturing technology transition strategy to transition API and Finished Drug Product Manufacturing for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} to Novartis' own manufacturing site or to Third Party CMOs as the case may be, as contemplated by Section 1.3.2;

(ix) review progress updates of the Parties' activities under such manufacturing technology transfer plan as contemplated by Section 1.3.2(b);

(x) assist with and participate in the resolution of pre-Option Exercise disputes that may arise during the Option Period; and

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

(b) **Obligation to Participate in the CSC**. Akcea's obligation to participate in the CSC will terminate upon Novartis' exercise (or expiration) of the Option for the last Product.

2.1.2. **Joint Development and Commercialization Committee After Option Exercise**. Within [***] ([***]) calendar days after the first Option Exercise for a Product, the Parties will establish a joint development and commercialization committee ("***JDCC***") to supervise the activities under the Strategic Plan related to such Product. The JDCC will consist of three representatives appointed by Akcea and three representatives appointed by Novartis (which may include representative(s) from each Party's Affiliates). Each JDCC member will be a senior clinical development or commercial leader, and at least one of each Party's members will have operational responsibility for such Party's respective activities under the Strategic Plan. The JDCC shall be chaired by Novartis. The chair will be responsible for overseeing the activities of the JDCC consistent with the responsibilities set forth below in this Section 2.1.2. The JDCC will determine its operating procedures at its first meeting, including the JDCC's policies for replacement of JDCC members, policies for participation by additional representatives or consultants invited to attend JDCC meetings, and the location of meetings, which will be codified in the written minutes of the first JDCC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JDCC meetings.

(a) **Role of the JDCC**. Without limiting any of the foregoing, subject to Section 2.1.3, the JDCC will perform the following functions, some or all of which may be addressed directly at any given JDCC meeting:

(i) Supervise the activities under the Strategic Plan, including reviewing updates to the key elements of the planning and strategy to support Development, Manufacturing, Regulatory Approvals and Commercialization;

(ii) establish teams, committees and working groups to oversee and manage activities under the Strategic Plan;

(iii) receive updates from Novartis regarding any CMO Agreements and strategic sublicenses granted by Novartis to Third Parties in Major Markets as contemplated by Section 5.2.1;

(iv) if regulatory or Development issues arise that are outside of Novartis' reasonable control that impede achievement of any Specific Performance Milestone Event on the stated timeline, discuss in good faith and revise the date by which the applicable Specific Performance Milestone Event will be or can be achieved as contemplated by Section 6.4.2;

(v) assisting with and participating in the resolution of disputes as contemplated in Section 13.1; and

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

2.1.3. Decision Making.

(a) **CSC Decision Making – During the Option Period**. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the CSC regarding the conduct of the Akcea Activities and the Pre-Option Novartis Activities. The CSC will endeavor to reach consensus on all decisions to be made by the CSC, *however*, if the CSC cannot unanimously agree on a matter to be decided by the CSC then (i) Akcea will have the final decision-making authority regarding the [***] and (ii) Novartis will have the final decision-making authority regarding the [***] and the [***]; *provided*, *however*, that such decision-making authority does not permit Novartis to [***].

(b) **JDCC Decision Making – After Option Exercise**. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the JDCC regarding any matters to be considered by the JDCC. The JDCC will endeavor to reach consensus on all decisions to be made by the JDCC, *however*, if the JDCC cannot unanimously agree on a matter to be decided by the JDCC then Novartis will have the final decision-making authority regarding any such decisions to be made by the JDCC; *provided, however*, that such decision-making authority does not permit Novartis to [***].

2.1.4. Obligation to Participate in the JDCC. Akcea's obligation to participate in the JDCC will terminate upon Novartis' exercise (or expiration) of the Option for the last Product. Thereafter, Akcea will have the right, but not the obligation, to participate on the JDCC upon Akcea's request *provided that*, if requested in writing by Novartis, Akcea shall not unreasonably refuse to participate in JDCC meeting(s).

2.2. Alliance Managers. Each Party shall appoint a representative to act as its alliance manager under this Agreement (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the CSC and the JDCC, and performing the activities listed in Schedule 2.2.

2.3. Collaboration Costs.

2.3.1. Novartis and Akcea will [***] the costs associated with the [***] and [***] under the Pre-Option Development Plan, which [***] Akcea estimates will cost US$[***] for [***]. Novartis will pay Akcea US$[***] for such [***] and [***] as follows:

(i) US$[***] payment upon [***] for the [***] and [***] (expected in [***] but no earlier than the [***]);

(ii) US$[***] payment upon the [***] in each of the [***] and [***] (expected in [***]); and

(iii) US$[***] payment upon the later of (x) [***] and [***], and (y) [***],

provided, in each case Novartis will pay the amounts under (i), (ii) and (iii) within [***] ([***]) calendar days from the date such invoice is received by Novartis (and Akcea will include with each such invoice [***] and [***]). In no event will [***] US$[***] for such [***] and [***].

2.3.2. Except as otherwise expressly provided in this Agreement, Akcea will be responsible for all costs associated with the Akcea Activities under the Pre-Option Development Plan and the activities Akcea agrees to conduct under ARTICLE 1, and Novartis will be responsible for all costs associated with any Pre-Option Novartis Activities and the activities Novartis agreed to conduct under ARTICLE 1.

2.3.3. If a Regulatory Authority requires any changes to the Akcea Activities during the Option Period, then the Parties will discuss such changes in good faith through the CSC. If the CSC cannot mutually agree on whether to implement such a change to the Akcea Activities, then Akcea will have the final decision-making authority regarding [***] and each Party will only be responsible for paying the additional cost of such changes to the extent [***]. If Novartis requests any changes to the Akcea Activities that are not required by a Regulatory Authority and Akcea agrees (through the CSC) to implement such changes, then Novartis will pay Akcea for the additional cost in accordance with Section 7.10 and Akcea and Novartis will update APPENDIX 2 with any such revised activities.

ARTICLE 3.
EXCLUSIVE OPTIONS

3.1. **Option Grants**. Subject to the terms and conditions of this Agreement, on a Product-by-Product basis, Akcea hereby grants to Novartis an exclusive option to obtain the license set forth in Section 5.1.1 or Section 5.1.2 (as applicable) with respect to such Product (each, an "***Option***").

3.2. **Option Fee**. In consideration of the Options granted to Novartis hereunder, Novartis shall pay to Akcea upon execution by the Parties of this Agreement a one-time payment of seventy-five million dollars (US$75,000,000) (the "***Upfront Option Fee***"). Such payment shall be payable within [***] ([***]) Business Days after receipt by Novartis of an original invoice from Akcea for such amount and in the form attached hereto as Exhibit X, which original invoice shall be issued no earlier than the Effective Date.

3.3. Option Exercise.

3.3.1. Subject to Section 3.4 below, on a Product-by-Product basis, each Option for a Product will be exercisable by Novartis at its sole discretion on or before (each an "***Option Deadline***") 5:00 pm (Eastern Time) on the 60th calendar day after the later of:

(a) Novartis' receipt of the Phase 2 Dose-Ranging Trial Data Package for such Product; and

(b) the End of Phase 2b Meeting for such Product.

3.3.2. If, by the Option Deadline, Novartis (i) notifies Akcea in writing that it wishes to exercise the applicable Option, and (ii) undertakes to pay Akcea the license fee set forth in Section 7.1 or Section 7.2 (as applicable), Akcea will grant to Novartis the license as set forth in Section 5.1.1 or Section 5.1.2 (as applicable) (on a Product-by-Product basis, an "***Option Exercise***"). Such payment set forth in Section 7.1 or Section 7.2 (as applicable) is due within [***] ([***]) Business Days after receipt by Novartis of an original invoice from Akcea for such amount and in the form attached hereto as Exhibit X, which invoice shall be issued no earlier than the date on which Novartis notifies Akcea in writing that it wishes to exercise the applicable Option. If, by the Option Deadline, Novartis has not both (y) provided Akcea a written notice stating that Novartis is exercising its Option, and (z) undertaken to pay Akcea the license fee in accordance with Section 7.1 or Section 7.2 (as applicable), then (A) Novartis' Option for the applicable Product will expire, (B) Novartis will promptly deliver to Akcea all data, results and information (including Novartis' Confidential Information for as long as pertaining to the Product and any regulatory documentation (including drafts)) related to the Pre-Option Novartis Activities for such Product in the possession of Novartis and its contractors, and (C) this Agreement will be deemed terminated under Section 11.2.1 with respect to such Product and the provisions of Section 11.3 will apply.

3.4. HSR Filing. If Novartis notifies Akcea within [***] ([***]) calendar days following the applicable End of Phase 2b Meeting for the Product that an HSR Filing is required for Novartis to receive the license under Section 5.1.1 or Section 5.1.2 (as applicable), each of Novartis and Akcea will, within [***] ([***]) calendar days after such notice from Novartis (or such later time as may be agreed to in writing by the Parties), file with the United States Federal Trade Commission ("***FTC***") and the Antitrust Division of the United States Department of Justice ("***DOJ***"), any HSR Filing required with respect to the transactions contemplated hereby, Novartis shall not exercise any Option under Section 3.3 until any applicable waiting period (and any extension thereof) under the HSR Act shall have expired or been terminated and the Option Deadline shall expire no sooner than [***] ([***]) calendar days after any waiting period (and any extensions thereof) under the HSR Act shall have expired or been terminated. The Parties will cooperate with one another to the extent necessary in the preparation of any such HSR Filing and each Party will request in their respective HSR Filing early termination of the waiting period under the HSR Act. Each Party will be responsible for its own costs and expenses associated with any HSR Filing.

3.5. **HSR Clearance**. In connection with obtaining such HSR Clearance from the FTC, the DOJ or any other governmental authority for an HSR Filing filed under Section 3.4, Akcea and Novartis will use their respective Commercially Reasonable Efforts to resolve as promptly as practicable any objections that may be asserted with respect to this Agreement or the transactions contemplated by this Agreement under any antitrust, competition or trade regulatory law.

3.6. **Conditions to Novartis' Obligations under this Agreement**. Novartis' obligation to complete the transactions contemplated in this Agreement is subject to the fulfillment or waiver of the following conditions:

3.6.1. **[***]**. From and after the Execution Date and until the Effective Date, there shall have occurred [***]; and

3.6.2. **[***]**. Akcea shall have duly executed and delivered to Novartis the [***].

3.7. **Mutual Conditions to Each Party's Obligations under this Agreement**. The obligations of Novartis on the one hand, and Ionis and Akcea (as applicable) on the other hand, to consummate the transactions contemplated under this Agreement is subject to the fulfillment or waiver of the following conditions:

3.7.1. **HSR Act Qualification; Initial Stock Purchase**. The filings required under the HSR Act in connection with the Stock Purchase Agreement shall have been made and the required waiting period shall have expired or been terminated and the Initial Closing (as defined in the Stock Purchase Agreement) under the Stock Purchase Agreement shall have occurred; and

3.7.2. **Absence of Litigation**. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or delay the occurrence of the Effective Date or the Initial Closing (as defined in the Stock Purchase Agreement), will have been instituted or be pending before any court, arbitrator, governmental body, agency or official.

ARTICLE 4.
EXCLUSIVITY COVENANTS

4.1. **Exclusivity Covenants**. The Parties agree as set forth below to certain exclusivity covenants with respect to each Product and Exclusive Target.

4.1.1. **Akcea's Exclusivity Covenants**. On a Product-by-Product and Exclusive Target-by-Exclusive Target basis, Akcea and its Affiliates will not (independently or with a Third Party):

(a) **During the Option Period**. During the Option Period, grant any license or other right to a Third Party that would diminish Novartis' rights under Section 3.1 or Section 5.1.1 or Section 5.1.2 (as applicable) or otherwise under this Agreement.

Furthermore, for [***] ([***]) months following the Effective Date, unless required to perform its obligations under this Agreement, neither Akcea nor any of its Affiliates shall (independently or with or through any Third Party) solicit, initiate, seek, encourage or support any inquiry, proposal or offer from, furnish any information to, or participate in any discussions or negotiations with any Third Party with respect to any licensing, acquisition or any collaboration or joint venture relating to the research, development or commercialization of any Product.

(b) **After the Option Period**. After the Option Period, [***], for a period of [***] months after the [***] of such Product [***].

4.1.2. **Novartis' Exclusivity Covenants**. On a Product-by-Product and Exclusive Target-by-Exclusive Target basis, Novartis and its Affiliates will not (independently or with a Third Party):

(a) **During the Option Period**. During the Option Period, [***]; and

(b) **After the Option Period**. After the Option Period, [***], for a period of [***] months after the [***] of such Product [***].

4.2. **Limitations and Exceptions to the Parties' Exclusivity Covenants**. Notwithstanding anything to the contrary in Section 4.1.1, the Parties and their Affiliates may perform the following activities:

(i) With regard to the Parties and their Affiliates:

(1) all activities permitted or contemplated under this Agreement, including those contained in Section 4.3 and Section 6.5; and

(2) the practice of any Jointly-Owned Program Technology, including granting a license to a Third Party under any Jointly-Owned Program Technology.

(ii) With regard to Akcea and its Affiliates:

(1) Any activities pursuant to the Prior Agreements;

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

(3) The research, Development, Manufacture or Commercialization of Volanesorsen on its own or with a Third Party.

4.3. **Competitive Oligo Transactions**. The Parties acknowledge that after the Effective Date a Party or its Affiliate may acquire (including through any merger or business combination) or be acquired by a Third Party. In the case of such a transaction where such Third Party is Developing or Commercializing a Competitive Oligo that would violate Section 4.1.1 or 4.1.2, notwithstanding anything to the contrary in this Agreement:

4.3.1. ***Akcea or its Affiliate Acquires or is Acquired by a Third Party***. On a Product-by-Product basis and after Novartis exercises its Option for such Product, for a period of [***] months after the [***] of such Product for the same Exclusive Target as such Competitive Oligo, if Akcea or its Affiliate acquires or is acquired by a Third Party with a Competitive Oligo, then within [***] months after such acquisition, Akcea (or its Affiliate) and such Third Party must either (i) [***] such Competitive Oligo, or (ii) not [***] (or, if such Competitive Oligo is already being [***], will stop [***] within [***] months) such Competitive Oligo. Any such transaction that occurs during the Option Period is [***] until such time as Novartis exercises its Option for the applicable Product for the same Exclusive Target as such Competitive Oligo, at which time [***].

4.3.2. ***Novartis or its Affiliate Acquires or is Acquired by a Third Party***. On a Product-by-Product basis and after Novartis exercises its Option for such Product, for a period of [***] months after the [***] of such Product for the same Exclusive Target as such Competitive Oligo, if Novartis or its Affiliate acquires or is acquired by a Third Party with a Competitive Oligo, then within [***] months after such acquisition, Novartis (or its Affiliate) and such Third Party must either (i) [***] such Competitive Oligo, or (ii) not [***] (or, if such Competitive Oligo is already being [***], will stop [***] within [***] months) such Competitive Oligo. Any such transaction that occurs during the Option Period is [***] until such time as Novartis exercises its Option for the applicable Product for the same Exclusive Target as such Competitive Oligo, at which time [***].

4.4. **Effect of Exclusivity on Indications**. Akcea and Novartis are subject to certain restrictive covenants under Section 4.1.1 or Section 4.1.2; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to research, Develop and Commercialize any therapeutic compound that is designed to directly modulate a gene that is *not* an Exclusive Target for any Indication, even if such therapeutic compound is designed to treat the same disease or condition as a Product.

ARTICLE 5.
LICENSE GRANTS; TECHNOLOGY TRANSFER AND SUPPORT

5.1. License Grants to Novartis.

5.1.1. AKCEA-APO(a)-L_{Rx} Development, Manufacture and Commercialization License. Subject to the terms and conditions of this Agreement, upon Novartis' exercise of the Option for AKCEA-APO(a)-L_{Rx} in accordance with ARTICLE 3 and Novartis' payment of the license fee under Section 7.1, Akcea grants to Novartis a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 5.2) license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured and Commercialize AKCEA-APO(a)-L_{Rx}.

5.1.2. AKCEA-APOCIII-L_{Rx} Development, Manufacture and Commercialization License. Subject to the terms and conditions of this Agreement, upon Novartis' exercise of the Option for AKCEA-APOCIII-L_{Rx} in accordance with ARTICLE 3 and Novartis' payment of the license fee under Section 7.2, Akcea grants to Novartis a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 5.2) license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured and Commercialize AKCEA-APOCIII-L_{Rx}.

5.2. Sublicense Rights. Novartis will have the right to grant sublicenses under the licenses granted to Novartis in Section 5.1 as expressly permitted by this Section 5.2.

5.2.1. Right to Grant Sublicenses. Novartis acknowledges that the licenses under Section 5.1 are personal to Novartis. Notwithstanding anything to the contrary, Novartis will have the right to grant sublicenses under the licenses granted under Section 5.1.1 and Section 5.1.2 above:

(i) under the Licensed Technology to an Affiliate of Novartis to Develop, Manufacture, have Manufactured and Commercialize or have Commercialized a Product; or

(ii) under the Licensed Technology to a Third Party contracted by Novartis or its Affiliate to further Develop and Commercialize a Product if any such arrangement between Novartis and such [***] is [***] the license (and collaboration) agreements Novartis enters into for [***]; or

(iii) under the Licensed Technology solely to a Third Party (including a [***]) with [***] (which [***], if required, will not be unreasonably withheld, conditioned or delayed) under the Akcea Manufacturing and Analytical Patents and Akcea Manufacturing and Analytical Know-How, in each case solely to Manufacture API or Products in a manufacturing facility owned or operated by such Third Party; or

(iv) in all other cases with Akcea's prior written consent (which consent will not be unreasonably withheld, conditioned or delayed), under the Licensed Technology to a Third Party solely to further Manufacture, Develop and Commercialize a Product;

provided that each such sublicense will contain terms and conditions consistent with the terms and conditions of this Agreement. Upon Akcea's request, Novartis will provide updates at JDCC meetings regarding CMOs and strategic sublicenses to Third Party(ies) granted by Novartis in Major Markets (which update will include the name of the Sublicensee and the material terms of the sublicense).

5.2.2. **Enforcement of Sublicense Agreements**. If, within [***] ([***]) calendar days after first learning of a material breach of the terms of any such sublicense agreement, Novartis does not take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 5.2, which failure could cause a material adverse effect on Akcea, Novartis hereby grants Akcea the right to enforce such sublicense terms on Novartis' behalf and will cooperate with and support Akcea (which cooperation will be at Novartis' sole expense and will include, Novartis joining any action before a court or administrative body filed by Akcea against such Sublicensee if and to the extent necessary for Akcea to have legal standing before such court or administrative body) in connection with enforcing such terms.

5.2.3. **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Akcea with respect to the rights sublicensed to the Sublicensee by Novartis; *so long as* (i) 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 Novartis, and (ii) such Sublicensee agrees to pay directly to Akcea such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Novartis. Upon Akcea's written request after such termination of this Agreement, Novartis will use Commercially Reasonable Efforts to deliver to Akcea within [***] calendar days a copy of any such sublicense with such Sublicensee (*provided that* Novartis may redact any information in such sublicense that does not relate to the Product or Products).

5.3. **Consequence of Natural Expiration of this Agreement**. If this Agreement naturally expires in accordance with Section 11.1, then with respect to any Product that is the subject of such expiration for which Novartis has a license under Section 5.1 at such time, Akcea grants to Novartis a perpetual, non-exclusive, worldwide, royalty-free license under [***] and the [***] to Research, Develop, Manufacture, have Manufactured and Commercialize such Product.

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

5.5. **License Conditions; Limitations**. Subject to Section 7.9, the licenses granted under Section 5.1.1 and Section 5.1.2 and the sublicense rights under Section 5.2 are subject to and limited by (i) the Prior Agreements, (ii) the Akcea In-License Agreements, in each case to the extent such agreements are disclosed to Novartis prior to the date Novartis exercises the applicable Option with respect to AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx} (as applicable), and (iii) Akcea's Co-Commercialization right to be agreed upon as contemplated in Section 6.5.

5.6. **Trademark and Domain Names**.

5.6.1. Novartis will be solely responsible for selecting, registering and maintaining the Trademarks used to Commercialize Products. Novartis will own and control the Trademarks and pay all relevant costs related thereto.

5.6.2. So long as Novartis Commercializes a Product under this Agreement, only Novartis will be authorized to initiate at its own discretion legal proceedings against any infringement or threatened infringement of the Trademarks for such Product.

5.6.3. Novartis will be responsible for registering, hosting, maintaining and defending the Domain Names under all generic Top Level Domains (gTLDs) and under all relevant country code Top Level Domains (ccTLD). For the avoidance of doubt, and subject to the terms of Section 11.3.4 for any Transition Services, Novartis may register such Domain Names in its own name, to host on its own servers, maintain and defend the Domain Names and use them for websites.

5.7. **Technology and Information Transfer**. On a Product-by-Product basis, within [***] ([***]) calendar days after Akcea grants Novartis the license for such Product under Section 5.1, Akcea will deliver to Novartis the following Licensed Know-How pursuant to a technology transfer plan to be mutually agreed by Akcea and Novartis:

5.7.1. **Licensed Know-How - Generally**. Copies of Licensed Know-How (other than the Akcea Manufacturing and Analytical Know-How) in Akcea's possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 5.1.1 or Section 5.1.2, as the case may be, to Novartis, which includes transferring to Novartis the applicable IND and delivering copies of information included in such IND and the data from the Phase 1 Trials and Phase 2 Trials conducted by Akcea, together with all regulatory documentation.

5.7.2. **Akcea Manufacturing and Analytical Know-How**. Solely for use by Novartis, its Affiliates or a Third Party as permitted under Section 5.2, copies of the Akcea Manufacturing and Analytical Know-How relating to Products in Akcea's possession that has not previously been provided hereunder, which is necessary for Novartis, its Affiliates or a Third Party to exercise the Manufacturing rights granted under Section 5.1.1 or Section 5.1.2, as the case may be.

5.7.3. **Akcea Assistance**. If requested by Novartis, Akcea will provide Novartis with a timely and reasonable level of assistance in connection with such Licensed Know-How under Section 5.7.1 and Section 5.7.2. Novartis will compensate Akcea in accordance with Section 7.10 for Akcea's and its Affiliates' activities conducted under Section 5.7.1 and Section 5.7.2.

5.8. **Cross-Licenses under Program Technology**.

5.8.1. **Enabling Patent License from Novartis to Akcea**. Subject to the terms and conditions of this Agreement (including Akcea's exclusivity obligations under Section 4.1.1 and without limiting the license(s) granted to Novartis under Section 5.1), Novartis hereby grants Akcea a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable license under any Novartis Program Technology (excluding any Product-Specific Patents) to research, Develop, manufacture, have manufactured and Commercialize products that include an [***] as an active pharmaceutical ingredient (other than a Product that is being Developed or Commercialized by Novartis, its Affiliates or Sublicensees under this Agreement).

5.8.2. **Enabling Patent License from Akcea to Novartis**. Subject to the terms and conditions of this Agreement (including Novartis' exclusivity obligations under Section 4.1.2 and without limiting the license(s) granted to Novartis under Section 5.1), Akcea hereby grants Novartis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable license under any Akcea Program Technology (excluding any Product-Specific Patents) to research, Develop, manufacture, have manufactured and Commercialize products that do not include an Oligonucleotide as an active pharmaceutical ingredient; *provided*, *however*, if Novartis delivers a written request to Akcea for the right to expand the license under this Section 5.8.2 to include the right to research, Develop, manufacture, have manufactured and Commercialize products that include [***] as an active pharmaceutical ingredient for a particular [***], Akcea will not unreasonably refuse to grant such a request and, if such request is refused by Akcea, Akcea will deliver to Novartis [***] confirming that [***] such request.

ARTICLE 6.
NOVARTIS' OBLIGATONS AFTER OPTION EXERCISE

6.1. **The Strategic Plan for Licensed Product(s)**. Subject to and in accordance with the terms of this Agreement, for each Product licensed to Novartis under Section 5.1, Novartis will use Commercially Reasonable Efforts to Develop and Commercialize such Product in accordance with a global strategic development and commercialization plan to be defined by Novartis (the "***Strategic Plan***").

The Strategic Plan will cover both the long-term global strategy for each Product and, on a rolling [***]-month basis, the more detailed activities Novartis will perform over the course of the next [***] months, including overview and timing of the CVOT Novartis will conduct for the CVRR Indication Novartis will pursue for each Product.

As determined by [***], the activities and strategy in the Strategic Plan will be driven by emerging data, the shifting competitive landscape over time, and scientific, reimbursement environment, and medical factors that impact regulatory, development and commercialization strategies. The Strategic Plan will contain the global strategy and launch planning and sequence in Major Markets as determined by [***]. When materially updating the Strategic Plan, Novartis will include the following components:

(i) The objectives of the Strategic Plan and estimated timelines;

(ii) The estimated timing and launch sequence per Indication for each Product;

(iii) The key global Clinical Studies (including the CVOT Novartis will conduct), including estimated timelines for the key milestones associated with such studies, the primary and secondary endpoints, approximate size and duration of such studies, and patient populations, in reasonable detail as determined by Novartis, that Novartis will conduct for each Product; and

(iv) Key elements of the planning and strategy to support Development, Manufacturing, Regulatory Approvals and Commercialization (including [***] and [***]).

Each time Novartis exercises its Option to a Product, such Product will be included in the Strategic Plan in accordance with the principles set forth in this Section 6.1.

6.2. **Initial Strategic Plan**. Novartis will deliver an initial draft Strategic Plan for each Product to Akcea within [***] ([***]) calendar days after the date Novartis licenses a Product under Section 5.1. [***] It is agreed that the Initial Strategic Plan will primarily cover details pertaining to the CVOT Novartis will conduct for such Product.

6.3. **Updating the Strategic Plan**.

6.3.1. Novartis will review and update the Strategic Plan every [***] months and the Parties will meet or hold a telephone conference to review such updates. Novartis will be responsible for coordinating and scheduling such meetings or telephone conferences, and the Parties will mutually determine the location of meetings. Each Party will be responsible for the costs of its own representatives attending such meetings. At such meeting or telephone conference, as applicable, the Parties will discuss, among other things:

(i) Material updates to the Strategic Plan;

(ii) Relevant new data and results from ongoing or completed Clinical Studies and non-clinical studies;

(iii) Technology advancements (including platform technology) potentially relevant to the Products;

(iv) Key elements of the manufacturing planning and strategy to support Development, Regulatory Approvals and Commercialization for the Products; and

(v) The evolving competitive landscape (including [***],[***] and [***]) and its potential impact on the Products and strategy.

6.3.2. **Material Changes to the Strategic Plan**. Novartis is responsible for preparing each updated Strategic Plan and the agenda for each meeting or telephone conference of the Parties to discuss such update, and will submit such updated plan and agenda to Akcea at least [***] ([***]) calendar days prior to the date of such next scheduled meeting or telephone conference, as applicable. The Parties' goal is to mutually agree on changes to the Strategic Plan materially changing the CVRR Indication, the details or timing of the CVOT for a Product (each, a "***Material Change***"). If, however, after good faith discussions, the Parties cannot mutually agree on a Material Change to the Strategic Plan, then Novartis will have final decision-making authority regarding [***].

6.3.3. **Ad Hoc Meetings.** At either Party's reasonable request, the Parties may meet or hold a telephone conference as mutually agreed on an *ad-hoc* basis to address any urgent matters that arise with respect to Products. Each Party will ensure that its representatives at such meetings are senior development and/or commercial executives.

6.4. **Commercialization and Novartis Diligence**.

6.4.1. **Generally**. Novartis will use Commercially Reasonable Efforts to Develop the Products, including pursuing the CVRR for each Product and conducting the activities set forth in the Strategic Plan in accordance with the timelines specified therein. Subject to JDCC governance and Section 6.5, Novartis will be solely responsible for all aspects of Commercialization of such Products, including planning and implementation, distribution, booking of sales, pricing and reimbursement. Novartis shall itself, or through its Affiliates or Sublicensees, use Commercially Reasonable Efforts to Commercialize each Product [***]. Notwithstanding the foregoing, Novartis' application of Commercially Reasonable Efforts shall not require Novartis to Commercialize a Product in any country or territory in which Novartis reasonably determines it is not commercially reasonable to do so for such Product. Subject to compliance with the foregoing, Novartis will have sole discretion and the final decision-making authority regarding the [***] under the Strategic Plan so long as such decisions are consistent with Novartis' obligations under Section 6.4.2.

6.4.2. **Specific Performance Milestone Events**. Novartis will achieve the specific performance milestone events set forth in SCHEDULE 6.4.2 ("***Specific Performance Milestone Events***"); *provided, however*, if [***] issues arise that are outside of Novartis' reasonable control that impede achievement of any such Specific Performance Milestone Event on the stated timeline, the Parties will meet and discuss in good faith through the JDCC and revise the date by which the applicable Specific Performance Milestone Event will be or can be achieved.

6.5. **Akcea's Right to Co-Commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx**. Akcea has the right to Co-Commercialize each Product with Novartis in selected markets with the terms and conditions of such Co-Commercialization to be mutually agreed between Akcea and Novartis. If, on or before the [***] calendar day after [***] or [***] for a particular Product, Akcea delivers written notice to Novartis indicating that Akcea intends to Co-Commercialize such Product with Novartis, then the Parties shall negotiate in good faith on the terms and conditions upon which Akcea will Co-Commercialize the Product.

6.6. **Regulatory Interactions**.

6.6.1. **Regulatory Interactions.** In accordance with the Strategic Plan, after Option Exercise, Novartis will (i) determine the regulatory plans and strategies for the Products, (ii) (either itself or through its Affiliates or sublicensees) make all Regulatory Filings with respect to the Products, and (iii) will be responsible for obtaining and maintaining Regulatory Approvals in the name of Novartis or its Affiliates or Sublicensees. Until Regulatory Approval of a Product, Novartis will provide Akcea with material correspondence with and material submissions (NDA, MAA, briefing documents, priority review or breakthrough request) to any Regulatory Authority in each Major Market for such Product, sufficiently in advance of providing such correspondence or submission to the applicable Regulatory Authority to enable Akcea to provide comments on the contents thereof. In the event Akcea does not provide comments within [***] calendar days from receipt (or shorter notice as reasonably indicated by Novartis), it is agreed that Novartis shall be entitled to submit such submission or correspondence as the case may be. In addition, until Regulatory Approval of a Product, Novartis will notify, at JDCC meeting, Akcea of any planned significant meetings with a Regulatory Authority for a Product in a Major Market, and will, at Akcea's request, consider in good faith inviting Akcea (or its Affiliate) to participate with one representative [***] under the direction of Novartis in any such meeting. For the avoidance of doubt, Akcea's performance under this Section 6.6.1 shall be at no cost to Novartis.

6.6.2. **Akcea Cooperation.**

(a) At no cost to Novartis, on a Product-by-Product basis, within [***] ([***]) calendar days after Akcea grants Novartis the license for such Product under Section 5.1, Akcea will transfer the IND for such Product to Novartis together with all regulatory documentation (including pending drafts) related to such Product.

(b) Following such IND transfer under Section 6.6.2(a), if requested by Novartis and mutually agreed by Akcea (such agreement not to be unreasonably withheld, delayed or conditioned), Akcea shall cooperate with and provide reasonable assistance to Novartis in connection with filings or submission to any Regulatory Authority relating to the Products, including by executing any required documents, providing access to personnel and providing Novartis with copies of all reasonably required documentation. After the first [***] hours of Akcea's time for any assistance under this Section 6.6.2(b), Novartis will compensate Akcea in accordance with Section 7.10 for Akcea's and its Affiliates' activities conducted under this Section 6.6.2(b). To the extent required to submit a regulatory filing or submission to a Regulatory Authority, Akcea shall grant or cause to be granted to Novartis and its Affiliates or Sublicensees cross-reference rights to any relevant drug master files and other filings submitted by Akcea or its Affiliates with any Regulatory Authority

6.6.3. **Class Generic Claims; Investigator's Brochure**. To the extent Novartis intends to make any claims in a Product label or regulatory filing that are class generic to Oligonucleotides, Akcea's or its Affiliate's generation 2.0 or 2.5 chemistry platform(s), Conjugate Technology, or any other Akcea technology included in a Product, Novartis will provide such claims and regulatory filings to Akcea in advance and will [***] any proposals and comments made by Akcea (or its Affiliates). Novartis will provide Akcea updated versions of the investigator's brochure when Development of the Products results in any substantive change to the safety or risk to the Products.

To the extent Akcea or Affiliates or licensors of Akcea intends to make any claims in a label or regulatory filing that (i) is reasonably likely to [***], and (ii) are [***], or any other [***], Akcea will provide such claims and regulatory filings to Novartis in advance and will consider in good faith any proposals and comments made by Novartis (or its Affiliates).

6.7. **Compliance**. Each Party will perform its activities pursuant to this Agreement (and will use reasonable efforts to require Third Parties to perform any such activities) in compliance with good laboratory practices (GLP), good clinical practices (GCP), and good manufacturing practices (GMP), in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted or which are otherwise affected.

6.8. **Pharmacovigilance and Ionis Internal ASO Safety Database**.

(a) On a Product-by-Product basis and within [***] ([***]) months after Option Exercise, the Parties shall agree upon and implement procedures for the mutual exchange of adverse events reports and safety information associated with the Products. Details of the operating procedures regarding such adverse events reports and safety information exchange shall be subject to a written pharmacovigilance agreement which shall be entered into within such [***] ([***]) month period.

(b) Akcea's Affiliate, Ionis, maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during non-clinical and clinical development (the "***Ionis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Akcea compounds, Novartis will cooperate in connection with populating the Ionis Internal ASO Safety Database. To the extent collected by Novartis and in the form in which Novartis stores such information for its own purposes, Novartis will provide Akcea with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies) and adverse events related to Products licensed by Novartis under this Agreement within a reasonable period of time (but not later than [***] ([***]) calendar days after Novartis' receipt of such information). In connection with any reported serious adverse event, Novartis will provide Akcea all serious adverse event reports within a reasonable time period of time but not later than [***] ([***]) calendar days after Novartis' receipt of such information. In addition, with respect to Products, Novartis will provide Akcea with copies of Annual safety updates filed with each IND (e.g. DSURs or IND annual reports) and the safety sections of any final Clinical Study reports within [***] ([***]) calendar days following the date such information is filed, as applicable. Furthermore, Novartis will provide in a timely manner to Akcea supporting data that Novartis determines to be reasonably related to such safety information provided by Novartis under this Section 6.8(a) and answer in a timely manner any follow-up questions reasonably requested by Akcea or its Affiliates to the extent such data and answers are reasonably available to Novartis. All such information disclosed by Novartis to Akcea will be Novartis Confidential Information and Novartis acknowledges and agrees that Akcea will provide all such information to Ionis to enable Ionis to populate the Ionis Internal ASO Safety Database. In addition, so long as Akcea does not disclose the identity of a Product or Novartis' identity, Akcea may disclose any such Novartis Confidential Information to (i) Akcea's other partners pursuant to Section 6.8(c) below if such information is regarding class generic properties of ASOs, (ii) any Third Party (other than a Regulatory Authority) that contributes to the populating of the Ionis Internal ASO Safety Database, or (iii) a Regulatory Authority. Novartis will deliver all such information to Akcea for the Ionis Internal ASO Safety Database to Akcea Therapeutics, Inc., 55 Cambridge Parkway, Cambridge, MA 02142, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Akcea). Novartis will also cause its Affiliates and Sublicensees to comply with this Section 6.8(b).

(c) From time to time, Akcea and Ionis utilize the information in the Ionis Internal ASO Safety Database to conduct analyses to keep Akcea, Ionis and their partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Akcea identifies safety or other related issues that may be relevant to a Product (including any potential class-related toxicity), Akcea will inform Novartis in a timely manner of such issues and, if requested allow Novartis to review such issues and conclusions and allow Novartis the opportunity to review and align on safety statement and health authority submissions in a timely manner before release.

(d) During the Agreement Term, Novartis may submit written requests to Akcea for Akcea to have queries run of the Ionis Internal ASO Safety Database relevant to Products licensed to Novartis under this Agreement, and Akcea will use Commercially Reasonable Efforts to promptly cause such queries to be run and deliver to Novartis the results of such queries. Any information disclosed between the Parties under this Section 6.8(d) will be treated as Confidential Information in accordance with ARTICLE 12 below.

ARTICLE 7.
FINANCIAL PROVISIONS

7.1. **License Fee for AKCEA-APO(a)-LRx**. Upon Novartis' written notice to Akcea stating that Novartis is exercising the Option for AKCEA-APO(a)-L_{Rx} in accordance with this Agreement, Novartis will pay to Akcea a license fee of US$150,000,000 within [***] ([***]) Business Days after receipt by Novartis of an original invoice from Akcea for such amount and in the form attached hereto as Exhibit X.

7.2. **License Fee for AKCEA-APOCIII-LRx**. Upon Novartis' written notice to Akcea stating that Novartis is exercising the Option for AKCEA-APOCIII-L_{Rx} in accordance with this Agreement, Novartis will pay to Akcea a license fee of US$150,000,000 within [***] ([***]) Business Days after receipt by Novartis of an original invoice from Akcea for such amount and in the form attached hereto as Exhibit X.

7.3. **Milestone Payments for Achievement of Development Milestone Events by AKCEA-APO(a)-LRx**. Novartis will pay Akcea the milestone payments as set forth in TABLE 1 below when a development milestone event listed in TABLE 1 is first achieved by AKCEA-APO(a)-L_{Rx}:

TABLE 1

Development Milestone Event	Milestone Event Payment
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]

7.4. **Milestone Payments for Achievement of Development Milestone Events by AKCEA-APOCIII-LRx**. Novartis will pay Akcea the milestone payments as set forth in TABLE 2 below when a development milestone event listed in TABLE 2 is first achieved by AKCEA-APOCIII-L_{Rx}:

TABLE 2	
Development Milestone Event	**Milestone Event Payment**
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]
[***]	US$[***]

7.5. **Milestone Payments for First Achievement of Sales Milestone Events by AKCEA-APO(a)-LRx**. Novartis will pay Akcea the sales milestone payments set forth in TABLE 3 below if a sales milestone event listed in TABLE 3 is achieved by AKCEA-APO(a)-L_{Rx}:

TABLE 3	
Sales Milestone Event for AKCEA-APO(a)-L_{Rx}	**Milestone Payment**
US$[***] in Annual Net Sales	US$[***]
US$[***] in Annual Net Sales	US$[***]
US$[***] in Annual Net Sales	US$[***]

7.6. **Milestone Payments for First Achievement of Sales Milestone Events by AKCEA-APOCIII-LRx**. Novartis will pay Akcea the sales milestone payments set forth in TABLE 4 below if a sales milestone event listed in TABLE 4 is achieved by AKCEA-APOCIII-L_{Rx}:

TABLE 4	
Sales Milestone Event for AKCEA-APOCIII-L_{Rx}	**Milestone Payment**
US$[***] in Annual Net Sales	US$[***]
US$[***] in Annual Net Sales	US$[***]
US$[***] in Annual Net Sales	US$[***]

7.7. Limitations on Milestone Payments; Exceptions; Notice.

7.7.1. Each milestone payment set forth in TABLE 1, TABLE 2, TABLE 3 and TABLE 4 above will be paid only once upon the first achievement of the milestone event by the applicable Product regardless of how many times such Product achieves such milestone event.

7.7.2. If a particular milestone event is not achieved by a Product, then upon achievement of a later milestone event by such Product the milestone event payment applicable to such earlier milestone event will also be due. For example, if Novartis proceeds directly to "*[***]*" without achieving the "*[***],*" then upon achieving the "*[***]*" milestone event, both the "*[***]*" and "*[***]*" milestone event payments are due.

7.7.3. If a particular milestone event is achieved by a Product contemporaneously with or in connection with another milestone event by such Product, then both milestone events will be deemed achieved and the milestone payments for both milestone events are due. For example, if Novartis achieves the "*[***]*" milestone event and the [***] ([***]) that was the subject of such milestone event contains one or more separate [***] that were also [***], then both the "*[***]*" and the "*[***]*" milestone event payments are due.

7.7.4. Each time a milestone event is achieved under this ARTICLE 7, Novartis will send Akcea a written notice thereof within [***] ([***]) calendar days following the date of achievement of such milestone event and the applicable milestone payment is due within [***] ([***]) calendar days after receipt by Novartis of an original invoice from Company for such amount and in the form attached hereto as Exhibit X.

7.7.5. Novartis and Akcea acknowledge and agree that nothing in this Agreement shall be construed as representing an estimate or projection of anticipated sales of any Product, and that the Milestones and Net Sales levels set forth above are only intended to define the Milestone Payment and royalty obligations to Akcea in the event such milestones or Net Sales level are achieved. Neither Akcea nor Novartis makes any representation or warranty, either express or implied, that it will be able to successfully Develop or Commercialize any Product or, if Commercialized, that any particular Net Sales of such Product will be achieved.

7.8. Royalty Payments.

7.8.1. **Royalty**. As partial consideration for the rights granted to Novartis hereunder, subject to the provisions of this Section 7.8.1 and Section 7.8.2, Novartis will pay to Akcea royalties on Annual worldwide Net Sales of Products sold by Novartis, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 5 below (the "***Novartis Royalty***"):

TABLE 5

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

Annual worldwide Net Sales will be calculated by taking the aggregate sum of Net Sales of a Product for all countries worldwide.

Novartis will pay Akcea royalties on Net Sales of Products arising from pre-Commercial sales (including, named patient and other similar programs under Applicable Laws), and Novartis will provide reports and payments to Akcea consistent with Section 7.11.1. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Initial Payment Period.

7.8.2. **Application of Royalty Rates**. All royalties set forth under Section 7.8.1 are subject to the provisions of this Section 7.8.2, and are payable as follows:

(a) ***Initial Payment Period***. Novartis' obligation to pay Akcea the Novartis Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim of the Orange Book Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product, and (iii) the tenth anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Initial Payment Period***").

(b) ***Generic Competition During the Initial Payment Period***. Notwithstanding the foregoing, on a country-by-country and Product-by-Product basis, if at any time during the Initial Payment Period a Generic Product is sold in such country, then Novartis will pay Akcea royalties on Net Sales of Products sold by Novartis, its Affiliates or Sublicensees in such country using the royalty adjustment set forth in this Section 7.8.2(b) for such country as follows:

(i) If the aggregate Net Sales of such Product in such country in any Calendar Year are between [***]% - [***]% lower as compared to the aggregate Net Sales of such Product in the last Calendar Year during which there were no Generic Products sold in such country, then, following such reduction in Net Sales, the applicable Net Sales from such country upon which royalties are calculated shall be adjusted to [***] percent ([***]%) for purposes of calculation of such royalties; or

(ii) If the aggregate Net Sales of such Product in such country in any Calendar Year are at least [***]% lower as compared to the aggregate Net Sales of such Product in the last Calendar Year during which there were no Generic Products sold in such country, then, following such reduction in Net Sales, the applicable Net Sales from such country upon which royalties are calculated shall be adjusted to [***] percent ([***]%) for the purpose of calculation of such royalties.

(c) ***Royalty Adjustment After the Initial Payment Period***. On a country-by-country and Product-by-Product basis, after the expiration of the Initial Payment Period and until the end of the Adjusted Payment Period for such Product, Novartis will pay Akcea a royalty on [***]% of the Net Sales of Products sold by Novartis, its Affiliates or Sublicensees on a Calendar Year-by-Calendar Year basis at the royalty rates set forth in TABLE 5 of Section 7.8.1 above. "***Adjusted Payment Period***" means, on a country-by-country and Product-by-Product basis, the period commencing upon the expiration of the Initial Payment Period and ending when (i) aggregate Net Sales of such Product in such country in a Calendar Year are at least [***]% lower as compared to the aggregate Net Sales of such Product in the immediately preceding Calendar Year, or (ii) Akcea (by itself or through an Affiliate or Third Party) commercializes a drug designed to directly modulate an Exclusive Target (other than Volanesorsen), whichever occurs first.

(d) ***End of Royalty Obligation for Products***. On a country-by-country and Product-by-Product basis, [***], Novartis' obligation to make royalty payments hereunder for such Product in such country will end on the expiration of the Adjusted Payment Period in such country.

(e) ***API Cost Adjustment***. The Parties may negotiate in good faith a potential adjustment to the Novartis Royalty in TABLE 5 of Section 7.8.1.

(f) ***Royalty Examples***. SCHEDULE 7.8.2(f) attached hereto contains examples of how royalties will be calculated under this Section 7.8.

(g) ***Limitation on [***] for [***]***.

In no event will the [***] under [***] and [***] in any given period [***] for such Product.

7.9. **Third Party Payment Obligations**. Any Third Party Obligations that become payable by Akcea or Novartis under an agreement such Party (or its Affiliate) has entered into to license or otherwise acquire Third Party Patent Rights will be promptly paid by a Party or shared by the Parties as expressly set forth in this Section 7.9.

7.9.1. **Existing In-License Agreements as of Option Exercise**.

(a) ***Akcea's Existing In-License Agreements***. On a Product-by-Product basis, certain of the Licensed Technology Controlled by Akcea as of the date of Option Exercise that may be licensed to Novartis under Section 5.1.1 or Section 5.1.2, as the case may be, are in-licensed or were acquired by Akcea or its Affiliates under (i) the agreements with Third Party licensors or sellers listed on APPENDIX 3, or (ii) the Ionis-Akcea License Agreement (such license or purchase agreements being the "***Akcea In-License Agreements***"), and certain milestone, royalty payments, license maintenance fees and other payments may become payable by Akcea or its Affiliates to such Third Parties under the Akcea In-License Agreements based on the Development or Commercialization of a Product by Novartis, its Affiliates or Sublicensees. Any payment obligations arising under the Akcea In-License Agreements will be paid by [***] as [***].

(b) ***Novartis' Existing In-License Agreements***. On a Product-by-Product basis, [***] will be solely responsible for any Third Party Obligations that become payable by Novartis or its Affiliates to Third Parties under any agreements or arrangements Novartis or its Affiliates has with such Third Parties as of the date of Option Exercise, based on the Development or Commercialization of a Product by Novartis, its Affiliate or Sublicensee under this Agreement. Any such payment obligations will be paid by [***] as [***].

7.9.2. **New In-Licensed Akcea Core Technology Patents, Akcea Manufacturing and Analytical Patents or Akcea Product-Specific Patents**.

(a) ***New In-Licensed Akcea Core Technology Patents or Akcea Manufacturing and Analytical Patents***. On a Product-by-Product basis, if, after the date of Option Exercise, Akcea obtains Third Party Patent Rights necessary to Develop, Manufacture or Commercialize a Product that would have been considered an Akcea Core Technology Patent or an Akcea Manufacturing and Analytical Patent had Akcea Controlled such Patent Rights on the Effective Date, Akcea will include such Third Party Patent Rights in the license granted to Novartis under Section 5.1.1 or Section 5.1.2 (as applicable) and any and all costs arising under such Third Party agreement as they apply to a Product will be paid solely by [***] as [***].

(b) ***New In-Licensed Akcea Product-Specific Patents***. On a Product-by-Product basis, if, after the date of Option Exercise, Akcea obtains Third Party Patent Rights necessary to Develop, Manufacture or Commercialize a Product that would have been considered an Akcea Product-Specific Patent had Akcea Controlled such Patent Rights on the Effective Date, Akcea will include such Third Party Patent Rights in the license granted to Novartis under Section 5.1.1 or Section 5.1.2 (as applicable) if [***] as [***] any and all costs arising under such Third Party agreement as they apply to Products; *provided*, *however*, if Akcea obtains any such Akcea Product-Specific Patents as a result of [***], then Akcea will include such Third Party Patent Rights in the license granted to Novartis under Section 5.1.1 or Section 5.1.2 (as applicable) and any and all costs arising under such Third Party agreement as they apply to a Product will be paid solely by [***] as [***].

7.9.3. Additional IP In-License Agreements.

(a) After the date of Option Exercise, on a Product-by-Product basis, Novartis will promptly provide Akcea written notice of any Additional IP Novartis believes it has identified and Akcea or its Affiliate will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional IP. If Akcea or its Affiliate obtains such a Third Party license, Akcea will include such Additional IP in the license granted to Novartis under Section 5.1.1 or Section 5.1.2 (as applicable), and [***] will pay any financial obligations under such Third Party agreement as [***].

(b) If, however, Akcea and its Affiliates elect not to obtain such a license to such Additional IP, Akcea will so notify Novartis, and Novartis may obtain such a Third Party license and, except as set forth in Section 7.9.3(d), Novartis may offset an amount equal to [***]% of [***] during a Calendar Quarter paid by Novartis under such Third Party license against any [***] during the same Calendar Quarter.

(c) If Akcea does not agree that certain intellectual property identified by Novartis pursuant to Section 7.9.3(a) is Additional IP under Section 7.9.3(b), Akcea will send written notice to such effect to Novartis, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of Oligonucleotides, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is Additional IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether Novartis is permitted to apply the offset under Section 7.9.3(b) above. The costs of any Third Party expert engaged under this Section 7.9.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

(d) Notwithstanding the determination of the Third Party lawyer under Section 7.9.3(c), if a Third Party Controlling Additional IP is awarded a final judgment from a court of competent jurisdiction arising from its claim against Novartis asserting that a license to such Additional IP is necessary for Novartis to practice an invention claimed within an Orange Book Patent to Commercialize a particular Product in a particular country or Novartis and Akcea mutually agree to settle such a Third Party claim, then, on a country-by-country and Product-by-Product basis, Novartis will be permitted to, subject to Section 7.8.2(g), offset against any [***] for such Product in such country (A) [***]% of the sum of any amounts paid by Novartis to such Third Party constituting [***] or [***] (excluding any [***] or [***]) awarded by such court against Novartis based on [***] occurring after Option Exercise and prior to the date of such final judgment or such settlement, and (B) [***]% of the sum of any royalties paid by Novartis to such Third Party on such Product sold in such country under such final judgment or such settlement. In no event will Novartis have the right to offset the sum of any amounts paid by Novartis to such Third Party constituting [***] or [***].

7.9.4. **Minimum Third Party Payments**. Any Minimum Third Party Payments Novartis is obligated to pay under this Agreement will be satisfied by paying Akcea directly.

7.10. **Invoices**. If the Parties explicitly refer to this Section 7.10, for any mutually agreed work performed by Akcea and/or Akcea's Affiliates at Novartis' request under this Agreement (other than the Akcea Activities) after (i) the first [***] hours of Akcea's time for any [***], (ii) the first [***] hours of Akcea's time for [***], or (iii) the first [***] hours of Akcea's time for [***], as applicable, Novartis will reimburse Akcea for the services rendered within [***] ([***]) Business Days from the date an invoice is received by Novartis; *provided that* any invoiced costs are for fees or services that have been rendered by Akcea plus out-of-pocket costs incurred by Akcea. Akcea's invoices will include Akcea's good faith estimate of the FTE cost incurred by Akcea in performing the services and the amount of any out-of-pocket costs incurred by Akcea. Before Akcea commences work for which it intends to invoice Novartis, Novartis and Akcea will agree to a budget for the work Novartis requests Akcea to perform that will include Akcea's good faith estimate of the FTE cost plus any out-of-pocket costs.

7.11. Payments.

7.11.1. **Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Novartis will make royalty payments to Akcea under this Agreement within [***] ([***]) calendar days following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used. If no royalties are payable in respect of a given Calendar Quarter, Novartis will submit a written royalty report to Akcea so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Novartis will provide Akcea with a single preliminary, non-binding Net Sales amount for the entire territory (worldwide) within [***] ([***]) Business Days after the end of the Calendar Quarter in order to provide Akcea with an indication of the approximate Net Sales for all Products that are likely to be due under the applicable royalty report pursuant to Section 7.8. Such "*preliminary Net Sales*" shall be provided as a courtesy estimate only and shall not be used as a basis of comparison against actual royalties due or be considered binding in any way. For the avoidance of doubt, royalty reports and "*preliminary Net Sales*" hereunder are Novartis' Confidential Information subject to the terms and conditions of this Agreement.

7.11.2. **Mode of Payment**. All payments under this Agreement will be (i) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Akcea in writing, and (iii) non-creditable (except as otherwise provided in Section 7.12) and non-refundable. All payments under this Agreement shall be made in US Dollars. Any sales incurred in a currency other than US Dollars shall be converted to the US Dollar equivalent using Novartis' then-current standard exchange rate methodology as consistently applied in its external reporting for the conversion of foreign currency sales into US Dollars. Novartis shall notify Akcea in the event of changes to this methodology. In addition, an "original invoice" will be deemed duly delivered by a Party to the other Party under this Agreement when delivered electronically to such other Party and, if so delivered electronically, will be promptly followed by delivery of a paper copy of such invoice.

7.11.3. **Records Retention**. Commencing with the First Commercial Sale of a Product, Novartis will keep complete and accurate records pertaining to the Net Sale of Products for a period of [***] ([***]) months after the Quarter in which such sales occurred in accordance with Novartis Accounting Standards.

7.12. Audits.

7.12.1. During the Agreement Term and for a period of [***] months thereafter, at Akcea's expense and upon written notice to Novartis, Novartis will permit an independent certified public accountant of internationally recognized standing (the "***Auditor***") appointed by Akcea and reasonably acceptable to Novartis, at reasonable times and upon reasonable notice, but in no case more than [***] per Calendar Year and not more frequently than [***] with respect to records covering any specific period of time, to examine such records as may be necessary for the sole purpose of verifying the accrual of any milestone payments, the calculation and reporting of Net Sales, and the correctness of any milestone or royalty payment made under this Agreement for any period within the preceding [***] months.

7.12.2. As a condition to and prior to examining any of Novartis' records, such Auditor will sign a nondisclosure agreement reasonably acceptable to Novartis in form and substance. Any and all of Novartis' records examined by such independent certified public accountant will be deemed Novartis' Confidential Information. Novartis and its Affiliates shall make their records available for inspection by such Auditor during regular business hours at such place or places where such records are customarily kept, upon receipt of reasonable advance notice from Akcea.

7.12.3. Upon completion of the audit, the accounting firm will provide both Novartis and Akcea with a written audit report disclosing whether the milestone or royalty payments made by Novartis are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). Before it is considered final, Novartis shall have the right to request a further determination by such Auditor as to matters which Novartis disputes within [***] ([***]) Business Days following receipt of such Audit Report. Novartis will provide Akcea and the Auditor with a reasonably detailed statement of the grounds upon which it disputes any findings in the Audit Report and the Auditor shall undertake to complete such further determination within [***] ([***]) Business Days after the dispute notice is provided, which determination shall be limited to the disputed matters. Any matters that remain unresolved shall be resolved in accordance with the dispute resolution procedures in Section 13.1. No Audit Report shall be considered final until conclusions are undisputed by both Parties or are otherwise conclusively determined.

7.12.4. If, as a result of any inspection of Novartis' books and records, it is undisputed (or later conclusively determined) that Novartis' payments under this Agreement were more or less than the milestone or royalty amount which should have been paid, then the relevant Party will make all payments required to be made by paying the other Party the difference between such amounts to eliminate any discrepancy revealed by said inspection within [***] ([***]) Business Days of receiving the final Audit Report, with interest calculated in accordance with Section 7.14; *provided*, *however*, that any such payment by Akcea to Novartis will be in the form of a credit against future royalty payments due under Section 7.8 equal to the difference between the amounts actually paid by Novartis to Akcea and the royalty amounts Novartis should have paid Akcea. Akcea will pay for such audit, except that if Novartis is found to have underpaid Akcea by more than [***]% of the amount that should have been paid for the audited period, Novartis will reimburse Akcea the reasonable fees and expenses charged by the Auditor for the audit.

7.13. Taxes.

7.13.1. **Taxes on Income**. Each Party alone will be solely responsible for paying any and all taxes (other than withholding taxes required by Applicable Law to be paid by Novartis or Akcea (as the case may be) levied on account of, or measured in whole or in part by reference to, the income of such Party.

7.13.2. **Indirect Taxes**. All payments are exclusive of Indirect Taxes. If any Indirect Taxes are chargeable in respect of any payments, the paying Party will pay such Indirect Taxes at the applicable rate in respect of such payments following receipt, where applicable, of an Indirect Taxes invoice in the appropriate form issued by the receiving Party in respect of those payments.

The Parties will issue invoices for all amounts payable under this Agreement consistent with Indirect Tax requirements and irrespective of whether the sums may be netted for settlement purposes. If such amounts of Indirect Taxes are refunded by the applicable Governmental Authority or other fiscal authority subsequent to payment, the Party receiving such refund will transfer such amount to the paying Party within [***] ([***]) Business Days of receipt. The Parties agree to reasonably cooperate to provide any information required by the Party pursuing a refund of Indirect Taxes paid.

7.13.3. **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper Governmental Authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so.

7.13.4. **Tax Cooperation**. At least [***] ([***]) Business days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary in order for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Laws. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 7.13.

The provisions of this Section 7.13 are to be read in conjunction with the provisions of Section 13.4 below.

7.14. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement, and any payments that are pending resolution of any dispute unless the dispute is ruled in favor of the paying Party, will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus [***]% or (ii) the maximum rate permissible under applicable law.

ARTICLE 8.
INTELLECTUAL PROPERTY

8.1. **Joint Patent Committee**.

8.1.1. Unless the Parties mutually agree to establish it sooner, the Parties will establish a "***Joint Patent Committee***" or "***JPC***" upon the [***]. The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this Section 8.1. If the JPC dissolves, each Party may designate a patent attorney who will be responsible for intellectual property matters under this Agreement. A strategy will be discussed with regard to (i) prosecution and maintenance, defense and enforcement of Akcea Product-Specific Patents that would be or are licensed to Novartis under Section 5.1 and Novartis Product-Specific Patents, (ii) defense against allegations of infringement of Third Party Patent Rights, (iii) licenses to Third Party Patent Rights or Know-How, and (iv) the timing and subject matter of any potential publications regarding a Product, in each case to the extent such matter would be reasonably likely to have a material impact on this Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party. Upon Novartis' exercise of (or the expiration or termination of) the last Option, each Party will no longer have the obligation, but will continue to have the right, to participate in the JPC, provided that, if requested by Novartis, Akcea shall consider in good faith and not unreasonably refuse to participate in the JPC.

8.1.2. The JPC will comprise an equal number of at most three members from each Party. The JPC 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 Section 8.1. 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 will be codified in the written minutes of the first JPC meeting. The Parties may escalate issues to the Executives for input and resolution pursuant to Section 13.1. Each Party's representatives on the JPC will consider comments and suggestions made by the other in good faith. Each Party will bear their own cost of participation on the JPC.

8.2. Ownership.

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

8.2.2. **Program Technology**. As between the Parties, Novartis is the sole owner of any Know-How discovered, invented or created solely by or on behalf of Novartis or its Affiliates under or in connection with this Agreement ("***Novartis Program Know-How***") and any Patent Rights that claim or cover Novartis Program Know-How ("***Novartis Program Patents***" and together with the Novartis Program Know-How, the "***Novartis Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Novartis to Akcea under this Agreement. As between the Parties, Akcea is the sole owner of any Know-How discovered, invented or created solely by or on behalf of Akcea or its Affiliates under or in connection with this Agreement ("***Akcea Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Akcea Program Patents***" and together with the Akcea Program Know-How, the "***Akcea Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Akcea to Novartis under this Agreement. Any Know-How discovered, invented or created jointly under or in connection with this Agreement by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf ("***Jointly-Owned Program Know-How***"), and any Patent Rights that claim or cover such Jointly-Owned Program Know-How ("***Jointly-Owned Program Patents***", and together with the Jointly-Owned Program Know-How, the "***Jointly-Owned Program Technology***"), are owned jointly by Novartis and Akcea on an equal and undivided basis, including all rights, title and interest thereto, subject to any rights or licenses expressly granted by one Party to the other Party under this Agreement.

Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Program Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting. Furthermore, the Parties acknowledge and agree that any such Jointly-Owned Program Technology is [***], and therefore shall not be [***] under this Agreement. The Parties acknowledge and agree that either Party may freely utilize or otherwise exploit any Jointly-Owned Program Technology without recourse, accounting or any other obligations to the other Party. This right includes the right to grant sublicenses or otherwise dispose of the Party's interest in any Jointly-Owned Program Technology, subject to the following limitations. If either Party ("***Offering Party***") intends to grant a license, assign or otherwise dispose of its rights in any [***] to a Third Party under such Party's interest in such [***] for the development and/or commercialization of a Product, the Offering Party will first provide the other Party notice of such intent and offer to such Party a right of first negotiation together with proposed terms for such a license (a "***ROFN Notice***"). Such Party will have [***] calendar days from the date such Party receives a ROFN Notice to send notice to the Offering Party of such Party's desire to exercise its right of first negotiation (a "***Negotiation Notice***"). If (i) such Party does not timely deliver a Negotiation Notice to the Offering Party, or (ii) such Party timely delivers a Negotiation Notice to the Offering Party but the Parties cannot agree on the terms of such a license by the [***] calendar day after the date the Offering Party receives such Negotiation Notice, then the Offering Party may grant a license to a Third Party under such Offering Party's interest in such [***] for the development and/or commercialization of a Product on terms [***].

Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, invention or creation of any Novartis Program Technology, Akcea Program Technology or Jointly-Owned Program Technology. The Novartis Program Patents, Akcea Program Patents and Jointly-Owned Program Patents are collectively referred to herein as the "***Program Patents***," the Novartis Program Know-How, Akcea Program Know-How and Jointly-Owned Program Know-How are collectively referred to herein as the "***Program Know-How***," and Novartis Program Technology, Akcea Program Technology and Jointly-Owned Program Technology are collectively referred to herein as "***Program Technology***."

8.2.3. In addition, the JPC (or the Parties' respective patent representatives if no JPC exists) will be responsible for the assessment of inventorship of Program Patents in accordance with United States patent laws. In case of a dispute in the JPC (or otherwise between Akcea and Novartis) over inventorship of Program Patents, if the JPC (or the Parties' respective patent representatives if no JPC exists) cannot resolve such dispute, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party (or its Affiliates) and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

8.3. Filing, Prosecution and Maintenance of Patents.

8.3.1. Licensed Patents.

(a) **Akcea Core Technology Patents and Akcea Manufacturing and Analytical Patents**. Akcea will control and be responsible for Prosecuting and Maintaining (i) the Akcea Core Technology Patents, and (ii) Akcea Manufacturing and Analytical Patents, including any Jointly-Owned Program Patents in (i) or (ii).

(b) **Akcea Product-Specific Patents**. Prior to the date Novartis exercises its Option for a Product in accordance with this Agreement, Akcea will control and be responsible for Prosecuting and Maintaining the Akcea Product-Specific Patents (including any Jointly-Owned Program Patents that are Product-Specific Patents). On a Product-by-Product basis, following the date Novartis exercises its Option for such Product in accordance with this Agreement (and so long as the applicable license to Novartis under Section 5.1 is in effect), Akcea will continue to control and be responsible for Prosecuting and Maintaining the Akcea Product-Specific Patents (including any Jointly-Owned Program Patents that are Product-Specific Patents) that (i) Cover an Akcea-Separate Product or (ii) Cover Conjugate Technology ("***Akcea Special Product-Specific Patents***") and Novartis will control and be responsible for Prosecuting and Maintaining all other Product-Specific Patents (including any Jointly-Owned Program Patents) that are not Akcea Special Product-Specific Patents.

(c) **Other Jointly-Owned Program Patents**. The Parties will decide through the JPC the appropriate Party to control and be responsible for Prosecuting and Maintaining all other Jointly-Owned Program Patents not provided for above.

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

(a) Each Party will keep the other Party informed through the JPC as to material developments with respect to the Prosecution and Maintenance of the Product-Specific Patents or Jointly-Owned Program Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 8.3.1 or this Section 8.3.2, including by providing copies of any office actions or office action responses or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, *inter partes* reviews, post-grant reviews, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If Novartis elects (i) not to file and prosecute patent applications for a Patent Right Novartis is responsible for Prosecuting and Maintaining under Section 8.3.1 above ("***Novartis-Prosecuted Patents***") in a particular country, (ii) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any Novartis-Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the Novartis-Prosecuted Patent in a particular country following a written request from Akcea to file and prosecute in such country, then Novartis will so notify Akcea promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Akcea to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Akcea will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Novartis-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such a case, Novartis will cooperate with Akcea to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Novartis-Prosecuted Patent in such country in Akcea's own name, but only to the extent that Novartis is not required to take any position with respect to such abandoned Novartis-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by Novartis under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Akcea assumes responsibility for the Prosecution and Maintenance of any such Novartis-Prosecuted Patent under this Section 8.3.2(b), Akcea will have no obligation to notify Novartis if Akcea intends to abandon such Novartis-Prosecuted Patent.

(c) The Parties, through the JPC, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Jointly-Owned Program Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(d) If the Party responsible for Prosecution and Maintenance pursuant to Section 8.3.1 intends to abandon a Jointly-Owned Program Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least [***] ([***]) calendar days before such Jointly-Owned Program Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 8.4) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Program Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Program Patents under this Section 8.3.2(d), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

8.4. **Patent Costs**. Except as set forth in Section 8.3.2 and this Section 8.4, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries designated by it in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under ARTICLE 8. Unless the Parties agree otherwise, the following Patent Costs will be paid by the Parties as follows:

8.4.1. Akcea and Novartis will [***] the Patent Costs associated with the Prosecution and Maintenance of each Akcea Special Product-Specific Patent with each Party's share of such Patent Costs calculated based on the [***]; and

8.4.2. Akcea and Novartis will [***] the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Program Patents;

provided that, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Akcea Special Product-Specific Patents or Jointly-Owned Program Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Akcea Special Product-Specific Patents or Jointly-Owned Program Patents (as applicable) and any such Patent Right will no longer be a Licensed Patent under this Agreement.

8.5. **Defense of Claims Brought by Third Parties; Oppositions**.

8.5.1. **AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx – Prior to Option Exercise**. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Product with respect to which Novartis has not yet exercised its Option, Akcea will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If Akcea elects to defend against such Proceeding, then Akcea will have the sole right to direct the defense and to elect whether to settle such claim.

8.5.2. **AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx – After Option Exercise**. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Product being Developed or Commercialized by Novartis under a license granted under Section 5.1, then Novartis will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If Novartis elects to defend against such Proceeding, then Novartis will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of Akcea, not to be unreasonably withheld, conditioned or delayed). Akcea will reasonably assist Novartis in defending such Proceeding and cooperate in any such litigation at Novartis' request and expense. Novartis will keep Akcea apprised of the progress of such Proceeding. If Novartis elects not to defend against a Proceeding, then Novartis will so notify Akcea in writing within [***] ([***]) calendar days after Novartis first receives written notice of the initiation of such Proceeding, and Akcea will have the right, but not the obligation, to defend against such a Proceeding at its sole cost and expense and thereafter Akcea will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of Novartis, which consent will not be unreasonably withheld, delayed or conditioned). In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at defending Party's request and expense. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 8.5. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 8.5, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

8.5.3. **Interferences, Reissues, Re-Examinations and Oppositions**. If a Third Party initiates a Proceeding related to an interference, reissue, re-examination or opposition of an Akcea Product-Specific Patent, then (A) if such Proceeding occurs prior to Option exercise (or after Option exercise with respect to an Akcea Special Product-Specific Patent), Akcea will have the right, but not the obligation, to control the defense of such Proceeding as Akcea determines in Akcea's sole discretion, and (B) if such Proceeding occurs after Option exercise and does not involve an Akcea Special Product-Specific Patent, Novartis will, at Novartis' expense, by written notice to Akcea either (i) control the defense of such Proceeding solely to the extent such Proceeding relates to an interference, reissue, re-examination or opposition of an Akcea Product-Specific Patent that *is not* an Akcea Special Product-Specific Patent, or (ii) have Akcea control the defense of such Proceeding, *provided* if Novartis makes no such election within a reasonable period of time, then Akcea will have the right, but not the obligation, to control the defense of such Proceeding and Akcea and Novartis will evenly split the cost of such defense. If Akcea elects not to defend against such a Proceeding under (A) in this section above, then Akcea will so notify Novartis in writing within [***] ([***]) calendar days after Akcea first receives written notice of the initiation of such Proceeding, and Novartis will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter Novartis will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of Akcea, which consent will not be unreasonably withheld, delayed or conditioned). In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the defending Party's request and expense. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 8.5. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 8.5, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

8.6. **Enforcement of Patents Against Competitive Infringement**. With respect to infringement, unauthorized use, misappropriation or threatened infringement by a Third Party of any Akcea Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product that binds to an Exclusive Target ("***Competitive Infringement***"), prior to the date Novartis exercises its applicable Option under this Agreement (or after Option exercise with respect to an Akcea Special Product-Specific Patent), Akcea will have the sole right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto. With respect to any Competitive Infringement involving an Akcea Licensed Patent that *is not* an Akcea Special Product-Specific Patent that occurs after the date Novartis exercises its applicable Option under this Agreement, the Parties will handle such Competitive Infringement in accordance with the remainder of this Section 8.6.

8.6.1. **Duty to Notify of Competitive Infringement**. If either Party learns of a Competitive Infringement by a Third Party, such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 8.6.6 below, such written notice will be given within [***] ([***]) calendar days.

8.6.2. **Control of Competitive Infringement Proceedings**. For any Competitive Infringement involving an Akcea Product-Specific Patent that *is not* an Akcea Special Product-Specific Patent for a Product licensed to Novartis under Section 5.1 that occurs after Novartis exercises its Option for such Product, so long as part of such Proceeding Novartis also enforces any Patent Rights Controlled by Novartis being infringed that Cover such Product, then Novartis will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Akcea will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however*, Novartis will have the right to control such litigation. If Novartis fails to initiate a Proceeding within a period of [***] ([***]) calendar days after receipt of written notice of such Competitive Infringement (subject to a [***] ([***]) calendar days extension to conclude negotiations, if Novartis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such [***] calendar day period), Akcea will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Novartis will have the right to be represented in any such action by counsel of its own choice at its own expense.

8.6.3. Joinder; Cooperation.

(a) If a Party initiates a Proceeding in accordance with this Section 8.6, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 8.6.4, the costs and expenses of each Party incurred pursuant to this Section 8.6.3(a) will be borne by the Party initiating such Proceeding; *provided* Novartis will only be requested to join such a Proceeding if such Proceeding relates to a Patent Right or Product licensed to Novartis under Section 5.1.

(b) If one Party initiates a Proceeding in accordance with this Section 8.6.3, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

8.6.4. Share of Recoveries. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to Section 8.5 or this Section 8.6 will be shared as follows:

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

(b) any remaining proceeds will be allocated as follows: (A) prior to Option exercise, to [***], and (B) after Option exercise, (x) if Novartis initiates or controls the defense of the Proceeding pursuant to Section 8.5.2 or Section 8.6.2, [***], or (y) if Akcea initiates or controls the defense of the Proceeding, [***] will receive and retain the remaining proceeds.

8.6.5. Settlement. Notwithstanding anything to the contrary in this ARTICLE 8, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 8 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right.

8.6.6. 35 USC 271(e)(2) Infringement. Notwithstanding anything to the contrary in this Section 8.6, for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 8.6.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of twenty five (25) calendar days, so that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within [***] ([***]) calendar days after such first Party's receipt of written notice of such Competitive Infringement.

8.7. **Other Infringement - Jointly-Owned Program Patents**. With respect to the infringement of a Jointly-Owned Program Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 8.7 will be shared as follows: (i) 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); (ii) (A) if the Parties jointly initiate a Proceeding pursuant to this Section 8.7, each Party will retain or receive 50% of such remaining proceeds; and (B) if only one Party initiates the Proceeding pursuant to this Section 8.7, such Party will retain or receive such remaining proceeds. Notwithstanding the provision of Section 8.6.4. the remaining proceeds contemplated under this section, if retained by Novartis, shall not be treated as if it were Net Sales,

8.8. **Patent Listing**. Novartis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Orange Book Patents. Prior to such listings, the Parties will meet, through the JPC, to evaluate and identify all applicable Patent Rights, and Novartis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the JPC for any such listing. Notwithstanding the preceding sentence, Novartis will retain final decision-making authority as to [***] for a Product that *[***]*, regardless of which Party owns such [***].

8.9. **Joint Research Agreement under the Leahy-Smith America Invents Act**. If a Party intends to invoke its rights under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act, it will notify the other Party and neither Party will make an election under such provision when exercising its rights under this ARTICLE 8 without the prior written consent of the other Party (such consent not to be unreasonably withheld, conditioned or delayed), and the Parties will use reasonable efforts to cooperate and coordinate their activities with such 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).

8.10. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 8 will be subject to the restrictions set forth in Section 5.5, *provided*, *however*, that, to the extent that Akcea has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Novartis hereunder and, this Agreement purports to grant any such rights to Novartis, Akcea will act in such regard with respect to such Patent Rights at Novartis' direction.

8.11. **Additional Rights and Exceptions**. Other than as set forth in this ARTICLE 8, Akcea retains the sole right to (i) commence, control, prosecute and settle any Proceeding involving Volanesorsen, and (ii) Prosecute and Maintain (A) Akcea Special Product-Specific Patents, (B) Akcea Core Technology Patents, and (C) Akcea Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Akcea Special Product-Specific Patents, Akcea Core Technology Patents and Akcea Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Akcea and Covering Akcea Special Product-Specific Patents, the Akcea Core Technology Patents or Akcea Manufacturing and Analytical Patents is at risk.

8.12. **Patent Term Extension**. The Parties will cooperate with each other in gaining patent term extension wherever applicable to a Product, and Novartis will determine which Akcea Product-Specific Patents (other than Akcea Special Product-Specific Patents) will be extended.

ARTICLE 9.
REPRESENTATIONS, WARRANTIES AND COVENANTS

9.1. **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants as of the Effective Date (and covenants as applicable) to the other Party that:

9.1.1. it is a corporation duly organized, validly existing, and in good standing under the laws of its jurisdiction of incorporation;

9.1.2. 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;

9.1.3. 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;

9.1.4. other than compliance with the HSR Act for the exercised Options granted hereunder, all necessary consents, approvals and authorizations of all Regulatory Authorities 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;

9.1.5. the execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the certificate of incorporation, bylaws or any similar instrument of such Party, as applicable, and (b) do not conflict with, violate, or breach or constitute a default or require any consent not already obtained under, any contractual obligation or court or administrative order by which such Party is bound;

9.1.6. all employees, consultants, or (sub)contractors (except academic collaborators or Third Parties under material transfer agreements) of such Party or Affiliates performing development activities hereunder on behalf of such Party will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to such Party or Affiliate, respectively, as the sole owner thereof;

9.1.7. (i) neither such Party nor, to the actual knowledge of such Party, any employee, agent or subcontractor of such Party involved or to be involved in the Development of the Products has been debarred under Subsection (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335a); (ii) no Person who is known by such Party to have been debarred under Subsection (a) or (b) of Section 306 of said Act will be employed by such Party in the performance of any activities hereunder; and (iii) to the actual knowledge of such Party, no Person on any of the FDA clinical investigator enforcement lists (including, but not limited to, the (1) Disqualified/Totally Restricted List, (2) Restricted List and (3) Adequate Assurances List) will participate in the performance of any activities hereunder;

9.1.8. during the term of this Agreement, neither Party nor any of its Affiliates shall disclose any Confidential Information of the other Party relating to any Product to any Third Party if such disclosure would fundamentally frustrate the purpose of this Agreement;

9.1.9. Akcea has taken reasonable precautions, and during the term of this Agreement each Party will take reasonable precautions, to preserve the confidentiality of the Licensed Know-How, including requiring each Person having access to the Licensed Know-How to be subject to confidentiality, non-use, and non-disclosure obligations protecting the Licensed Know-How as the confidential, proprietary materials and information of Akcea;

9.1.10. there are no claims pending or, to each Party's Knowledge, threatened against such Party or any of its Affiliates, nor is such Party or any of its Affiliates a party to any judgment or settlement, that would be reasonably expected to adversely affect or restrict the ability of such Party to consummate any of the transactions contemplated under this Agreement or to perform any of its obligations under this Agreement, or which would affect any of the Licensed Technology, including the Licensed Patents, or Akcea's Control thereof, or any Product;

9.1.11. all non-clinical and clinical studies and trials conducted by a Party on AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, have been and will be conducted in accordance with Applicable Law and, as applicable, GLP and GCP;

9.1.12. except for any activities Akcea is obligated to conduct under the Prior Agreements as in effect on the Effective Date, each Party does not and during the term of this Agreement will not conduct any activities which would violate ARTICLE 4; and

9.1.13. Each Party and its Affiliates have conducted and will conduct their business in compliance with the Foreign Corrupt Practices Act of 1977, the UK Bribery Act of 2010 and any other applicable anti-corruption Laws.

9.2. **Representations, Warranties and Covenants of Akcea**. Akcea hereby represents and warrants as of the Effective Date and any applicable bring-down date under Section 1.2.4 (and covenants as applicable) to Novartis that:

9.2.1. Except for certain Akcea Core Technology Patents noted in APPENDIX 4 that are jointly-owned by Ionis and Novartis, Akcea or Ionis is the sole and exclusive owner or exclusive licensee of, and has the right to grant all rights and licenses it purports to grant to Novartis with respect to, the Licensed Technology, including the Licensed Patents, in each case under this Agreement for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, free and clear of all liens, claims, security interests or other encumbrances of any kind (including prior license grants other than under the Akcea In-License Agreements) that would interfere, or the exercise of which would interfere, with Novartis's exercise of any license or right granted, or that may be granted, hereunder;

9.2.2. Except for certain Akcea Core Technology Patents noted in APPENDIX 4 that are jointly-owned by Ionis and Novartis, Akcea or Ionis is listed in the records of the appropriate governmental agencies as the sole and exclusive owner of record or exclusive licensee for each registration, grant and application included in the Licensed Patents;

9.2.3. the Licensed Technology was not and will not be funded by the U.S. federal government or otherwise subject to any rights of the U.S. federal government under the Bayh-Dole Act;

9.2.4. all Licensed Patents have been filed, prosecuted and maintained properly and correctly in all material respects;

9.2.5. neither Akcea nor any of its Affiliates has previously entered into, or during the term of this Agreement will enter into, any agreement, whether written or oral, with respect to, or has otherwise assigned, transferred, licensed, conveyed or otherwise encumbered, or during the term of this Agreement will otherwise assign, transfer, license, convey or otherwise encumber, any portion of its right, title or interest in or to, the Licensed Technology (including by granting any covenant not to sue with respect thereto) in such a way as to make the representation set forth in Section 9.2.1 not true;

9.2.6. each Akcea Product-Specific Patent and, to Akcea's Knowledge, each of the other Licensed Patents, properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent Right is issued or such application is pending;

9.2.7. to Akcea's Knowledge, the issued patents in the Licensed Patents are valid and enforceable without any claims, challenges, oppositions, nullity actions, interferences, *inter-partes* reexaminations, *inter-partes* reviews, post-grant reviews, derivation proceedings or other proceedings pending or threatened;

9.2.8. to Akcea's Knowledge, neither Akcea nor any of its Affiliates has committed any act, or omitted to commit any act, that may cause the Licensed Patents to expire prematurely or be declared invalid or unenforceable;

9.2.9. all application, registration, maintenance and renewal fees in respect of the Licensed Patents existing as of the Effective Date have been paid and all necessary documents and certificates have been filed with the relevant agencies for the purpose of maintaining such Licensed Patents;

9.2.10. as of the Effective Date, neither Akcea nor any of its Affiliates has received any written Claim alleging that any of the Licensed Technology is invalid or unenforceable;

9.2.11. where Akcea's or its Affiliates' ownership of any of the Licensed Technology is based upon or depends on a sequence of historical transfers of title to any of the Licensed Technology (i.e., chain of title to the applicable Licensed Technology) being valid, effective and free from defects and other problems, if at any time there is a potential defect with the validity or effectiveness in such transfers or other problems in such chain of title, then Akcea and its Affiliates shall, at their expense, with urgency and diligence, use reasonable efforts to make any and all corrections and clarifications, including preparing any documents and obtaining any necessary Third Party signatures and consents, as may be necessary, including filing such documents in any patent office as appropriate, to remedy any such problems and to restore such chain of title;

9.2.12. as of the Effective Date, Akcea has not received any written claim alleging that any of Akcea's activities relating to AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx} infringes or misappropriates any intellectual property rights of a Third Party;

9.2.13. (i) the licenses granted to Akcea under the Akcea In-License Agreements are in full force and effect, (ii) Akcea has not received any written notice, and is not aware, of any breach by any party to the Akcea In-License Agreements, and (iii) Akcea's performance of its obligations under this Agreement (including the Pre-Option Development Plan as it exists on the Effective Date) will not constitute a breach of Akcea's obligations under the Akcea In-License Agreements or the licenses granted to Akcea thereunder;

9.2.14. to Akcea's Knowledge, in respect of the pending United States patent applications included in the Licensed Patents, Akcea or its Affiliates have submitted all material prior art of which it or they are aware in accordance with the requirements of the United States Patent and Trademark Office;

9.2.15. to Akcea's Knowledge, (i) there are no rights of any Person that may be infringed, misappropriated or violated by any of the activities specifically anticipated by Akcea as of the Effective Date to be performed under this Agreement, and (ii) the manufacture (as manufactured by Akcea or its Affiliate), use and sale of each Product in the product presentation existing on the Execution Date does not and will not infringe any of Akcea's or any Third Party's Patent Rights, Know-How or other intellectual property rights; Provided that Novartis cannot assert a claim against Akcea for breach of this Section 9.2.15 related to any Third Party Patent Rights Novartis has Knowledge of as of the Effective Date;

9.2.16. Akcea has not used, and during the term of this Agreement will not knowingly use in the Development, Manufacture or Commercialization of any Product any Know-How that is encumbered by any contractual right of or obligation to a Third Party that conflicts or interferes with any of the rights or licenses granted or that may be granted to Novartis hereunder;

9.2.17. As of the Effective Date, neither Akcea or any of its Affiliates has granted any right or license to practice any Know-How related to, or Patent Rights that Cover, the Development, Manufacture or Commercialization of any Product that conflicts or interferes with any of the rights or licenses granted or that may be granted to Novartis hereunder;

9.2.18. As of the Effective Date, neither Akcea nor any of its Affiliates has initiated or been involved in any Claim in which it has alleged that any Third Party is or was infringing or misappropriating any Licensed Technology, nor has any such Claim been threatened by Akcea or any of its Affiliates, nor do Akcea or any of its Affiliates know of any valid basis for any such Claim;

9.2.19. except for the Akcea In-License Agreements, as of the Effective Date, there are no agreements pursuant to which Akcea or any of its Affiliates has in-licensed or otherwise acquired the right to practice any Know-How related to, or Patent Rights that Cover, the Development, Manufacture or Commercialization of any Product;

9.2.20. to Akcea's Knowledge, no officer, employee or consultant of Akcea or any of its Affiliates is, or during the term of this Agreement will be, subject to any agreement that requires such individual to assign any interest in any Licensed Technology to any Third Party;

9.2.21. the Patents listed in APPENDICES 4, 5 and 6 are a complete and correct listing of the relevant Akcea Core Technology Patents, Akcea Manufacturing and Analytical Patents, and Akcea Product Specific Patents which are owned or otherwise Controlled by Akcea;

9.2.22. other than the Akcea Core Technology Patents, Akcea Manufacturing and Analytical Patents, and Akcea Product Specific Patents, no other Patent Rights are owned by or licensed to Akcea or any of its Affiliates as of the Effective Date that are necessary or reasonably useful for the Development, Manufacture or Commercialization of a Product;

9.2.23. Except as otherwise expressly provided in this Agreement, Akcea or its Affiliate shall be and remain solely responsible for fulfilling and performing at its cost and expense, any and all obligations under each Akcea In-License Agreement, including timely, full and complete payment of any and all amounts due thereunder or in connection therewith to the other parties thereto;

9.2.24. Akcea shall not, and shall cause its Affiliates not to, incur or permit to exist, with respect to any Licensed Technology, any lien, encumbrance, charge, security interest, mortgage, liability, assignment, grant of license or other obligation that is or would be inconsistent with the licenses and other rights granted to, or that may be granted to, Novartis under this Agreement;

9.2.25. Akcea shall not enter into any amendment to any Akcea In-License Agreement that adversely affects any rights granted to, or that may be granted to, Novartis hereunder without the prior written consent of Novartis;

9.2.26. Akcea will promptly furnish Novartis with true and complete copies of all amendments to the Akcea In-License Agreements arising after the Effective Date;

9.2.27. Akcea will remain, and cause its Affiliates to remain, in compliance in all material respects with all Akcea In-License Agreements; and

9.2.28. Akcea will furnish Novartis with copies of all notices received by Akcea or any of its Affiliates relating to any alleged breach or default by Akcea or any of its Affiliates under any Akcea In-License Agreement within seven (7) calendar days after receipt thereof and thereafter furnish Novartis with copies of all correspondence and summaries of material discussions between the applicable parties to the Akcea In-License Agreement relating to the alleged breach, including any proposed resolution of the matter.

9.3. DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 9, NOVARTIS AND AKCEA MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND NOVARTIS AND AKCEA EACH SPECIFICALLY DISCLAIM ANY 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 PATENT RIGHTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 10.
INDEMNIFICATION; INSURANCE

10.1. **Indemnification by Novartis**. Novartis agrees to defend Akcea, its Affiliates and their respective directors, officers, employees and their respective successors, heirs and assigns (collectively, the "***Akcea Indemnitees***"), and will indemnify and hold harmless the Akcea Indemnitees, from and against any liabilities, losses, costs, damages, fees or expenses payable to a Third Party, and reasonable attorneys' fees and other legal expenses with respect thereto (collectively, "***Losses***") arising out of any claim, action, lawsuit or other proceeding by a Third Party (collectively, "***Third Party Claims***") brought against any Akcea Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by a Novartis employee, consultant, Affiliate, Sublicensee, or (sub)contractor in the performance of the activities Novartis agrees to perform under this Agreement, including, the Manufacture, Development or Commercialization of any Product, or (b) any breach by Novartis of any of its representations, warranties or covenants pursuant to this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Akcea Indemnitee, (ii) any breach by Akcea of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Akcea Indemnitee, and *provided that* Novartis shall not be obliged to so indemnify, defend and hold harmless the Akcea Indemnities for any claims for which Akcea has an obligation to indemnify Novartis Indemnities pursuant to Section 10.2.

10.2. **Indemnification by Akcea**. Akcea agrees to defend Novartis, its Affiliates and their respective directors, officers, employees and their respective successors, heirs and assigns (collectively, the "***Novartis Indemnitees***"), and will indemnify and hold harmless the Novartis Indemnitees, from and against any Losses arising out of Third Party Claims brought against any Novartis Indemnitee and resulting from or occurring as a result of: (a) any activities that an Akcea employee, consultant, Affiliate, Sublicensee, or (sub)contractor has undertaken in respect of Products either prior to the Effective Date or outside the scope of this Agreement, or in the performance of the activities Akcea agreed to perform under this Agreement, including, the Manufacture, Development or Commercialization of any Product or Terminated Product, or (b) any breach by Akcea of any of its representations, warranties or covenants pursuant to this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Novartis Indemnitee, (ii) any breach by Novartis of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Novartis Indemnitee, and *provided that* Akcea shall not be obliged to so indemnify, defend and hold harmless the Novartis Indemnities for any claims for which Novartis has an obligation to indemnify Akcea Indemnities pursuant to Section 10.1.

10.3. **Notice of Claim**. All indemnification claims provided for in Section 10.1 or Section 10.2 will be made solely by such Party to this Agreement (the "***Indemnified Party***"). The Indemnified Party will give the indemnifying Party prompt written notice (an "***Indemnification Claim Notice***") of any Losses or the discovery of any fact upon which the Indemnified Party intends to base a request for indemnification under Section 10.1 or Section 10.2, but in no event will the indemnifying Party be liable for any Losses to the extent such Losses result from any delay in providing such notice. The failure or delay to so notify the Indemnified Party shall not relieve the indemnifying Party of any obligation or liability to the Indemnified Party, except to the extent that the indemnifying Party demonstrates that its ability to defend or resolve such Claim is adversely affected as a result of such failure or delay. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party will furnish promptly to the indemnifying Party copies of all papers and official documents received or sent in respect of any Losses and Third Party Claims.

10.4. **Defense, Settlement, Cooperation and Expenses**.

10.4.1. **Control of the Defense**. At its option, the indemnifying Party may assume the defense and handling of any Third Party Claim by giving written notice to the Indemnified Party within [***] ([***]) calendar days after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption and handling of the defense of a Third Party Claim by the indemnifying Party shall not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor shall it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. If the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party will as soon as is reasonably possible deliver to the indemnifying Party all original notices and documents (including court papers) received or sent by the Indemnified Party in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, except as provided in this Section 10.4.1, the Indemnified Party will be responsible for the legal costs or expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim.

10.4.2. **Right to Participate in Defense**. Without limiting Section 10.4.1, any Indemnified Party will be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided*, *however*, that such employment will be at the Indemnified Party's own cost and expense unless (a) the employment thereof has been specifically authorized by the indemnifying Party in writing, (b) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 10.4.1 (in which case the Indemnified Party will control the defense), or (c) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties under Applicable Law, ethical rules or equitable principles in which case the indemnifying Party will be responsible for any such costs and expenses of counsel for the Indemnified Party.

10.4.3. **Settlement**. With respect to any Third Party Claims relating solely to the payment of money damages in connection with a Third Party Claim and that will not admit liability or violation of Law on the part of the Indemnified Party or result in the Indemnified Party's becoming subject to injunctive or other relief or otherwise adversely affecting the business of the Indemnified Party in any manner (such as granting a license or admitting the invalidity of a Patent Right Controlled by an Indemnified Party), and as to which the indemnifying Party will have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party will have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, will deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 10.4.1, the indemnifying Party will have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss *provided* it obtains the prior written consent of the Indemnified Party (which consent will not be unreasonably withheld, delayed or conditioned). The indemnifying Party will not be liable for any settlement, consent to entry of judgment, or other disposition of a Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party will admit any liability with respect to or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party, such consent not to be unreasonably withheld, delayed or conditioned.

10.4.4. **Cooperation**. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party will, and will cause each other Indemnified Party to, cooperate in the defense or prosecution thereof and will furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation will include access during normal business hours afforded to indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnified Parties and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party will reimburse the Indemnified Party for all its reasonable out-of-pocket costs and expenses in connection therewith.

10.4.5. **Costs and Expenses**. Except as provided above in this Section 10.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim will be reimbursed on a Calendar Quarter basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

10.5. **Insurance**.

10.5.1. **Akcea's Insurance Obligations**. Akcea will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of Products.

10.5.2. **Novartis' Insurance Obligations**. Novartis hereby represents and warrants to Akcea that it will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement (including product liability), including its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by Novartis under this Agreement.

10.6. **LIMITATION OF CONSEQUENTIAL DAMAGES**. **EXCEPT FOR (A) THIRD PARTY CLAIMS THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 10, (B) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OR FRAUD UNDER THIS AGREEMENT, (C) A PARTY'S BREACH OF ARTICLE 4, (D) NOVARTIS' BREACH OF SECTION 6.5, OR (E) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

ARTICLE 11.
TERM; TERMINATION

11.1. **Agreement Term; Expiration**. This Section 11.1, ARTICLE 12 and ARTICLE 13 of this Agreement are effective as of the Execution Date and the remainder of this Agreement will become effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 11, will continue in full force and effect until this Agreement expires as follows:

11.1.1. where all Options have expired unexercised;

11.1.2. on a country-by-country and Product-by-Product basis, on the date of expiration of all payment obligations by Novartis under this Agreement with respect to such Product in such country; or

11.1.3. in its entirety upon the expiration of all payment obligations by Novartis under this Agreement with respect to the last Product in all countries pursuant to Section 11.1.2.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 11.1 or earlier termination of this Agreement pursuant to Section 11.2, is the "***Agreement Term***." If the Effective Date has not occurred by the [***] calendar day after the Execution Date, then either Party will have the right to terminate this Agreement, including this Section 11.1, ARTICLE 12 and ARTICLE 13, with immediate effect by providing written notice of such termination to the other Party. If by the [***] calendar day after the Execution Date, the Parties anticipate that the Effective Date may not occur by the [***] calendar day after the Execution Date, within [***] calendar days upon receiving written notice, the Parties will promptly meet to discuss in good faith any additional actions or amendments to the Agreement the Parties may take or agree upon to cause the Effective Date to occur as soon as reasonably practicable.

Other than the provisions of this Section 11.1, ARTICLE 12 and ARTICLE 13 which shall apply as of the Execution Date, the rights and obligations of the Parties under this Agreement will not become effective until the Effective Date. Upon the occurrence of the Effective Date, all other provisions of this Agreement shall become effective automatically without the need for further action by the Parties.

11.2. **Termination of the Agreement**.

11.2.1. **Novartis' Termination for Convenience**. At any time following payment by Novartis of the Upfront Option Fee under Section 3.2, subject to Section 11.3 below, Novartis will be entitled to terminate this Agreement in its entirety or in part on a Product-by-Product basis for convenience by providing [***] ([***]) calendar days written notice to Akcea of such termination.

11.2.2. **Termination for Material Breach**.

(a) **Novartis' Right to Terminate**. If Novartis has reason to believe that Akcea is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, which is governed by Section 11.2.3 below), then Novartis may deliver notice of such material breach to Akcea. If the breach is curable, Akcea will have [***] ([***]) calendar days to cure such breach. If Akcea fails to cure such breach within such [***] ([***]) calendar days period, or if the breach is not subject to cure, Novartis may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product basis if such breach does not relate to this Agreement in its entirety, by providing written notice to Akcea.

(b) **Akcea's Right to Terminate**. If Akcea has reason to believe that Novartis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1 or ARTICLE 6, which is governed by Section 11.2.3 below), then Akcea may deliver notice of such material breach to Novartis. If the breach is curable, Novartis will have [***] ([***]) calendar 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 [***] ([***]) calendar days following such notice). If Novartis fails to cure such breach within such [***] ([***]) calendar day or [***] ([***]) calendar day period, as applicable, or if the breach is not subject to cure, Akcea may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product basis if such breach does not relate to this Agreement in its entirety, by providing written notice to Novartis.

11.2.3. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Akcea fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 (as determined in accordance with Section 13.1), Novartis will notify Akcea and, within [***] ([***]) calendar days thereafter, Akcea and Novartis will meet through the CSC or JDCC (as applicable) and attempt to resolve the matter in good faith, and to devise a mutually agreeable plan to address any outstanding issues related to Akcea's use of Commercially Reasonable Efforts in ARTICLE 1. Following such a meeting, if Akcea fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 and such failure constitutes a material breach of this Agreement, then subject to Section 11.2.4 below, Novartis will have the right, at its sole discretion, to terminate this Agreement in whole or in part on a Product-by-Product basis.

(b) If Novartis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 or ARTICLE 6 (as determined in accordance with Section 13.1), Akcea will notify Novartis and, within [***] ([***]) calendar days thereafter, Akcea and Novartis 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 Novartis' use of Commercially Reasonable Efforts in ARTICLE 1 or ARTICLE 6. Following such a meeting, if Novartis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 or ARTICLE 6, and such failure constitutes a material breach of this Agreement then subject to Section 11.2.4 below, Akcea will have the right, at its sole discretion, to terminate this Agreement in part on a Product-by-Product basis.

11.2.4. **Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party in Section 11.2.2 or Section 11.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such [***] calendar day cure period or [***] calendar day notice period (as applicable), the Non-Breaching Party *will not* have the right to terminate this Agreement in accordance with Section 11.2.2 or Section 11.2.3, unless and until it has been determined in accordance with Section 13.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within [***] ([***]) calendar days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

11.2.5. **Termination for Insolvency**.

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

(b) All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") or analogous provisions of Applicable Law outside the U.S. licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code or analogous provisions of Applicable Law outside the U.S. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code or analogous provisions of Applicable Law outside the U.S. Upon the commencement of a bankruptcy proceeding of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and all embodiments which, if not already in its possession, will be promptly delivered to the non-bankrupt Party upon written request.

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

(a) asserts invalidity as a defense in any court proceeding brought by Akcea or its Affiliates asserting infringement of a Licensed Patent; or

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

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

11.2.7. **Termination for Safety Issue**. Each Party shall have the right to terminate this Agreement without any further obligations or liabilities towards the other Party (other than the consequences of termination set forth in Section 11.3 below), if, during the term of the Agreement, such Party delivers written notice to the other Party that such Party reasonably and in good faith has determined that the continued Development or Commercialization of such Product presents safety concerns that pose an unacceptable risk or threat of harm in humans, or (ii) would violate any Applicable Law, ethical principles, or principles of scientific integrity.

11.3. **Consequences of Expiration or Termination of this Agreement**.

11.3.1. **Consequence of Termination of this Agreement**. If this Agreement is terminated by a Party in accordance with Section 11.2 in its entirety or on a Product-by-Product basis at any time and for any reason, the following terms will apply to any such termination, but only to the extent of any such termination (i.e., with respect to the terminated Product (the "***Terminated Product***" and its Exclusive Target, the "***Terminated Target***"), or in its entirety):

(a) **Options**. If not exercised prior to the date of termination, Novartis' Option will terminate with respect to any Terminated Product.

(b) **Licenses**. Any license granted by Akcea to Novartis under Section 5.1 will terminate. Novartis and its Affiliates and, subject to Section 5.2.3, its Sublicensees will cease selling Terminated Products under such licenses, unless Akcea elects to have Novartis continue to sell the applicable Terminated Product as part of the Transition Services under Section 11.3.4; *provided, that* (i) in any case, unless otherwise agreed by the Parties under Section 11.3.4, Novartis and its Affiliates and Sublicensees will have the right to sell any remaining inventory of Terminated Product over a period of no greater than [***] months after the effective date of such termination, Novartis will pay Akcea royalties in accordance with Section 7.8 on the Net Sales of such inventory of such Products, to the extent not already paid; and (ii) if there are any Clinical Studies being conducted at the date of termination, Novartis shall be entitled to continue Developing and Manufacturing Products to the extent and for the period necessary to effect an orderly transfer or wind down of such Clinical Studies in a timely manner and in accordance with all Applicable Laws.

(c) **Exclusivity**. Neither Party will have any further obligations under ARTICLE 4 of this Agreement insofar as it relates to a Terminated Product and the Terminated Target.

(d) **Pre-Option Development Plan**. Neither Party will have any further obligations with respect to the Terminated Product under the Pre-Option Development Plan.

(e) **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 to which it does not retain rights under the surviving provisions of this Agreement. 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. Each Party will also be permitted to retain such additional copies of or any computer records or files containing the other Party's Confidential Information that have been created solely by automatic archiving and back-up procedures, to the extent created and retained in a manner consistent with the retaining Party’s standard archiving and back-up procedures, but not for any other use or purpose. All Confidential Information shall continue to be subject to the terms of this Agreement for the period set forth in ARTICLE 12.

(f) **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 under ARTICLE 7 accrue as of the date the applicable milestone event is achieved even if the payment is not due at that time.

(g) **Survival**. The following provisions of this Agreement will survive the expiration or earlier termination of this Agreement: Section 5.2.3 (Effect of Termination on Sublicenses); Section 5.3 (Consequences of Natural Expiration of this Agreement); Section 5.8 (Cross-Licenses Under Program Technology); Section 7.11.3 (Records Retention); Section 7.12 (Audits); Section 8.2.1 (Akcea Technology and Novartis Technology); Section 8.2.2 (Program Technology); Section 9.3 (Disclaimer of Warranty); ARTICLE 10 (Indemnification; Insurance); ARTICLE 11 (Term; Termination); ARTICLE 12 (Confidentiality); ARTICLE 13 (Miscellaneous); APPENDIX 1 (to the extent definitions are embodied in the foregoing listed Articles and Sections).

11.3.2. **Akcea: Special Consequences of Certain Terminations**. If (A) Novartis terminates the Agreement under Section 11.2.1 or Section 11.2.7 or (B) Akcea terminates this Agreement under Section 11.2.2(b), Section 11.2.3(b), Section 11.2.5, Section 11.2.6, or Section 11.2.7, then, in addition to the terms set forth in Section 11.3.1, the following additional terms will also apply but only with respect to the Terminated Product:

(a) Novartis will and hereby does grant to Akcea:

(i) a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all Novartis Technology (excluding Novartis Background Technology) Controlled by Novartis as of the date of such termination that Covers the Terminated Product as of such date;

(ii) a sublicensable, worldwide, non-exclusive royalty-bearing license or sublicense, as the case may be, under all Novartis Background Technology Controlled by Novartis as of the date of such termination that Covers the Terminated Product as of such date; *provided*, *however*, that Akcea will not sublicense to [***] any Novartis Background Know-How claiming or covering [***] without Novartis' prior written consent (such consent not to be unreasonably withheld, delayed or conditioned); and

(iii) in each case solely to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Terminated Product. Novartis will execute confirmatory license grants of the licenses granted to Akcea under this Section 11.3.2(a) within [***] ([***]) calendar days following the effective date of termination.

If, after the effective date of such termination, Akcea or any of its Affiliates or Sublicensees Commercializes a Terminated Product previously licensed to Novartis under Section 5.1.1 or Section 5.1.2 (as applicable), then Akcea will pay Novartis a mutually agreed royalty on terms to be negotiated in good faith.

(b) Within [***] ([***]) calendar days following the date of termination, Novartis will deliver to Akcea for use with respect to the Development and Commercialization of the Terminated Product, any Know-How, data, results, regulatory information, pricing and market access strategy information, health economic study information, material communications with payors, regulatory filings in the possession of Novartis, or copies thereof, as of the date of such termination that relate solely to such Terminated Product;

(c) Within [***] ([***]) calendar days following the date of termination, Novartis will grant to Akcea an exclusive, royalty-free, fully paid up license under any Trademarks that are specific to a Terminated Product solely for use with such Terminated Product;

(d) Akcea will control and be responsible for all aspects of the Prosecution and Maintenance of all Akcea Product-Specific Patents and Jointly-Owned Program Patents and Novartis will provide Akcea with (and will instruct its counsel to provide Akcea with) all of the information and records in Novartis' and its counsel's possession related to the Prosecution and Maintenance of such Akcea Product-Specific Patents and Jointly-Owned Program Patents, in each case only in respect of the Terminated Product;

(e) If requested by Akcea, Novartis will sell to Akcea all remaining API or Finished Drug Product in Novartis' possession at a price equal to [***] (or [***]) at the time such material was [***]; and

(f) Akcea may request Novartis to support (or cause to be supported by Novartis' CMO) a technology transfer to Akcea (or Akcea's designated Third Party supplier) of any technology, information and data reasonably related to Novartis' or such CMO's manufacturing and supply of API and/or Finished Drug Product for such Product, and if so requested, Novartis will, at no cost to Akcea for the first [***] hours of Novartis' time, support (or cause to be supported by Novartis' CMO) such a technology transfer and Novartis will (or will cause Novartis' CMO to) continue to (i) provide reasonable support and cooperation with Akcea's regulatory filings and interactions with Regulatory Authorities related to Novartis' or such CMO's API and/or Finished Drug Product manufacturing (including any required inspections), and (ii) supply (or cause to be supplied by Novartis' CMO) API and/or Finished Drug Product to Akcea, at a price equal to [***] ([***]) at the time such material was [***], for a period of up to [***] ([***]) months to enable Akcea to identify and contract with a suitable Third Party API and/or Finished Drug Product manufacturer.

11.3.3. **Novartis: Special Consequences of Certain Terminations**. If Novartis terminates this Agreement under Section 11.2.2(a), Section 11.2.3(a) or Section 11.2.5, all of the provisions of Section 11.3.1 will apply, *except* that Novartis, its Affiliates, and Sublicensees will have the right to sell any remaining inventory of Product and Novartis will pay Akcea royalties in accordance with Section 7.8 on the Net Sales of such inventory of such Products to the extent not already paid (unless Akcea elects to have Novartis continue to sell the applicable Terminated Product as part of the Transition Services under Section 11.3.4 (in which case Akcea will own all revenue derived from the Product after the termination date)).

11.3.4. **Transition Services**.

(a) In the case where (i) Novartis terminates the Agreement under Section 11.2.1 (Novartis' Termination for Convenience) or Section 11.2.7 (Termination for Safety Issue), or (ii) Akcea terminates this Agreement under Section 11.2.2(b) (Akcea's Right to Terminate), Section 11.2.3(b) (Remedies for Failure to Use Commercially Reasonable Efforts), or Section 11.2.6 (Termination for Patent Challenge) with respect to one or more Products, the Parties wish to provide a mechanism to ensure that patients who were being treated with the Product prior to such termination or who desire access to the Product can continue to have access to such Product while the regulatory and commercial responsibilities for the Product are transitioned from Novartis to Akcea. As such, Akcea may request Novartis perform transition services that are necessary or useful to (1) provide patients with continued access to the applicable Products, (2) enable Akcea (or Akcea's designee) to assume and execute the responsibilities under all Regulatory Approvals and ongoing Clinical Studies for the applicable Product, and (3) ensure long-term continuity of supply for the Product (collectively, the "***Transition Services***"), including Transition Services related to commercial matters, patient continuity, medical affairs, government and managed care contracts, quality, and supply chain and manufacturing. The Parties shall negotiate in good faith a Transition Services agreement and Novartis shall use Commercially Reasonable Efforts to provide such Transition Services on terms to be mutually agreed upon between the Parties for a maximum duration of [***] months (unless agreed otherwise).

ARTICLE 12.
CONFIDENTIALITY

12.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Confidential Information disclosed by the other Party or its Affiliates (the "***Disclosing Party***"). Subject to the other provisions of this ARTICLE 12, each Party shall hold as confidential such Information of the other Party and its Affiliates in the same manner and with the same protection as such Receiving Party maintains its own Confidential Information.

12.2. **Prior Confidentiality Agreement Superseded**. As of the Effective Date, this Agreement supersedes the Confidential Disclosure Agreement executed by Ionis and Novartis on February 4, 2016 (including any and all amendments thereto). All information exchanged among Ionis, Akcea and Novartis under such Confidential Disclosure Agreement are deemed Confidential Information hereunder and subject to the terms of this ARTICLE 12.

12.3. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose Confidential Information of the Disclosing Party to (i) employees, agents, contractors, consultants and advisors of the Receiving Party and its Affiliates, and sublicensees and to (ii) Third Parties to the extent reasonably necessary for the performance of its obligations or exercise of rights granted or reserved in this Agreement, in each case under confidentiality provisions no less restrictive than those in this Agreement. In addition, a Receiving Party or its Affiliates may disclose Confidential Information of the Disclosing Party (i) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 12.4 below), complying with applicable governmental regulations, obtaining Regulatory Approvals, conducting non-Clinical Studies or Clinical Studies, marketing a Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided*, *however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (ii) on a need-to-know basis, in communication with actual or potential lenders, potential acquirers, investors, merger partners, consultants, or professional advisors, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iii) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (iv) as mutually agreed to in writing by the Parties.

12.4. **Press Release; Publications; Disclosure of Agreement**.

12.4.1. **Announcement of Transaction**. On or promptly after the Execution Date and, on a Product-by-Product basis, on or promptly after exercise by Novartis of the Options, Novartis and Akcea (and/or Ionis) will issue a public announcement in form and substance mutually agreed by the Parties.

12.4.2. **Other Disclosures**.

(a) ***During the Option Period***. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 12.4, during the Option Period, neither Novartis nor its Affiliates will make any public announcements, press releases or other public disclosures concerning a Product, this Agreement or the terms or the subject matter hereof without the prior written consent of Akcea, which consent will not be unreasonably withheld, conditioned or delayed.

If, during the Option Period, Akcea intends to make any public announcements, press releases or other public disclosures regarding this Agreement or the terms or the subject matter hereof, or that will materially impact a Product, (i) unless Akcea's or its Affiliate's existing confidentiality obligations to a Third Party prohibit it from doing so, Akcea will submit such proposed public disclosure to Novartis for review at least [***] ([***]) Business Days in advance of such proposed public disclosure, (ii) Novartis will have the right to review and recommend changes to such communication, and (iii) Akcea will in good faith consider any changes that are timely recommended by Novartis.

(b) ***After Option Exercise***. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 12.4, after Option Exercise with respect to a Product, neither Akcea nor its Affiliates will make any public announcements, press releases or other public disclosures regarding this Agreement or the terms or the subject matter hereof, or that will materially impact a Product, without the prior written consent of Novartis, which consent will not be unreasonably withheld, conditioned or delayed.

If, after Option exercise, Akcea or its Affiliates intend to make any public announcements, press releases or other public disclosures that will materially impact a Product, (i) unless Akcea's or its Affiliate's existing confidentiality obligations to a Third Party prohibit it from doing so, Akcea will submit such proposed public disclosure to Novartis for review at least [***] ([***]) Business Days in advance of such proposed public disclosure, (ii) Novartis will have the right to review and recommend changes to such communication, and (iii) Akcea will in good faith consider any changes that are timely recommended by Novartis.

If, after Option Exercise with respect to a Product, Novartis intends to make any public announcements, press releases or other public disclosures regarding this Agreement or the terms or the subject matter hereof, or that are significant to a Product (limited to disclosures concerning Product regulatory filings and approvals in Major Markets, reimbursement matters in Major Markets, data from Phase III clinical trials or supporting new indications regulatory filings, safety or efficacy issues, pricing or sales projections), (i) Novartis will submit such proposed public disclosure to Akcea for review at least [***] ([***]) Business Days in advance of such proposed public disclosure, (ii) Akcea will have the right to review and recommend changes to such communication, and (iii) Novartis will in good faith consider any changes that are timely recommended by Akcea.

Notwithstanding the foregoing, any public announcements, press releases or other public disclosures that involve work conducted by Akcea with a Product will (A) for work solely performed by Akcea, not require Novartis' consent (but Akcea will provide Novartis the review and comment rights above), (B) for work jointly performed by Novartis and Akcea, be issued jointly by Akcea and Novartis with content as mutually agreed, (C) acknowledge Akcea's and Ionis' role in discovering and developing such Product, and (D) contain Akcea's and Ionis' stock ticker symbols (e.g., Nasdaq: IONS) only to the extent such public disclosures include Novartis stock ticker symbol.

12.4.3. **Use of Name**. Except as set forth in Section 12.4.8, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

12.4.4. **Notice of Significant Events; Disclosure of Information Related to Products**. Each Party will use Commercially Reasonable Efforts to immediately notify (and provide as much advance notice as possible, but at a minimum [***] ([***]) Business Days advance notice to) the other Party of any event materially related or significant to a Product so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event. If Novartis intends to make a press release or similar public communication disclosing information that may materially impact a Product licensed by Novartis hereunder (i) Novartis will submit such proposed communication to Akcea for review at least [***] ([***]) Business Days in advance of such proposed public disclosure, (ii) Akcea will have the right to review and recommend changes to such communication, and (iii) Novartis will in good faith consider any changes that are timely recommended by Akcea. For the purpose of this Section 12.4.4, an event materially related or significant to a Product or information that may materially impact a Product shall be limited to events or information concerning Product regulatory filings, regulatory approvals in Major Markets, reimbursement matters in Major Markets, data from Phase III clinical trials or supporting new indications regulatory filings, safety and efficacy issues, pricing or sales projections. If Akcea intends to make a press release or similar public communication disclosing material information that can negatively impact the Product, unless Akcea's or its Affiliate's existing confidentiality obligations to a Third Party prohibit it from doing so, (i) Akcea will submit such proposed communication to Novartis for review at least [***] ([***]) Business Days in advance of such proposed public disclosure, (ii) Novartis will have the right to review and recommend changes to such communication, and (iii) Akcea will in good faith consider any changes that are timely recommended by Novartis.

12.4.5. **Scientific or Clinical Presentations**. Upon exercise of the Option on a Product-by-Product basis, Novartis shall be solely responsible for any Scientific or Clinical Presentations related to the Product. Any Scientific or Clinical Presentation relating to the Product that represents work in which Akcea (or its Affiliate) and for which Akcea is an author or a co-author, authorship will be mutually agreed to by Novartis and Akcea before any such abstract, presentation or publication is submitted to the Third Party publisher for publication and will appropriately represent the contribution of Akcea (or its Affiliate), Novartis and any Third Party collaborators. Industry-recognized principles of both inclusion of authors and order of authors will be applied to respect appropriately the contributions of all parties to the inventions or data being presented or published. For abstract, presentation or publication that are authored or co-authored with Akcea according to the preceding sentence, each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising under this Agreement. Each Party will first submit to the other Party an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least [***] ([***]) Business Days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. If at any time during such [***] ([***]) Business Day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to [***] ([***]) calendar days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication. In Scientific or Clinical presentation, Novartis will acknowledge Akcea (as an affiliate of Ionis) role in discovering the Product and that the Product is under license from Akcea. For the avoidance of doubt, the term of this Section 12.4.5 shall be limited to publication authored or co-authored by Akcea personnel in peer reviewed journal and limited to abstracts authored or co-authored by Akcea at international congresses.

12.4.6. **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

12.4.7. **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or a Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

12.4.8. **Acknowledgment**. Novartis will acknowledge in any press release, public presentation or publication regarding a Product, Akcea's and/or Ionis' role in discovering and developing the Product, that the Product is under license from Akcea and otherwise acknowledge Akcea's contributions, and Akcea's and, if referring to Ionis or Akcea as an Affiliate of Ionis, Ionis' and Akcea's stock ticker symbol (e.g., Nasdaq: IONS). Akcea and Ionis may include each Product (and identify Novartis as its partner for the Product) in Akcea's and Ionis' respective drug pipelines, any press release, public presentation or publication mentioning a Product.

ARTICLE 13.
MISCELLANEOUS

13.1. **Dispute Resolution**.

13.1.1. **General**. The Parties recognize that a dispute may arise relating to this Agreement ("***Dispute***"). Except as set forth in Sections 7.9.3(c), 8.2.3 and 13.1.5, any Dispute between the Parties or their respective Affiliates will be resolved in accordance with this Section 13.1.

13.1.2. **Continuance of Rights and Obligations during Pendency of Dispute Resolution**. If there are any Disputes in connection with this Agreement, including Disputes related to termination of this Agreement under ARTICLE 11, all rights and obligations of the Parties will continue until such time as any Dispute has been resolved in accordance with the provisions of this Section 13.1.

13.1.3. **Escalation**. Subject to Section 13.1.5, any claim, Dispute, or controversy as to the breach, enforcement, interpretation or validity of this Agreement will be referred to the Chief Executive Officer of Novartis Pharmaceuticals Unit and to the Chief Executive Officer of Akcea (the "***Executives***") for attempted resolution. If the Executives are unable to resolve such Dispute within [***] ([***]) calendar days of such Dispute being referred to them, then, upon the written request of either Party to the other Party, the Dispute will be subject to arbitration in accordance with Section 13.1.4, except as expressly set forth in Section 13.1.5 or Section 13.3.

13.1.4. **Arbitration**.

(a) If the Parties cannot resolve the Dispute through Escalation, and a Party desires to pursue resolution of the Dispute, any Dispute will be finally settled under the Rules of Arbitration of the ICC by a panel of three arbitrators appointed in accordance with said Rules, *provided however*, that the third arbitrator, who will act as president of the arbitral tribunal, will not be appointed by the International Court of Arbitration, but by the two arbitrators which have been appointed by either of the Parties in accordance with Article 12 para 4 of said Rules.

(b) The place of arbitration will be New York, New York and the language to be used in any such proceeding (and for all testimony, evidence and written documentation) will be English. The IBA Rules on the Taking of Evidence in International Arbitration will apply on any evidence to be taken up in the arbitration.

(c) Without limiting any other remedies that may be available under law, the arbitrators will have no authority to award consequential damages not permitted to be recovered pursuant to Section 10.6. The Parties agree to select the arbitrator(s) within [***] ([***]) calendar days after initiation of the arbitration. The hearing will be concluded within [***] ([***]) calendar days after selection of the arbitrator(s) and the award will be rendered within [***] calendar days after the conclusion of the hearing, or of any post hearing briefing, which briefing will be completed by both Parties within [***] ([***]) calendar 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 practicable.

(d) If the arbitration proceedings have been initiated under this Section 13.1.4 in order to fully or partially terminate this Agreement in accordance with Section 11.2.2 for material breach, both Parties will – during the pendency of the arbitration proceedings – strive to find an amicable solution to resolve the Dispute with the support of the arbitrators. If through such process Akcea and Novartis agree to a remediation plan and to a failure remedy that will apply if such breach is not cured (which may include the non-breaching Party's right to terminate this Agreement upon written notice to the breaching Party), then if the breaching Party subsequently materially fails to execute such remediation plan within [***] ([***]) calendar days after the date the Parties agreed to such remediation plan (or during a longer period of time if such breach is not reasonably curable within such [***]-calendar day period, so long as the breaching Party is pursuing a cure in good faith) the non-breaching Party will have the right to exercise and receive the applicable failure remedy. In such case the Parties will mutually terminate the pending arbitration procedure and, so long as the non-breaching Party has received the applicable failure remedy, the non-breaching Party will not be entitled to reinitiate the arbitration proceedings to seek the full or partial termination of this Agreement on the same or essentially the same facts.

(e) EXCEPT IN THE CASE OF COURT ACTIONS PERMITTED BY SECTION 13.1.5 AND FOR CLAIMS NOT SUBJECT TO ARBITRATION PURSUANT TO SECTION 13.1.4 AS SET FORTH IN SECTION 13.1.5, EACH PARTY HERETO WAIVES: (1) ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY, (2) WITH THE EXCEPTION OF RELIEF MANDATED BY STATUTE, ANY CLAIM TO PUNITIVE, EXEMPLARY, MULTIPLIED, INDIRECT, CONSEQUENTIAL OR LOST PROFITS/REVENUES DAMAGES, AND (3) ANY CLAIM FOR ATTORNEY FEES, COSTS AND PREJUDGMENT INTEREST.

(f) 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 arbitrators; *provided, however*, the arbitrators 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.), and/or the fees and costs of the administrators and the arbitrators.

13.1.5. **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 may be an appropriate remedy. In addition, except as set forth otherwise in Section 7.9.3(c) and Section 8.2.3 either Party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of Patent Rights or other intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 13.1.4.

13.2. **Governing Law; Jurisdiction; Venue; Service of Process**. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of New York, U.S.A., without reference to conflicts of laws principles. The United Nations Convention on Contract for the International Sales of Goods (1980) shall not apply to the interpretation of this Agreement.

13.3. **Recovery of Losses**. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 7.8.2(e), Section 10.1 or Section 10.2, and the offsets under Sections 7.9.3(b) and Section 7.9.3(d)). Except for the offset and credits explicitly set forth in Section 7.12, Section 7.9.3(b), and Section 7.9.3(d), a final and binding decision of the arbitrators in accordance with Section 13.1.4 or by the court of competent jurisdiction in accordance with Section 13.1.5 neither Party will have the right to set off any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

13.4. **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction. In addition, Akcea may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Novartis' consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Except in the case where Akcea assigns or transfers its rights to receive payments under this Agreement to a Third Party, any permitted assignee will assume all obligations of its assignor under this Agreement. Subject to the terms of this Agreement, this Agreement will be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns. Unless explicitly agreed otherwise in writing between the Parties, if any assignment of this Agreement or of any rights or obligations under this Agreement results in higher withholding taxes compared to the withholding taxes applicable prior to such assignment, then such higher withholding taxes will be borne by the assigning Party ("***Transferring Party***") such that the Party ("***Non-Transferring Party***") entitled to receive a given payment under this Agreement receives the amount of such payment such Party would have otherwise received under this Agreement but for the assigning Party's transfer or assignment. Any purported assignment or transfer made in contravention of this Section 13.4 will be null and void. This Section 13.4 will apply to the assignment of Licensed Technology *mutatis mutandis*.

13.5. To the extent the Non-Transferring Party utilizes a [***] in any year, the Non-Transferring Party will [***] the Transferring Party an amount equal to (i) [***]% of the [***] or (ii) [***] the Non-Transferring Party resulting from the [***], which [***] will be calculated as the sum of (a) the amount [***] multiplied by the highest [***] applicable to the Non-Transferring Party; plus (b) any [***] of the [***] by the Non-Transferring Party. To assist the Transferring Party in determining when a [***] from the Non-Transferring Party pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which the Transferring Party [***] (i.e., [***]) payment under this Section 13.4, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party [***] or [***]), the Non-Transferring Party will provide the Transferring Party with the relevant portions of the Non-Transferring Party's Annual tax returns (federal and state) and, in years in which the Non-Transferring Party utilizes the [***], supporting documentation for such [***].

13.6. **Change of Control Event Involving Novartis or Akcea**. A Party subject to a Change of Control Event will provide written notice to the other Party within [***] ([***]) calendar days following the closing of a Change of Control Event, and such notice will identify the Third Party acquiring company (the "***Acquirer***") and the contact information of the person at the Acquirer with whom the other Party will work to schedule meetings between the Acquirer and the other Party. Within [***] ([***]) calendar days following the closing of such Change of Control Event, the Party or the Acquirer will meet or hold a teleconference with the other Party at a mutually agreed date, time and/or place to discuss any possible impacts of the Change of Control Event for this Agreement. In the event of a change of control involving Akcea, within [***] calendar days following the announcement of a Change of Control Event, Novartis, Akcea and Ionis shall meet and negotiate in good faith any amendment required to this Agreement reflecting obligations that may have been assumed by Ionis on behalf of Akcea and rights that may be owned by Ionis but that may be required for Novartis to fully exercise the licenses granted under this Agreement.

13.7. Subcontracting.

13.7.1. Subject to the terms of this Section 13.7, each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement. Each Party will be responsible for any income or non-income taxes that arise as a result of such Party's use of any Third Party subcontractors hereunder, including payroll, income, withholding, sales and use, VAT, customs, duties excise or property taxes, and such taxes will not be reimbursable expenditures.

13.7.2. Akcea agrees that, where Novartis wishes to (sub)contract with a Third Party with respect to any of the rights granted under Section 1.3.2, Akcea will, within [***] ([***]) calendar days of any request by Novartis, provide Novartis with a letter of authorization as necessary for Novartis to be able to contract with such Third Party in accordance with the terms of this Agreement. Novartis will use Commercially Reasonable Efforts to ensure that CMOs Novartis may use to conduct the manufacturing activities contemplated by Section 1.3.2 will be obligated to assign to Novartis all right, title and interest in and to any inventions developed by such (sub)contractors in the performance of such activities. In addition, Novartis will use Commercially Reasonable Efforts to include in agreements with CMOs, the [***] in the event the applicable Option is terminated, expires unexercised or this Agreement is terminated.

13.8. 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, war, terrorism, cyber-attacks, 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 shall promptly 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 and shall use commercially reasonable efforts to minimize the duration of any force majeure and resume performance of its obligation as promptly as practicable. Notwithstanding the foregoing, if such Force Majeure event induced delay or failure of performance continues for a period [***] ([***]) calendar days, after which time the Parties will negotiate in good faith any permanent or transitory 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.

13.9. **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 (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Akcea, addressed to:	Akcea Therapeutics, Inc. 55 Cambridge Parkway Cambridge, MA 02142 Attention: Chief Executive Officer Fax: 760-602-1855
with a copy to: (so long as Ionis and Akcea are Affiliates)	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to Novartis, addressed to:	Novartis Pharma AG Lichtstrasse 35 4002, Basel, Switzerland Attention: General Counsel [***]
with a copy to:	Novartis Pharma AG Lichtstrasse 35 4002, Basel, Switzerland Attention: Head Global Business Development & Licensing [***]

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 facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service.

13.10. **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement shall 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 shall be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term. No waiver shall be effective unless it has been given in writing and signed by the Party giving such waiver.

13.11. **Severability**. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

13.12. **Entire Agreement; Modifications**. This Agreement (including the attached Appendices and Schedules) 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 thereto 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.

13.13. **Independent Contractors**. Nothing herein will be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party will assume, either directly or indirectly, any liability of or for the other Party. Neither Party will have the authority to bind or obligate the other Party and neither Party will represent that it has such authority.

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

13.15. **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with their respective Applicable Law.

13.16. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

13.17. **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

13.18. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Appendices identifying the Licensed Technology 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.

13.19. **Counterparts**. This Agreement (or any notice, invoice or other document to be delivered by a Party hereunder) 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, and facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

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

13.21. **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, which directly or indirectly relate to activities under this Agreement, the other Party will be immediately notified in writing.

13.22. **Remedies at Law**. Without limiting Section 13.3 and except as expressly stated in this Agreement, the rights and remedies provided in this Agreement and all other rights and remedies available to either Party at law or in equity are, to the extent permitted by law, cumulative and not exclusive of any other right or remedy now or hereafter available at law or in equity.

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

IN WITNESS WHEREOF, THE PARTIES HAVE CAUSED THIS AGREEMENT TO BE EXECUTED BY THEIR REPRESENTATIVES THEREUNTO DULY AUTHORIZED AS OF THE EXECUTION DATE.

NOVARTIS PHARMA AG

By: /s/ Paul Hudson

Name: Paul Hudson

Title: CEO

NOVARTIS PHARMA AG

By: /s/ Nigel Sheail

Name: Nigel Sheail

Title: Head of Business Development & Licensing

SIGNATURE PAGE TO STRATEGIC COLLABORATION, OPTION AND LICENSE AGREEMENT

IN WITNESS WHEREOF, THE PARTIES HAVE CAUSED THIS AGREEMENT TO BE EXECUTED BY THEIR REPRESENTATIVES THEREUNTO DULY AUTHORIZED AS OF THE EXECUTION DATE.

AKCEA THERAPEUTICS, INC.

By: /s/ Paula Soteropolous
Name: Paula Soteropolous
Title: President & CEO

SIGNATURE PAGE TO STRATEGIC COLLABORATION, OPTION AND LICENSE AGREEMENT

LIST OF APPENDICES AND SCHEDULES

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***[***]***" means [***]% of [***]' good faith estimate of the total number of subjects to be enrolled in such [***] at the time such [***] is Initiated are enrolled in such [***] in accordance with the protocol; *provided, however*, if, after the Initiation of such [***], the total number of subjects to be enrolled in such [***] materially changes, then "*[***]*" will mean [***]% of such lower or higher total number of subjects to be enrolled in such [***] are enrolled in such [***] in accordance with the approved protocol (as amended from time to time).

"***Acceptance of NDA Filing***" means 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."

"***Accounting Standards***" means, with respect to Akcea, U.S. GAAP (United States Generally Accepted Accounting Principles) and means, with respect to Novartis, the IFRS (International Financial Reporting Standards), in each case, as generally and consistently applied throughout each Party's organization. Each Party shall promptly notify the other in the event that it changes the Accounting Standards pursuant to which its records are maintained, it being understood that each Party may only use internationally recognized accounting standards (e.g., U.S. GAAP, IFRS or equivalent).

"***Additional IP***" means Third Party (excluding Ionis) intellectual property that is necessary to practice a Licensed Patent to Commercialize a Product. For clarity, Additional IP does not include any Patent Rights claiming (or intellectual property related to) formulation or delivery technology, other active ingredients or Conjugate Technology (other than the THA Cluster).

"***Adjusted Payment Period***" has the meaning set forth in Section 7.8.2(c).

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 11.1.

"***Akcea***" has the meaning set forth in the Preamble of this Agreement.

"***Akcea Activities***" means the non-clinical and/or clinical activities for which Akcea or its Affiliates are designated as responsible under the Pre-Option Development Plan.

"***AKCEA-APO(a)-L$_{Rx}$***" means the Oligonucleotide known as ISIS 681257 (also known as IONIS-APO(a)-L$_{Rx}$) having the following sequence and chemistry: 5'-THA-AH$_{P=O}$^{Me}UG$_{P=O}$^{Me}C$_{P=O}$^{Me}U$_{P=O}$^{Me}C$_{P=O}$^{Me}CGTTGGTG^{Me}CT^{Me}U$_{P=O}$G$_{P=O}$^{Me}U^{Me}U^{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 Oligonucleotide 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 structure and the choice for the symbol depends on whether the sugar is 2′-deoxy-D-ribose or D-ribose. The $_{P=O}$ designates the location of a phosphate diester linkage. Each of the other internucleoside linkages is a phosphorothioate diester linkage. AH designates the location of the aminohexyl linker and THA is 5-N-{tris[(6-(2-acetamido-3,4,6-tri-O-acetyl-β-D-galactopyranosyloxy)hexylamino)-3-oxopropoxymethyl]methyl}amino-5-oxopentanoyl.

"***AKCEA-APOCIII-L$_{Rx}$***" means the Oligonucleotide known as ISIS 678354 (also known as IONIS-APOCIII-L$_{Rx}$) having the following sequence and chemistry: 5'-THA-AH$_{P=O}$AG^{Me}C^{Me}U^{Me}U^{Me}CTTGT^{Me}C^{Me}CAG^{Me}C^{Me}U^{Me}U^{Me}UA^{Me}U-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 Oligonucleotide 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 structure and the choice for the symbol depends on whether the sugar is 2′-deoxy-D-ribose or D-ribose. The $_{P=O}$ designates the location of a phosphate diester linkage. Each of the other internucleoside linkages is a phosphorothioate diester linkage. AH designates the location of the aminohexyl linker and THA is 5-N-{tris[(6-(2-acetamido-3,4,6-tri-O-acetyl-β-D-galactopyranosyloxy)hexylamino)-3-oxopropoxymethyl]methyl}amino-5-oxopentanoyl.

"***Akcea Core Technology Patents***" means any Patent Rights owned, used, developed by, or licensed to Akcea or its Affiliates, in each case to the extent Controlled by Akcea or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to Oligonucleotides that are necessary to Develop, Manufacture or Commercialize a Product, other than Akcea Product-Specific Patents or Akcea Manufacturing and Analytical Patents. A list of Akcea Core Technology Patents as of the Effective Date is set forth on Appendix 4 attached hereto.

"***Akcea Indemnitees***" has the meaning set forth in Section 10.1.

"***[***] Information***" has the meaning set forth in [***].

"***Akcea In-License Agreements***" has the meaning set forth in Section 7.9.1(a). The Akcea In-License Agreements are set forth on Appendix 3.

"***Akcea Know-How***" means any Know-How, excluding Akcea's interest in any Jointly-Owned Program Know-How, owned, used, developed by, or licensed to Akcea or its Affiliates, in each case to the extent Controlled by Akcea or its Affiliates on the Effective Date or at any time during the Agreement Term that is necessary to Develop, Manufacture or Commercialize a Product. Akcea Know-How does not include the Akcea Manufacturing and Analytical Know-How.

"***Akcea Manufacturing and Analytical Know-How***" means Know-How, excluding Akcea's interest in any Jointly-Owned Program Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Akcea or its Affiliates, in each case to the extent Controlled by Akcea or its Affiliates on the Effective Date or at any time during the Agreement Term that is necessary to Develop, Manufacture or Commercialize a Product. Akcea Manufacturing and Analytical Know-How do not include the Akcea Know-How.

"***Akcea Manufacturing and Analytical Patents***" means Patent Rights, including Akcea's interest in any Jointly-Owned Program Patents, that claim Manufacturing Technology owned, used, developed by, or licensed to Akcea or its Affiliates, in each case to the extent Controlled by Akcea or its Affiliates on the Effective Date or at any time during the Agreement Term that are necessary to Develop, Manufacture or Commercialize a Product. A list of Akcea Manufacturing and Analytical Patents as of the Effective Date is set forth on APPENDIX 5 attached hereto.

"***Akcea Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Akcea or its Affiliates on the Effective Date or at any time during the Agreement Term that are necessary to Develop, Manufacture or Commercialize a Product. A list of Akcea Product-Specific Patents as of the Effective Date is set forth on APPENDIX 6 attached hereto.

"***Akcea Program Know-How***" has the meaning set forth in Section 8.2.2.

"***Akcea Program Patents***" has the meaning set forth in Section 8.2.2.

"***Akcea Program Technology***" has the meaning set forth in Section 8.2.2.

"***Akcea-Separate Product***" means a product (that is not a Product) and associated method(s) of use being developed or commercialized by Akcea, its Affiliate or sublicensee (e.g., Volanesorsen).

"***Akcea Special Product-Specific Patents***" has the meaning set forth in Section 8.3.1(b).

"***Akcea Supported Pass-Through Costs***" means the licensing costs and payments payable by Akcea under [***] to Third Parties to the extent arising from any Third Party intellectual property in-licensed or acquired by Akcea or its Affiliates under a Third Party agreement that is (i) included in the Licensed Patents or Licensed Know-How and (ii) necessary to Develop, Manufacture or Commercialize a Product.

"***Alliance Manager***" has the meaning set forth in Section 2.2.

"***Annual***" or "***Annually***" 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).

"***APO(a)***" means the RNA or the protein product encoded by, or the DNA of, the gene, apolipoprotein(a) (GenBank accession # NM_005577.2; Gene ID: 4018), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***APOCIII***" means the RNA or the protein product encoded by, or the DNA of, the gene, apolipoprotein C-III (GenBank accession # NM_000040.1; Gene ID: 345), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***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.

"***Auditor***" has the meaning set forth in Section 7.12.1.

"***Audit Report***" has the meaning set forth in Section 7.12.3.

"***Bankruptcy Code***" has the meaning set forth in Section 11.2.5(b).

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any calendar day other than a Saturday or Sunday on which banking institutions in New York, New York are open for business.

"***Calendar Quarter***" means a period of three consecutive months ending on the last calendar day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last calendar day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2017, the Effective Date) and ending on December 31.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control Event***" means any (a) direct or indirect acquisition of all or substantially all of the assets of a Party, (b) direct or indirect acquisition by a Person, or group of Persons acting in concert, of 50% or more of the voting equity interests of a Party, (c) tender offer or exchange offer that results in any Person, or group of Persons acting in concert, beneficially owning 50% or more of the voting equity interests of a Party, or (d) merger, consolidation, other business combination or similar transaction involving a Party, pursuant to which any Person owns all or substantially all of the consolidated assets, net revenues or net income of a Party, taken as a whole, or which results in the holders of the voting equity interests of a Party immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold 50% or more of the combined voting power of the surviving, purchasing or continuing entity immediately after such merger, consolidation, other business combination or similar transaction, in all cases where such transaction is to be entered into with any Person other than the other Party to this Agreement or its Affiliates.

"***CIOM Form***" means the Suspect Adverse Reaction Report Form as defined by the Council for International Organizations of Medical Sciences.

"***Clinical Study***" or "***Clinical Studies***" means, with respect to a Product, a Phase 1 Trial, Phase 2 Trial, Phase 2 Dose-Ranging Trial, Phase 3 Trial, Phase 4 Trial or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA, JNDA or other similar marketing application.

"***CMO***" means a Third Party contract manufacturer Manufacturing API, clinical supplies or Finished Drug Product for any purpose under this Agreement.

"***CMO Agreement***" has the meaning set forth in Section 1.3.2(c).

"***Co-Commercialize***" or "***Co-Commercialization***" means, with respect to a Product, conducting activities to market and sell such Product, including:

- field force detailing Products to Lipid Specialists;
- providing input on medical affairs communications;
- providing input on marketing materials and strategy;
- participating in field force trainings; and
- participating in Novartis presence at medical meetings and congresses.

"***Collaboration***" means the conduct of the Pre-Option Development Plan in accordance with this Agreement.

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to registering, marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a product (including a Product) following receipt of Regulatory Approval for such product in the applicable country, including conducting pre-and post-Regulatory Approval activities, including studies reasonably required to increase the market potential of such product and studies to provide improved formulation and product delivery, and launching and promoting the product in each country.

"***Commercially Reasonable Efforts***" means the level of effort, budget and resources normally used by a company in the pharmaceutical industry of similar size as the respective Party or in case there is no such industry standard, the level of effort, budget and resources normally used by the respective Party for a product owned or controlled by it, which is of similar profitability and at a similar stage in its development or product life, taking into account with respect to a product *inter alia* any issues of patent coverage, safety and efficacy, pricing, product profile, the proprietary position of the product, the competitive environment for the product and the likely timing of the product(s) entry into the market, the regulatory environment of the product and other relevant scientific, technical and commercial factors. Commercially Reasonable Efforts will be determined on a Product-by-Product and country-by-country basis.

"***Competitive Infringement***" has the meaning set forth in Section 8.6.

"***Competitive Oligo***" means an Oligonucleotide which acts to directly modulate an Exclusive Target.

"***Complete***," "***Completed***," or "***Completion***" means, with respect to a Clinical Study, the point in time at which database lock for such study has occurred and, if such study has a statistical analysis plan, the primary endpoint and key safety data (including tables, listings and figures validated by Akcea's statistician(s)) generated based on that database lock under the statistical analysis plan for such study are available.

"***Confidential Information***" means any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed by the Disclosing Party or otherwise received or accessed by the Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(a) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(b) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(c) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Conjugate Technology***" means a group of atoms covalently bound to an Oligonucleotide designed to enhance one or more properties of the Oligonucleotide, such as targeting 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 of antisense drugs.

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided, however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Akcea Supported Pass-Through Costs in the case of Akcea, and other than Novartis Supported Pass-Through Costs in the case of Novartis), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation unless the first Party is obliged to pay such costs under this Agreement. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party owned or controlled by such Third Party immediately prior to the date such Third Party becoming an Affiliate of a Party hereunder will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Core European Countries***" means the United Kingdom, Germany, France, Italy and Spain.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person would infringe a Valid Claim included in such patent.

"***CVOT***" has the meaning set forth in Section 1.1.

"***CVRR***" has the meaning set forth in Section 1.2.5.

"***Develop***," "***Developing***" or "***Development***" means, with respect to a product (including a Product) after such product is designated as a development candidate, any and all non-clinical, clinical or regulatory activity with respect to such product to seek approval by a regulatory authority to market and sell such product (including the submission of all necessary filings with applicable Regulatory Authorities to support such non-clinical and clinical activities and Regulatory Approval), including pharmacokinetic and toxicology studies required to meet the requirements for filing an IND and filing an IND with any regulatory authority, human clinical trials conducted after Regulatory Approval of such product to seek approval by a regulatory authority to market and sell such product for additional Indications.

"***Disclosing Party***" has the meaning set forth in Section 12.1.

"***Dispute***" has the meaning set forth in Section 13.1.1.

"***DOJ***" has the meaning set forth in Section 3.4.

"***Domain Names***" means any Domain Name identical or similar with the Trademarks under any ccTLD (country code Top Level Domain) and gTLD (generic Top Level Domain) address area.

"***Effective Date"*** means the date when the conditions stipulated in Section 3.6 and Section 3.7 are fulfilled or waived.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***End of Phase 2b Meeting***" means the first meeting with the FDA following Completion of the Phase 2 Dose-Ranging Trial and pertaining to the clinical program for a Product. In the case where FDA declines Akcea's request for a face-to-face End of Phase 2b Meeting, such meeting will be deemed to have occurred upon Akcea's or its Affiliate's receipt of a written response from FDA to the questions posed by Akcea or its Affiliate for such meeting and Akcea having provided to the FDA any additional information in the possession of or readily available to Akcea requested by the FDA as the case may be.

"***Exclusive Target***" means (i) APO(a), and (ii) APOCIII. Each Exclusive Target will remain an Exclusive Target under this Agreement during the period Novartis has the right to exercise its Option applicable to such Exclusive Target and, after Novartis exercises the applicable Option, so long as Novartis, its Affiliates or Sublicensees are Developing and/or Commercializing the Product applicable to such Exclusive Target under this Agreement.

"***Executives***" has the meaning set forth in Section 13.1.3.

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

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

"***Finished Drug Product***" means any drug product containing API as an active ingredient, in finished form for Development or Commercialization by a Party under this Agreement.

"***First Commercial Sale***" means, on a Product-by-Product basis, the first sale of such Product by Novartis, its Affiliate or its Sublicensee to a Third Party in a country after Regulatory Approval of such Product has been obtained in such country.

"***FTC***" has the meaning set forth in Section 3.4.

"***FTE***" means the efforts of one or more employees of Akcea equivalent to the efforts of one full-time Akcea employee for one year, or in the case of less than a full-time dedicated person, a full-time equivalent person-year based upon a total of [***] ([***]) hours per year of work.

"***Generic Product***" means (i) the identical Third Party oligonucleotide-based therapeutic as the Product in such country and (ii) such Third Party oligonucleotide-based therapeutic product has been approved by a Regulatory Authority in such country. Upon manufacturing, use or sale of such Generic Product with respect to any country that is [***] (each, a "***[***]***"), if Novartis, its Affiliate or Sublicensee has the right to enforce any Orange Book Patents or any other Patent Right Controlled by Novartis, its Affiliate or Sublicensee being infringed by the manufacture, use or sale of such Generic Product in such [***] and Novartis, its Affiliate or Sublicensee fails to use Commercially Reasonable Efforts to so enforce such Orange Book Patents and other Patent Rights against the Third Party who is selling such Generic Product in such [***], then such Third Party product will not be a "*Generic Product*" in such [***] under this Agreement.

"***Governmental Authority***" means any United States federal, state or local or any foreign government, or political subdivision thereof, or any local, state, national or multinational organization or authority or any authority, agency or commission entitled to exercise any administrative, executive, judicial, legislative, police, regulatory or taxing authority or power, any court or tribunal (or any department, bureau or division thereof), or any arbitrator or arbitral body.

"***HSR Act***" means the United States Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended from time to time.

"***HSR Clearance Date***" means the earliest date on which the Parties have actual knowledge that all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Filing***" means filings by Akcea and Novartis with the FTC and the DOJ of a Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) with respect to the matters set forth in this Agreement, together with all required documentary attachments thereto.

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***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 filing (or foreign equivalent filing) to obtain Regulatory Approval to market and sell a Product for such disease.

"***Indirect Taxes***" means value added taxes, sales taxes, consumption taxes and other similar taxes required by law to be disclosed on the invoice.

"***Initial Payment Period***" has the meaning set forth in Section 7.8.2(a).

"***Initiation***" or "***Initiate***" means, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Ionis-Akcea License Agreement***" means that certain Development, Commercialization and License Agreement between Ionis and Akcea dated December 18, 2015, as amended.

"***Ionis Internal ASO Safety Database***" has the meaning set forth in Section 6.8(b).

"***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).

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 8.1.1.

"***Jointly-Owned Program Know-How***" has the meaning set forth in Section 8.2.2.

"***Jointly-Owned Program Patents***" has the meaning set forth in Section 8.2.2.

"***Jointly-Owned Program Technology***" has the meaning set forth in Section 8.2.2.

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable, and in each case that are unpatented.

"***Knowledge***" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Effective Date; *provided that*, with respect to information regarding the status of Patent Rights or other intellectual property rights, "*Knowledge*" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Effective Date after performing a diligent investigation with respect to such facts and information as is customary in the conduct of its business with respect to such Patent Rights or other intellectual property rights (and not, for clarity, a diligent investigation solely in connection with this Agreement).

"***Licensed Know-How***" means Akcea Manufacturing and Analytical Know-How, Akcea Program Know-How, and Akcea Know-How. For clarity, Licensed Know-How does not include (i) any Know-How covering formulation technology or delivery devices (other than Conjugate Technology), and (ii) Akcea's and its Affiliate's interest in any Jointly-Owned Program Know-How.

"***Licensed Patents***" means the Akcea Product-Specific Patents, Akcea Core Technology Patents, Akcea Manufacturing and Analytical Patents, and Akcea Program Patents. For clarity, Licensed Patents do not include (i) any Patent Rights claiming formulation technology or delivery devices (other than Conjugate Technology), and (ii) Akcea's and its Affiliate's interest in any Jointly-Owned Program Patents.

"***Licensed Technology***" means, on a Product-by-Product basis, any and all Licensed Patents and Licensed Know-How to the extent necessary to Develop, Manufacture or Commercialize a Product. Licensed Technology expressly excludes Akcea's and its Affiliate's interest in any Jointly-Owned Program Technology.

"***Losses***" has the meaning set forth in Section 10.1.

"***MAA***" means a marketing authorization application filed with the EMA after completion of Clinical Studies 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, with respect to a Product in Europe, approval of the MAA from the applicable Regulatory Authority in at least three Core European Countries sufficient for the manufacture, distribution, use, marketing and sale of such Product and either (x) pricing and reimbursement approval in such three Core European Countries in accordance with Applicable Laws has been obtained, or (y) the sale of a Product in such three Core European Countries has occurred.

"***Major Market***" means any of the following countries: [***].

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for non-clinical and clinical purposes, of API or a Product in finished form.

"***Manufacturing Tech Transfer Notice***" has the meaning set forth in Section 1.3.2(b).

"***Manufacturing Technology***" means (i) methods and materials used in the synthesis or analysis of an Oligonucleotide regardless of sequence or chemical modification, (ii) methods of making components of an Oligonucleotide, and (iii) methods and materials used in making the Product.

"***Material Change***" has the meaning set forth in Section 6.3.2.

"***Minimum Third Party Payments***" means the amount of royalty and other financial obligations Akcea or its Affiliates are obligated to contractually pay to Third Parties (including any Akcea Supported Pass-Through Costs) to satisfy Akcea's or its Affiliate's obligations under Third Party licenses for Third Party technology Covering a Product that is sublicensed by Akcea to Novartis under this Agreement due to Novartis' exercise of rights sublicensed by Akcea to Novartis under this Agreement and provided Akcea has provided to Novartis written evidence of such Minimum Third Party Payment obligations. For the avoidance of doubt, Minimum Third Party Payments shall not include any and all royalty or other financial obligations that (i) Akcea or its Affiliates owe to one another or (ii) Akcea or its Affiliates owe to Ionis or its Affiliates if Akcea and Ionis are no longer Affiliates.

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Regulatory Approval for a Product in the United States.

"***NDA Approval***" means, with respect to a Product in the United States, FDA approval of an NDA sufficient for the manufacture, distribution, use, marketing and sale of such Product.

"***Negotiation Notice***" has the meaning set forth in Section 8.2.2.

"***Net Sales***" means the net sales recorded by Novartis or any of its Affiliates or Sublicensees for any Product sold to Third Parties other than Sublicensees as determined in accordance with Novartis' Accounting Standards as consistently applied, less a deduction of [***] percent ([***]%) for direct expenses related to the sales of the Product, distribution and warehousing expenses and uncollectible amounts on previously sold products. The deductions booked on an accrual basis by Novartis and its Affiliates under its Accounting Standards to calculate the recorded net sales from gross sales are as follows: (i) normal trade and cash discounts; (ii) amounts repaid or credited by reasons of defects, rejections, recalls or returns; (iii) rebates and chargebacks to customers and third parties (including, without limitation, Medicare, Medicaid, Managed Healthcare and similar types of rebates); (iv) any amounts recorded in gross revenue associated with goods provided to customers for free; (v) amounts provided or credited to customers through coupons and other discount programs; (vi) delayed ship order credits, discounts or payments related to the impact of price increases between purchase and shipping dates or retroactive price reductions; (vii) fee for service payments to customers for any non-separable services (including compensation for maintaining agreed inventory levels and providing information); and (viii) other reductions or specifically identifiable amounts deducted for reasons similar to those listed above in accordance with Novartis' Accounting Standards as consistently applied. With respect to the calculation of Net Sales: (x) Net Sales only include the value charged or invoiced on the first arm's length sale to a Third Party and sales between or among Novartis and its Affiliates and Sublicensees shall be disregarded for purposes of calculating Net Sales (for the avoidance of doubt, in the case of sale or other disposal of a Product between or among Novartis and its Affiliates or sublicensees, for resale to Third Party, Net Sales shall be calculated on the value charged or invoiced on the first arm's-length sale thereafter to a Third Party); and (y) if a Product is delivered to the Third Party before being invoiced (or is not invoiced), Net Sales will be calculated at the time all the revenue recognition criteria under Novartis Accounting Standards are met.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Novartis***" has the meaning set forth in the Preamble of this Agreement.

"***Novartis Background Technology***" means Novartis Background Patents and Novartis Background Know-How that are not Novartis Program Technology.

"***Novartis Background Know-How***" means Know-How Controlled by Novartis or its Affiliates as of the Effective Date or any time during the Agreement Term that is not Program Know-How, to the extent necessary to Develop, Manufacture or Commercialize a Product.

"***Novartis Background Patents***" means Patent Rights Controlled by Novartis or its Affiliates as of the Effective Date or any time during the Agreement Term that are not Program Patents, to the extent necessary to Develop, Manufacture or Commercialize a Product.

"***Novartis Royalty***" has the meaning set forth in Section 7.8.1.

"***Novartis Indemnitees***" has the meaning set forth in Section 10.2.

"***Novartis Know-How***" means any Know-How owned, used, developed by, or licensed to Novartis or its Affiliates, in each case to the extent Controlled by Novartis or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the Novartis Program Know-How.

"***Novartis Patents***" means any Patent Rights included in the Novartis Technology.

"***Novartis Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to Novartis or its Affiliates, in each case to the extent Controlled by Novartis or its Affiliates on the Effective Date or at any time during the Agreement Term that are necessary to Develop, Manufacture or Commercialize a Product.

"***Novartis Program Know-How***" has the meaning set forth in Section 8.2.2.

"***Novartis Program Patents***" has the meaning set forth in Section 8.2.2.

"***Novartis Program Technology***" has the meaning set forth in Section 8.2.2.

"***Novartis-Prosecuted Patents***" has the meaning set forth in Section 8.3.2(b).

"***Novartis Supported Pass-Through Costs***" means the licensing costs and payments payable to Third Parties as they apply to a Product that are not Akcea Supported Pass-Through Costs.

"***Novartis Technology***" means Novartis' interest in Novartis Program Technology, Novartis Product-Specific Patents, Novartis Know-How, Novartis Patents, including Novartis Background Technology, and any Trademarks described in Section 5.6, owned, used, developed by, or licensed to Novartis or its Affiliates (other than from Akcea pursuant to this Agreement) that are necessary to Develop, Manufacture or Commercialize a Product.

"***Offering Party***" has the meaning set forth in Section 8.2.2.

"***Oligonucleotide"*** means a short single-stranded nucleic-acid product comprised of at least six linked natural or chemically-modified nucleosides.

"***Option***" has the meaning set forth in Section 3.1.

"***Option Deadline***" has the meaning set forth in Section 3.3.1.

"***Option Exercise***" has the meaning set forth in Section 3.3.2.

"***Option Period***" means, on an Option-by-Option basis, the period commencing on the Effective Date and ending on the date such Option is terminated or expires unexercised.

"***Orange Book Patents***" means, on a country-by-country basis, the Licensed Patents that are listed with, and/or are required to be listed with, applicable Regulatory Authorities Covering any Product being Developed by Novartis, its Affiliates or Sublicensees hereunder that Novartis, its Affiliate or Sublicensee intends to, or has begun to, Commercialize, and that have become the subject of an NDA, MAA or other marketing application submitted to any applicable Regulatory Authority, such listings to include, without limitation, all so-called "*Orange Book*" listings required under the Hatch-Waxman Act and all so-called "*Patent Register*" listings as required in Canada. For purposes of determining royalties payable under Section 7.8, Orange Book Patents will include any and all foreign equivalent and counterpart Patent Rights to the Patent Rights described above.

For the avoidance of doubt, on a country-by-country basis, where there is:

(A) a mandatory patent listing process in such country, only Licensed Patents that are listed in such country's patent listing will be considered "*Orange Book Patents*" (and therefore royalty-bearing) in such country, irrespective of whether the foreign equivalent Patent Rights of such Licensed Patents are listed in another country;

(B) a voluntary patent listing process in such country, both (x) Licensed Patents that are listed in such country's patent listing, and (y) Licensed Patents that are not listed in such country's patent listing but are the foreign equivalent Patent Rights of the Licensed Patents listed in the mandatory patent listing of another country, in each case will be considered "*Orange Book Patents*" (and therefore royalty-bearing) in such country; and

(C) no patent listing process in such country, Licensed Patents that are the foreign equivalent of the Licensed Patents listed in the mandatory patent listing of another country, in each case will be considered "*Orange Book Patents*" (and therefore royalty-bearing) in such country, irrespective of whether the foreign equivalent Patent Rights of such Licensed Patents are listed in another country.

For example, if country "A" has a mandatory patent listing process that only requires that Licensed Patents "X" "Y" and "Z" be listed, and country "B" has a mandatory patent listing process that only requires that Licensed Patents "Y" and "Z" be listed, then Licensed Patents "X" "Y" and "Z" will be royalty-bearing Orange Book Patents in country "A", and only Licensed Patents "Y" and "Z" will be royalty-bearing Orange Book Patents in country "B".

For another example, if country "A" has a voluntary patent listing process that permits but does not require that Licensed Patents "X" "Y" and "Z" be listed and Novartis only lists in such patent listing Licensed Patents "X" and "Y", and country "B" has a mandatory patent listing process that requires that Licensed Patents "X" "Y" and "Z" be listed, then the applicable foreign equivalent of Licensed Patents "X" "Y" and "Z" will be royalty-bearing Orange Book Patents in country "A" and in country "B".

"***Original Akcea Schedules***" has the meaning set forth in Section 1.2.4.

"***Party***" or "***Parties***" means Novartis and Akcea individually or collectively.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Akcea or its Affiliates before or after the Effective Date to any Third Party under the Akcea Core Technology Patents, the Akcea Manufacturing and Analytical Patents, or the Akcea Manufacturing and Analytical Know-How (but not under the Akcea Product-Specific Patents) to (a) use Oligonucleotides (or supply Oligonucleotides to end users) solely to conduct research, or (b) enable such Third Party to manufacture or formulate Oligonucleotides, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) Akcea and its Affiliates do not assist such Third Party to identify, discover or make an Oligonucleotide designed to bind to an Exclusive Target; and (2) material transfer, collaboration, or sponsored research agreements with academic collaborators or non-profit institutions solely to conduct non-commercial research.

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

"***Phase 1 Trial***" means, with respect to a Product, a human clinical trial that is intended to initially evaluate the safety, metabolism and pharmacokinetics of such Product that would otherwise satisfy the requirements of 21 C.F.R. 312.21(a) or an equivalent clinical trial in a country other than the United States.

"***Phase 2 Trial***" means, with respect to a Product, a human clinical trial for which the primary endpoints include a determination of safety, dose ranges or an indication of efficacy of such Product in patients being studied as described in 21 C.F.R. §312.21(b), or an equivalent clinical trial in a country other than the United States, and that is prospectively designed to generate sufficient data (if successful) to commence pivotal clinical trials.

"***Phase 2 Dose-Ranging Trial***" means the Phase 2 dose-ranging trial for a Product described in the Pre-Option Development Plan.

"***Phase 2 Dose-Ranging Trial Data Package***" has the meaning set forth in Section 1.2.4.

"***Phase 3 Trial***" means, with respect to a Product, a human clinical trial (regardless of whether actually designated as "Phase 3") that is prospectively designed, along with other Phase 3 Trials, to demonstrate statistically whether such Product is safe and effective for use in humans in the Indication being investigated as described in 21 C.F.R. §312.21(c), or an equivalent clinical trial in a country other than the United States.

"***Phase 4 Trial***" means, with respect to a Product, (a) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain a Regulatory Approval for such Product or (b) any Clinical Study conducted after the first Regulatory Approval in the same disease state for which such Product received Regulatory Approval other than for purposes of obtaining Regulatory Approval.

"***Pre-Option Development Plan***" means the development plan for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} attached hereto as APPENDIX 2.
"***Pre-Option Novartis Activities***" means any activities Novartis will perform under this Agreement prior to Option Exercise, including any activities the Parties mutually agree Novartis will be responsible for conducting under the Pre-Option Development Plan.

"***Prior Agreements***" means the agreements listed on APPENDIX 7 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means, as applicable (i) AKCEA-APO(a)-L_{Rx}, and/or (ii) AKCEA-APOCIII-L_{Rx}.

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

"***Program Know-How***" has the meaning set forth in Section 8.2.2.

"***Program Patents***" has the meaning set forth in Section 8.2.2.

"***Program Technology***" has the meaning set forth in Section 8.2.2.

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "*Prosecution and Maintenance*" or "*Prosecute and Maintain*" will not include any other enforcement actions taken with respect to a Patent Right.

"***Receiving Party***" has the meaning set forth in Section 12.1.

"***Regulatory Approval***" means (i) an NDA Approval, (i) an MAA Approval, or (iii) such other approval by a Regulatory Authority in any other jurisdiction sufficient for the manufacture, distribution, use, marketing and sale of a Product, which for the avoidance of doubt shall include pricing and reimbursement approval from a Regulatory Authority when applicable.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"***ROFN Notice***" has the meaning set forth in Section 8.2.2.

"***Specific Performance Milestone Events***" has the meaning set forth in Section 6.4.2.

"***Stock Purchase Agreement***" means that certain Stock Purchase Agreement by and among Akcea, Ionis and Novartis executed on the Execution Date.

"***Strategic Plan***" has the meaning set forth in Section 6.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or Novartis Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Terminated Product***" has the meaning set forth in Section 11.3.1.

"***Terminated Target***" has the meaning set forth in Section 11.3.1.

"***THA Cluster***" means 5-N-{tris[(6-(2-acetamido-3,4,6-tri-O-acetyl-β-D-galactopyranosyloxy)hexylamino)-3-oxopropoxymethyl]methyl}amino-5-oxopentanoyl.

"***Third Party***" means a Person other than the Parties or their respective Affiliates.

"***Third Party Claims***" has the meaning set forth in Section 10.1.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between a Party and a Third Party that relate to a Product or an Exclusive Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Trademark***" means any trademark owned and controlled by Novartis and used by Novartis in connection with the marketing of a Product.

"***Transition Services***" has the meaning set forth in Section 11.3.4(a).

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Updated Akcea Schedules***" has the meaning set forth in Section 1.2.4.

"***Valid Claim***" means a claim of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision. For the avoidance of doubt, Jointly-Owned Program Patents shall not be royalty bearing as such Patent Rights are excluded from Licensed Patents.

"***Volanesorsen***" means the Oligonucleotide known as ISIS 304801 having the following sequence and chemistry: 5′-AG^{Me}C^{Me}U^{Me}U^{Me}CTTGT^{Me}C^{Me}CAG^{Me}C^{Me}U^{Me}U^{Me}UA^{Me}U-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. Each of the 19 internucleoside linkages is a phosphorothioate diester linkage.

APPENDIX 2

Pre-Option Development Plan

[***]

APPENDIX 3

Akcea In-License Agreements

[***]

APPENDIX 4

Akcea Core Technology Patents

[***]

APPENDIX 5

Akcea Manufacturing and Analytical Patents

[***]

APPENDIX 6

Akcea Product-Specific Patents

(Relevant to AKCEA-APO(a)-L_{Rx})

[***]

(**Relevant to AKCEA-APOCIII-L_{Rx}**)

[***]

APPENDIX 7

Prior Agreements

[***]

SCHEDULE 1.3.1

API Supply Terms

Terms for AKCEA-APO(a)-LRx API Supply

For the supply of AKCEA-APO(a)-L_{Rx} API, Novartis will pay Akcea US$[***] per gram for such API. Total supply of AKCEA-APO(a)-L_{Rx} API not to exceed [***] kgs (unless mutually agreed otherwise by the Parties).

AKCEA-APO(a)-LRx API Delivery Schedule:

- [***] – [***] kilograms of API delivered to Novartis after [***]; and
- Remaining quantities of API to be delivered to Novartis in [***] in accordance with the terms of the Quality Agreement to be agreed upon in [***].

[***]% will be paid by Novartis within [***] calendar days after Novartis's receipt of an invoice following the date the respective API quantities are delivered (including batch manufacturing documentation and records) at the address specified on the order ([***], INCOTERMS® 2010); *provided*, if delivery address specified by Novartis is [***] Novartis will reimburse Akcea for the incremental cost associated with delivery [***] (e.g., any increased insurance costs, costs of carriage and freight, import/export duty, value added taxes; such incremental cost shall be evidenced by relevant documentation).

Terms for AKCEA-APOCIII-LRx API Supply

For the supply of AKCEA-APOCIII-L_{Rx} API, Novartis will pay Akcea US$[***] per gram for such API. Total supply of AKCEA-APOCIII-L_{Rx} API not to exceed [***] kgs (unless mutually agreed otherwise by the Parties). Akcea will be deemed to have satisfied the amount of API ordered by Novartis if Akcea delivers the quantity of API specified in such order within plus or minus [***]% (i.e., [***] - [***] grams per batch).

AKCEA-APOCIII-LRx API Delivery Schedule:

- [***] kilograms of API delivered to Novartis in [***]; and
- Akcea will endeavor to deliver the remaining quantities of API in [***], *provided that*, any remaining quantity Akcea cannot deliver in [***] will be delivered as soon as practicable thereafter.

For the first lot of API delivered to Novartis in [***], (i) [***]% will be paid by Novartis when such API is [***] (and within [***] calendar days after Novartis's receipt of an invoice); (ii) [***]% will be paid by Novartis when [***] (and within [***] calendar days after Novartis's receipt of an invoice), and (iii) the remaining [***]% will be paid by Novartis within [***] calendar days after Novartis's receipt of an invoice following the date such API is delivered at the address specified on the order ([***], INCOTERMS® 2010; *provided*, if delivery address specified by Novartis is [***] Novartis will reimburse Akcea for the incremental cost associated with delivery [***] (e.g., any increased insurance costs, costs of carriage and freight, import/export duty, value added taxes)).

For the second and any subsequent lot(s) of API to be delivered to Novartis after [***], (i) [***]% will be paid by Novartis when such API is [***] (and within [***] calendar days after Novartis's receipt of an invoice); (ii) [***]% will be paid by Novartis when [***] (but no earlier than [***] and within [***] calendar days after Novartis's receipt of an invoice), and (iii) the remaining [***]% will be paid by Novartis within [***] calendar days after Novartis's receipt of an invoice following the date such API is delivered at the address specified on the order ([***], INCOTERMS® 2010; *provided*, if delivery address specified by Novartis is [***] Novartis will reimburse Akcea for the incremental cost associated with delivery [***] (e.g., any increased insurance costs, costs of carriage and freight, import/export duty, value added taxes; such incremental cost shall be evidenced by relevant documentation).

Such API will be manufactured using Akcea's or its Affiliate's process and Akcea's or its Affiliate's standard operating procedures (SOPs) and specifications.

Quality Assurance and General Supply Terms and Conditions.

For both AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, the Parties shall agree on a Quality Agreement in [***]. Such QA agreement will govern a QA plan and activities such as, but not limited to, specifications, certificate of analysis, re-testing date of API, etc. Such QA Agreement shall also detail the specifications for the API, procedure for batch release and acceptance. Furthermore, the Parties shall agree on general terms and conditions for the supply of API in a manner consistent with industry standards. Such terms and conditions shall include Delivery Terms (which shall be [***], INCOTERMS® 2010; *provided*, if delivery address specified by Novartis is [***] Novartis will reimburse Akcea for the incremental cost associated with delivery [***] (e.g., any increased insurance costs, costs of carriage and freight, import/export duty, value added taxes), right of rejection (including remedies in case of rejection).

SCHEDULE 1.3.2

Manufacturing Transition Activities And Pre-Option Novartis Activities

[***]

SCHEDULE 2.1.1

Collaboration Steering Committee

CSC Representatives

Akcea

[***]

Novartis

[***]

JDCC

[***]

SCHEDULE 2.2

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(b) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first one hundred (100) calendar days upon the Option Exercise of the First Product to support the Collaboration;

(c) Organizing CSC and JDCC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the CSC and JDCC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

SCHEDULE 6.4.2

Post-Option Novartis' Development and Commercialization Activities

General Activities Applicable to all Products

- conducting all non-Clinical Studies and Clinical Studies on the Product as deemed necessary or desirable by Novartis or any applicable Regulatory Authority with Commercially Reasonable Efforts;
- preparing and filing all regulatory filings for the Product in each Major Market, including all INDs, NDAs, MAAs, JNDAs and other filings with Commercially Reasonable Efforts;
- Manufacturing or having Manufactured (including process development, validation and scale up) API, Clinical Supplies and Finished Drug Product for ongoing Development and Commercialization requirements, consistent with Novartis' internal practices and all Applicable Laws and using Commercially Reasonable Efforts; and
- conducting, at Novartis' sole expense, Commercialization activities in connection with the marketing, promotion, and sale of the Product with Commercially Reasonable Efforts in each and every Major Market (except for co-commercialization Akcea may conduct if mutually agreed between the Parties)

Specific Performance Milestone Events Applicable to all Products

- Initiate a [***] within [***] months after Novartis exercises the option for the Product;
- [***] or [***] covering the Product within [***] months after [***] for the first [***] for the Product, unless the FDA or EMA require any additional actions for [***], as applicable, in which case Novartis shall evaluate such actions and use Commercially Reasonable Efforts to complete such action; and
- Use Commercially Reasonable Efforts to market the approved Product [***] as soon as practicable after receiving Regulatory Approval for the Product [***].

SCHEDULE 7.8.2(F)

Royalty Calculation Examples

Example of the application of royalty payments to Akcea under the following assumptions:

[***]

EXHIBIT X

Novartis' Form of Invoice

[***]

Exhibit 10.2

Execution Copy

STOCK PURCHASE AGREEMENT

This Stock Purchase Agreement (***"Agreement"***) is entered into as of January 5, 2017 (the ***"Execution Date"***), by and among **Novartis Pharma AG** (***"Novartis"***), a company organized under the laws of Switzerland, having its principal place of business at Lichtstrasse 35, 4002 Basel, Switzerland, **Ionis Pharmaceuticals, Inc.** (***"Ionis"***), a Delaware corporation having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010, and **Akcea Therapeutics, Inc.** (***"Akcea"***), a Delaware corporation having its principal place of business at 55 Cambridge Parkway, Suite 100, Cambridge, MA 02142.

Recitals

A. Ionis has agreed to sell, and Novartis has agreed to purchase, $100 million of shares of Ionis's common stock (the ***"Ionis Common Stock"***) subject to and in accordance with the terms and provisions hereof.

B. Novartis has agreed to purchase, and Akcea has agreed to sell to Novartis, $50 million of shares of Akcea's common stock (the ***"Akcea Common Stock"***) if Akcea completes a Qualified Initial Public Offering during the period commencing on the Execution Date and ending on the date that is the 15-month anniversary of the Execution Date (such period, the ***"Akcea Option Period"***), subject to and in accordance with the terms and provisions hereof; and, if no Qualified Initial Public Offering has occurred during the Akcea Option Period, Novartis has agreed to purchase, and Ionis has agreed to sell to Novartis, $50 million of shares of Ionis Common Stock in the 90-day period commencing upon the end of the Akcea Option Period (such period the ***"Ionis Option Period"*** and together with the Akcea Option Period, the ***"Option Period"***).

C. Simultaneously with the execution of this Agreement, Akcea and Novartis are entering into a Strategic Collaboration, Option and License Agreement (the "***Collaboration Agreement***").

D. The capitalized terms used herein and not otherwise defined have the meanings given to them in Appendix 1.

Agreement

For good and valuable consideration, the parties agree as follows:

Section 1. Sale and Purchase of Ionis Stock

1.1 Purchase of Ionis Stock. Subject to the terms and conditions of this Agreement, at the Initial Closing, Ionis will issue and sell to Novartis, and Novartis will purchase from Ionis, 1,631,435[1] shares of Common Stock (the ***"Ionis Shares"***) for an aggregate purchase price of US$100,000,000 (the ***"Purchase Price"***).

[1] Price per share is determined by adding a 25% premium to the average of the daily per share volume-weighted average price as displayed under the heading "Bloomberg VWAP" on Bloomberg page "IONIS.UQ <equity> AQR" over the 20-trading day period ending on and including the last trading day prior to the Execution Date. Number of Shares is determined by dividing $100 million by the price per share, rounding down to the nearest whole share.

1.2 Payment. At the Closing, Novartis will pay the Purchase Price by wire transfer of immediately available funds in accordance with wire instructions provided by Ionis to Novartis prior to the Closing, and Ionis will deliver the Ionis Shares in book entry form to Novartis.

1.3 Initial Closing. The closing of the transaction contemplated by this Section 1 (the ***"Initial Closing"***) will be held at the offices of Ionis within three trading days after the conditions to closing set forth in Section 8 are satisfied or waived (other than those conditions that by their nature are to be satisfied or waived at the Closing) or at such other place, time and/or date as may be jointly designated by Novartis and Ionis (the ***"Initial Closing Date"***). Subject to the closing conditions set forth in Section 8, the Parties will endeavor to effect the Initial Closing on the trading day immediately following the termination of any waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended (the "***HSR Act***").

1.4 HSR Clearance. Subject to the terms and conditions of this Agreement, in connection with the acquisition of the Ionis Shares, each of Novartis and Ionis shall use commercially reasonable efforts to (i) make all required filings and submissions under the HSR Act as determined by Novartis in consultation with Ionis, as promptly as practicable, but in no event later than 15 days after the Execution Date, and (ii) obtaining as promptly as practicable the termination of any waiting period under the HSR Act.

Section 2. Purchase of Shares of Akcea Common Stock or Additional Shares of Ionis Common Stock.

2.1 Purchase of Akcea Shares. If Akcea completes a Qualified Initial Public Offering during the Akcea Option Period, then Novartis agrees to purchase (and Akcea hereby agrees to sell) from Akcea $50 million of Akcea Common Stock. The price per share will be the initial public offering price per share to the public set forth in the final prospectus for Akcea's Qualified Initial Public Offering (the "***Akcea IPO Price***"). The shares sold will be Akcea's primary shares and the number of shares Novartis will purchase will be determined by dividing $50 million by the price per share, rounding down to the nearest whole share; *provided*, that Novartis shall only purchase such number of shares as would not (x) cause its beneficial ownership to exceed 14.99% of Akcea's outstanding common stock immediately after such purchase or (y) result in an aggregate purchase price that exceeds 30% of the sum of the aggregate gross proceeds received by Akcea in (i) such Qualified Initial Public Offering and (ii) the issuance pursuant to this section 2.1 (the number of shares of Akcea Common Stock so purchased the "***Purchased Akcea Shares***"). If the number of shares of Akcea Common Stock to be purchased under this Agreement is reduced as a result of the preceding sentence, Novartis shall purchase shares of Ionis Common Stock equal to (a) $50 million minus the aggregate purchase price for the Purchased Akcea Shares, divided by (b) the price per share of Ionis Common Stock as set forth in Section 2.2, using the 20-trading day period ending on and including the trading day immediately prior to the closing date of Akcea's Qualified Initial Public Offering. This option (and Akcea's and Ionis's obligation to sell Common Stock under this Section 2.1) will automatically expire if unexercised by the expiration of the Akcea Option Period. Any shares of Akcea Common Stock purchased by Novartis under this Section 2 are referred to as ("***Akcea Shares***")

2.2 Purchase of Additional Ionis Shares.

(a) If Akcea does not complete a Qualified Initial Public Offering during the Akcea Option Period, Novartis agrees to purchase (and Ionis hereby agrees to sell) from Ionis an additional $50 million of Ionis Common Stock during the Ionis Option Period. At any time during the Ionis Option Period Ionis may deliver a notice to sell Novartis the Ionis Common Stock under this Section 2.2 (such notice, a ***"Put Notice"***). By the 15th trading day following Novartis' receipt of the Put Notice (such trading date, the ***"Pricing Deadline"***), Novartis will deliver to Ionis a written notice specifying a trading day (such trading day, the ***"Pricing Trigger Date"***) during the period between the Pricing Deadline and the 30th trading day (inclusive) following Novartis' receipt of the Put Notice to use as the basis to set the purchase price for the Ionis Common Stock, using the formula described in this section. If, by the Pricing Deadline Novartis has not delivered a written notice to Ionis specifying a Pricing Trigger Date, then the Pricing Trigger Date will be the date of the Pricing Deadline. Subject to the closing conditions set forth in Section 8, the Parties will endeavor to effect the Subsequent Closing for the purchase under this Section 2.2 on the trading day immediately following the Pricing Trigger Date. Novartis undertakes that during the period from receipt of the Put Notice until the first trading day after the Subsequent Closing, Novartis shall not purchase or sell Ionis Common Stock (or otherwise make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale of the Ionis Common Stock) unless required to comply with its obligations under this Agreement or as required by law.

(b) The price per share for the purchase under this Section 2.2 will be determined by adding a 25% premium to the average of the daily per share volume-weighted average price as displayed under the heading "Bloomberg VWAP" on Bloomberg page "IONIS.UQ <equity> AQR" over the 20-trading day period ending on and including the Pricing Trigger Date. The number of shares Novartis may purchase will be determined by dividing $50 million by the price per share, rounding down to the nearest whole share; *provided*, that if as a result of such purchase, Novartis and its Affiliates would beneficially own greater than 9.99% of Ionis's outstanding common stock immediately after such purchase, Novartis shall only purchase such number of shares as would not cause its and its Affiliates' beneficial ownership to exceed 9.99% of Ionis's outstanding common stock immediately after such purchase.

(c) If (i) between the date Ionis provides Novartis a Put Notice and prior to the scheduled date of the Subsequent Closing, Ionis learns new information or events occur that would make one or more of Ionis' representations and warranties under Section 3 untrue or incorrect on the Subsequent Closing, and (ii) as a result the Subsequent Closing does not occur because the closing condition under Section 8.3(d) was not satisfied or waived, then Novartis' obligation to purchase (and Ionis' obligation to sell) the Ionis Common Stock under Section 2.2(a) will reset and the Ionis Option Period will automatically be extended by 30 days.

2.3 Subsequent Closing. The closing of the transactions contemplated by this Section 2 (the ***"Subsequent Closing"***) will be held at the offices of Ionis, and

(a) If Novartis purchases Akcea Common Stock under Section 2.1, such closing will occur contemporaneously with the closing of Akcea's initial public offering; *provided* the conditions to closing set forth in Section 8 are satisfied or waived (other than those conditions that by their nature are to be satisfied or waived at the Subsequent Closing) or at such other place, time and/or date as may be jointly designated by Novartis and Akcea.

(b) If Novartis purchases Ionis Common Stock under Section 2.2, such closing will occur within three trading days after the conditions to closing set forth in Section 8 are satisfied or waived (other than those conditions that by their nature are to be satisfied or waived at the Subsequent Closing) or at such other place, time and/or date as may be jointly designated by Novartis and Ionis; or

(c) Any shares of Ionis Common Stock or Akcea Common Stock purchased by Novartis under this Section 2 are referred to as ***"Subsequent Shares"*** and together with the Ionis Shares, the ***"Shares"***. The Initial Closing and the Subsequent Closing may each be referred to as a ***"Closing"*** and the date of each such Closing as a ***"Closing Date"***.

2.4 HSR Clearance. In connection with the issuance of the Subsequent Shares, each of Novartis, Ionis, and Akcea shall use commercially reasonable efforts to (i) make all required filings and submissions under the HSR Act as determined by Novartis in consultation with Ionis and Akcea, no later than ten days after Novartis provides Ionis or Akcea with the notice required under Section 2.1 or Section 2.2 of this Agreement, and (ii) obtaining as promptly as practicable the termination of any waiting period under the HSR Act.

2.5 Change of Control.

(a) Ionis and/or Akcea shall notify Novartis in writing within 10 days following the closing of a Change of Control of Ionis and/or Akcea, which notice (a ***"Change of Control Notice"***) shall set forth the material terms of such Change of Control of Ionis and/or Akcea.

(b) In the event of a Change of Control of Ionis (i) the purchase and sale obligation under Section 2.2 with respect to Ionis' Common Stock will automatically terminate, and (ii) the purchase and sale obligation under Section 2.1, solely with respect to Akcea's Common Stock will continue during the Akcea Option Period. For the avoidance of doubt, in the event of a Change of Control of Ionis, Novartis shall not be required to purchase any shares of Ionis' Common Stock following such Change of Control.

(c) In the event of a Change of Control of Akcea (i) the purchase and sale obligation under Section 2.1 with respect to Akcea's Common Stock will automatically terminate, and (ii) the purchase and sale obligation under Section 2.2 with respect to Ionis' Common Stock will apply through the 18-month anniversary of the Execution Date.

Section 3. REPRESENTATIONS AND WARRANTIES OF IONIS

Except as otherwise specifically contemplated by this Agreement, Ionis hereby represents and warrants to Novartis that:

3.1 Private Placement. Subject to the accuracy of the representations made by Novartis in Section 4, the Shares will be issued and sold to Novartis in compliance with applicable exemptions from the registration and prospectus delivery requirements of the Securities Act and the registration and qualification requirements of all applicable securities laws of the states of the United States. It has not engaged any brokers, finders or agents, or incurred, or will incur, directly or indirectly, any liability for brokerage or finder's fees or agents' commissions or any similar charges in connection with this Agreement and the transactions contemplated hereby. It has not, directly or through any agent, sold, offered for sale, solicited offers to buy or otherwise negotiated in respect of, any security (as defined in the Securities Act), that is or will be integrated with the sale of the Shares in a manner that would require registration of the Shares under the Securities Act.

3.2 Organization and Qualification. It is duly incorporated, validly existing and in good standing under the laws of the State of Delaware, with full corporate power and authority to conduct its business as currently conducted and proposed to be conducted. It is duly qualified to do business and is in good standing in every jurisdiction in which the nature of the business conducted by it or property owned by it makes such qualification necessary, except where the failure to be so qualified or in good standing, as the case may be, would not have a Material Adverse Effect on it.

3.3 Authorization; Enforcement. It has all requisite corporate power and authority to enter into and to perform its obligations under this Agreement, to consummate the transactions contemplated hereby and to issue the Shares in accordance with the terms hereof. The execution, delivery and performance of this Agreement by it and the consummation by it of the transactions contemplated hereby (including the issuance of the Shares) have been duly authorized by its Board of Directors and no further consent or authorization of its Board of Directors, or its stockholders, is required. This Agreement has been duly executed by such party and constitutes a legal, valid and binding obligation of such party enforceable against such party in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, or moratorium or similar laws affecting creditors' and contracting parties' rights generally and except as enforceability may be subject to general principles of equity and except as rights to indemnity and contribution may be limited by state or federal securities laws or public policy underlying such laws.

3.4 Issuance of Shares. The Shares are duly authorized and, upon issuance in accordance with the terms of this Agreement, will be validly issued, fully paid and non-assessable and will not be subject to preemptive rights or other similar rights of its stockholders.

3.5 No Conflicts; Government Consents and Permits.

(a) Neither it nor any of its subsidiaries is (A) in violation of its Certificate of Incorporation or Bylaws or (B) in default in the performance or observance of any material obligation, agreement, indenture, instrument, covenant or condition contained in any indenture, mortgage, deed of trust, loan agreement, lease or other agreement or instrument to which it is a party or by which it or any of its properties may be bound, except in the case of (B) for such defaults as would not, individually or in the aggregate, be expected to have a Material Adverse Effect. The execution, delivery and performance of this Agreement by such party and the consummation by such party of the transactions contemplated hereby (including the issuance of the Shares) will not (i) conflict with or result in a violation of any provision of such party's Certificate of Incorporation or Bylaws, (ii) violate or conflict with, or constitute or result in a breach of any provision of, or constitute a default under, any material obligation, agreement, indenture, instrument, covenant or condition contained in any indenture, mortgage, deed of trust, loan agreement, lease or other agreement or instrument to which it is a party or by which it or any of its properties may be bound, or (iii) violate or conflict with, or result in a violation of or conflict with, any law, rule, regulation, order, judgment or decree (including United States federal and state securities laws and regulations and regulations of any self-regulatory organizations) applicable to such party.

(b) Such party is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory or self-regulatory agency in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms hereof, or to issue and sell the Shares in accordance with the terms hereof other than such as have been made or obtained, and except for (i) any post-closing filings required to be made under federal or state securities laws, (ii) any required filings or notifications regarding the issuance or listing of additional shares with Nasdaq, and (iii) expiration or termination of any waiting period required under the HSR Act.

3.6 SEC Documents.

(a) The Ionis Common Stock is registered pursuant to Section 12(b) or 12(g) of the Exchange Act. Ionis has delivered or made available (by filing on the SEC's electronic data gathering and retrieval system (EDGAR)) to Novartis complete copies of its most recent Annual Report on Form 10-K and each subsequent Quarterly Report on Form 10-Q filed with the SEC prior to the Effective Date (and with respect to each Closing, between the Effective Date and prior to the applicable Closing Date) (collectively, the ***"SEC Documents"***). As of its date, each SEC Document complied in all material respects with the requirements of the Exchange Act, and all other federal, state and local laws, rules and regulations applicable to it, and, as of its date, such SEC Document did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading.

(b) There are no outstanding or unresolved comments in comment letters received from the SEC or its staff.

3.7 Full Disclosure. As of the date hereof, and other than the transactions that are the subject of this Agreement and the Collaboration Agreement, no material fact or circumstance exists that would be required to be disclosed in a current report on Form 8-K or in a registration statement filed under the Securities Act, were such a registration statement filed on the date hereof, that has not been disclosed in an SEC Document.

3.8 Financial Statements; Controls and Related Matters.

(a) Ionis's financial statements, together with the related notes and schedules included in the SEC Documents comply as to form in all material respects with all applicable accounting requirements and the published rules and regulations of the SEC and all other applicable rules and regulations with respect thereto. Such financial statements, together with the related notes and schedules, have been prepared in accordance with GAAP applied on a consistent basis during the periods involved (except (i) as may be otherwise indicated in such financial statements or the notes thereto or (ii) in the case of unaudited interim statements, to the extent they may not include footnotes or may be condensed or summary statements), and fairly present in all material respects Ionis's financial condition and its consolidated subsidiaries as of the dates thereof and the results of operations and cash flows for the periods then ended (subject, in the case of unaudited statements, to normal year-end audit adjustments).

(b) Ionis and each of its subsidiaries (i) make and keep accurate books and records and (ii) maintain and have maintained effective internal control over financial reporting as defined in Rule 13a-5 under the Exchange Act and a system of internal accounting controls sufficient to provide reasonable assurance that (A) transactions are executed in accordance with management's general or specific authorization, (B) transactions are recorded as necessary to permit preparation of its financial statements in conformity with U.S. GAAP and to maintain accountability for its assets, (C) access to its assets is permitted only in accordance with management's general or specific authorization, (D) the reported accountability for its assets is compared with existing assets at reasonable intervals and appropriate action is taken with respect to any differences and (E) the interactive data in eXtensible Business Reporting Language incorporated by reference in the SEC Documents fairly present the information called for in all material respects and is prepared in all material respects in accordance with the SEC's rules and guidelines applicable thereto.

(c) Since the date of the most recent balance sheet of Ionis and its consolidated subsidiaries reviewed or audited by Ernst & Young LLP and the audit committee of the Board of Directors of Ionis, (i) Ionis has not been advised of (A) any significant deficiencies in the design or operation of internal controls that would adversely affect the ability of Ionis or any of its subsidiaries to record, process, summarize and report financial data, or any material weaknesses in internal controls or (B) any fraud, whether or not material, that involves management or other employees who have a significant role in the internal controls of Ionis and each of its subsidiaries, and (ii) since that date, there have been no significant changes in internal controls or in other factors that would significantly affect internal controls, including any corrective actions with regard to significant deficiencies and material weaknesses.

(d) Since the date as of the most recent financial statements and except as otherwise described in the SEC Documents, Ionis has not (i) issued or granted any securities (except pursuant to Ionis's previous or currently existing equity incentive and other similar officer, director or employee benefit plans), (ii) incurred any liability or obligation, direct or contingent, other than liabilities and obligations that were incurred in the ordinary course of business, (iii) entered into any material transaction not in the ordinary course of business or (iv) declared or paid any dividend on its capital stock.

3.9 No Material Adverse Effect. Except as described in the SEC Documents, neither it nor any of its subsidiaries has sustained, since the date of the latest financial statements included in the SEC Documents, any loss or interference with its business from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor dispute or court or governmental action, order or decree, and, since such date, there has not been any change in the total current assets, capital stock or long-term debt of it or any of its subsidiaries (other than a change in the number of outstanding shares of common stock due to the issuance of shares upon the exercise of options under previous or currently existing equity incentive and other similar officer, director or employee benefit plans) or any adverse change, or any development involving a prospective adverse change, in or affecting the condition (financial or otherwise), results of operations, stockholders' equity, properties, management, business or prospects of Ionis and its subsidiaries, taken as a whole, in each case except as would not, in the aggregate, have a Material Adverse Effect.

3.10 Property. It and each of its subsidiaries has good and marketable title in fee simple to all real property and good and marketable title to all personal property owned by it, in each case free and clear of all liens, encumbrances and defects, except such as are described in the SEC Documents and such as do not affect the value of such property and do not interfere with the use made and proposed to be made of such property by it or any of its subsidiaries, except as would not, in the aggregate, have a Material Adverse Effect. All assets held under lease by it or any of its subsidiaries are held by them under valid, subsisting and enforceable leases, with such exceptions as do not interfere with the use made and proposed to be made of such assets by it or any of its subsidiaries, except, as would not, in the aggregate, have a Material Adverse Effect.

3.11 Capitalization. Ionis has an authorized capitalization as set forth on its most recently filed SEC Document. All of the issued shares of capital stock of Ionis have been duly authorized and validly issued, are fully paid and non-assessable, conform in all material respects to the description thereof contained in the SEC Documents and were issued in compliance with federal and state securities laws and not in violation of any preemptive right, resale right, right of first refusal or similar right. All of Ionis's options, warrants and other rights to purchase or exchange any securities for shares of Ionis's capital stock have been duly authorized and validly issued, conform to the description thereof contained in the SEC Documents and were issued in compliance with federal and state securities laws. There are no outstanding options to purchase, or any rights or warrants to subscribe for, or any securities or obligations convertible into, or any contracts or commitments to issue or sell, any shares of Ionis's capital stock, any shares of capital stock of any subsidiary, or any such warrants, convertible securities or obligations, except as set forth in the SEC Documents and except for shares of Ionis capital stock and options to purchase shares of Ionis capital stock granted under, or contracts or commitments pursuant to, Ionis's previous or currently existing equity incentive and other similar officer, director or employee benefit plans. There is no and has been no policy or practice of Ionis to intentionally coordinate the grant of options to employees with the release or other public announcement of material information regarding Ionis or its results of operations or prospects to minimize the exercise price of such options. All of the issued shares of capital stock of each subsidiary of Ionis have been duly authorized and validly issued, are fully paid and non-assessable and are owned directly or indirectly by Ionis, free and clear of all liens, encumbrances, equities or claims, except for such liens, encumbrances, equities or claims as would not, in the aggregate, have a Material Adverse Effect.

3.12 No Registration Rights. Except as identified in the SEC Documents, there are no contracts, agreements or understandings between Ionis and any person granting such person the right to require Ionis to file a registration statement under the Securities Act with respect to any securities of Ionis owned or to be owned by such person or to require Ionis to include such securities in any securities being registered pursuant to any registration statement filed by Ionis under the Securities Act.

3.13 No Litigation. Except as described in the SEC Documents, there are no legal or governmental proceedings pending to which Ionis or any of its subsidiaries is a party or of which any property or assets of Ionis or any of its subsidiaries is the subject that would, in the aggregate, have a Material Adverse Effect; and to Ionis's knowledge, no such proceedings are threatened or contemplated by any court or arbitrator or federal, state, local or foreign governmental agency or regulatory authority having jurisdiction over the properties or assets of Ionis or any of its subsidiaries or any of their properties or assets ("***Governmental Authorities***") or others.

3.14 Exhibits. There are no legal or governmental proceedings or contracts or other documents that would be required to be described in a registration statement of Ionis under the Securities Act or, in the case of documents, required to be filed as exhibits to such registration statement pursuant to Item 601(10) of Regulation S-K that have not been described or incorporated by reference in the SEC Documents. Neither Ionis nor any of its subsidiaries has knowledge that any other party to any such contract, agreement or arrangement has any intention not to render full performance as contemplated by the terms thereof. The statements made or incorporated by reference in the SEC Documents insofar as they purport to constitute summaries of the terms of statutes, rules or regulations, legal or governmental proceedings or contracts and other documents, constitute accurate summaries of the terms of such statutes, rules and regulations, legal and governmental proceedings and contracts and other documents in all material respects.

3.15 Investment Company Act. Neither Ionis nor any subsidiary is, and after giving effect to the offer and sale of the Shares will be, required to register as, (i) an "investment company" or a company "controlled" by an "investment company" within the meaning of the United States Investment Company Act of 1940, as amended (the ***"Investment Company Act"***), and the rules and regulations of the SEC thereunder or (ii) a "business development company" (as defined in Section 2(a)(48) of the Investment Company Act).

3.16 Disclosure Controls. Ionis and each of its subsidiaries have established and maintain disclosure controls and procedures (as such term is defined in Rule 13a-15 under the Exchange Act). Such disclosure controls and procedures are designed to ensure that the information required to be disclosed by Ionis in the reports they file or submit under the Exchange Act (assuming Ionis was required to file or submit such reports under the Exchange Act) is accumulated and communicated to management of Ionis and its subsidiaries, including their respective principal executive officers and principal financial officers, as appropriate, to allow timely decisions regarding required disclosure to be made. Such disclosure controls and procedures are effective in all material respects to perform the functions for which they were established.

3.17 Independent Public Accountants. Ernst & Young LLP, who have certified certain financial statements of Ionis, whose report appears in the SEC Documents are independent public accountants as required by the Securities Act and the rules and regulations thereunder.

3.18 Regulatory Compliance. Except as described in the SEC Documents or as provided to Novartis in advance of the applicable Closing via electronic data room; and only to the extent where the failure of such representation and warranty to be true and complete would be reasonably expected to materially and adversely affect any of the Patent Rights (as defined in the Collaboration Agreement) or Know-How (as defined in the Collaboration Agreement) relating to, or the prospects for the research, development and/or commercialization by Ionis or its subsidiaries of, AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx}, Ionis and each of its subsidiaries: (A) are and at all times have been in full compliance with all statutes, rules, regulations, or guidances applicable to the ownership, testing, development, manufacture, packaging, processing, use, distribution, marketing, labeling, promotion, sale, offer for sale, storage, import, export or disposal of any product or product candidate manufactured or distributed by the Company and its subsidiaries ("***Applicable Laws***"); (B) have not received any U.S. Food and Drug Administration ("***FDA***") Form 483, notice of adverse finding, warning letter, untitled letter or other correspondence or notice from the FDA or any other Governmental Authority alleging or asserting noncompliance with any Applicable Laws or any licenses, certificates, approvals, clearances, authorizations, permits and supplements or amendments thereto required by any such Applicable Laws ("***Authorizations***"); (C) possess all Authorizations and such Authorizations are valid and in full force and effect and are not in violation of any term of any such Authorizations; (D) have not received written notice of any claim, action, suit, proceeding, hearing, enforcement, investigation, arbitration or other action from any Governmental Authority or third party alleging that any product operation or activity is in violation of any Applicable Laws or Authorizations and have no knowledge that any such Governmental Authority or third party is considering any such claim, litigation, arbitration, action, suit, investigation or proceeding; (E) have not received notice that any Governmental Authority has taken, is taking or intends to take action to limit, suspend, modify or revoke any Authorizations and have no knowledge that any such Governmental Authority is considering such action; (F) have filed, obtained, maintained or submitted all reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments as required by any Applicable Laws or Authorizations and represent that all such reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments were complete and correct on the date filed (or were corrected or supplemented by a subsequent submission); and (G) have not, either voluntarily or involuntarily, initiated, conducted, or issued or caused to be initiated, conducted or issued, any recall, market withdrawal or replacement, safety alert, post-sale warning, "dear doctor" letter, or other notice or action relating to the alleged lack of safety or efficacy of any of its product or any alleged product defect or violation and, to Ionis's knowledge, no third party has initiated, conducted or intends to initiate any such notice or action.

3.19 Trials. Solely with respect to AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx} and except as described in the SEC Documents or as provided to Novartis in advance of the applicable Closing via electronic data room, (A) the studies, tests and preclinical and clinical trials conducted by or on behalf of Ionis and each of its subsidiaries or with respect to such products were and, if pending, are being conducted in all material respects in accordance with experimental protocols, procedures and controls pursuant to accepted professional scientific standards and all Applicable Laws and Authorizations, including, without limitation, the U.S. Federal Food, Drug and Cosmetic Act and the rules and regulations promulgated thereunder; (B) the descriptions of the results of such studies, tests and trials contained in the SEC Documents with respect to such products are accurate and complete in all material respects and fairly present the data derived from such studies, tests and trials; (C) Ionis is not aware of any studies, tests or trials, the results of which Ionis believes reasonably refute the study, test, or trial results described or referred to in the SEC Documents for such products when viewed in the context in which such results are described and the clinical state of development; and (D) neither Ionis and its subsidiaries, nor, to the knowledge of Ionis, any party with which Ionis or any of its subsidiaries' has entered into an agreement related to the research, development, manufacture, testing, or commercialization of such products, have received any notices or correspondence from any Governmental Authority requiring the termination, suspension or material modification of any studies, tests or preclinical or clinical trials for such products. All of the descriptions in the SEC Documents of the legal and governmental procedures and requirements of the FDA or any foreign, state or local governmental body exercising comparable authority are accurate in all material respects.

3.20 Permits. Ionis and each of its subsidiaries have such permits, licenses, patents, franchises, certificates of need and other approvals or authorizations of such Governmental Authorities ("***Permits***") as are necessary under applicable law to own their properties and conduct their businesses in the manner described in the SEC Documents, except for any of the foregoing that would not, in the aggregate, have a Material Adverse Effect or except as described in the SEC Documents; each of Ionis and its subsidiaries has fulfilled and performed all of its obligations with respect to the Permits, and no event has occurred that allows, or after notice or lapse of time would allow, revocation or termination thereof or results in any other impairment of the rights of the holder or any such Permits, except for any of the foregoing that would not have a Material Adverse Effect or except as described in the SEC Documents.

3.21 ERISA. (i) Each "employee benefit plan" (within the meaning of Section 3(3) of the Employee Retirement Security Act of 1974, as amended ("***ERISA***")) for which Ionis or any member of its "Controlled Group" (defined as any organization which is a member of a controlled group of corporations within the meaning of Section 414 of the Internal Revenue Code of 1986, as amended (the ***"Code"***)) would have any liability (each a "***Plan***") has been maintained in material compliance with its terms and with the requirements of all applicable statutes, rules and regulations including ERISA and the Code; (ii) with respect to each Plan subject to Title IV of ERISA (a) no "reportable event" (within the meaning of Section 4043(c) of ERISA) has occurred or is reasonably expected to occur, (b) no "accumulated funding deficiency" (within the meaning of Section 302 of ERISA or Section 412 of the Code), whether or not waived, has occurred or is reasonably expected to occur, (c) the fair market value of the assets under each Plan exceeds the present value of all benefits accrued under such Plan (determined based on those assumptions used to fund such Plan) and (d) neither the Company or any member of its Controlled Group has incurred, or reasonably expects to incur, any liability under Title IV of ERISA (other than contributions to the Plan or premiums to the Pension Benefit Guaranty Corporation in the ordinary course and without default) in respect of a Plan (including a "multiemployer plan," within the meaning of Section 4001(c)(3) of ERISA); and (iii) each Plan that is intended to be qualified under Section 401(a) of the Code is so qualified and nothing has occurred, whether by action or by failure to act, which would cause the loss of such qualification.

3.22 Labor. Except as described in the SEC Documents, no labor disturbance by the employees of Ionis or any of its subsidiaries exists or, to the knowledge of Ionis, is imminent that would have a Material Adverse Effect, and Ionis is not aware of any existing or imminent labor disturbance by, or dispute with, the employees of any of Ionis's or any of Ionis's subsidiaries' collaborative partners, principal suppliers, contractors or customers that would have a Material Adverse Effect.

3.23 Taxes. Ionis and each of its subsidiaries have filed all federal, state, local and foreign income and franchise tax returns required to be filed through the date hereof, subject to permitted extensions, such tax returns are true and complete in all material respects, all taxes due thereon have been paid, and no material tax deficiency has been determined adversely to Ionis or any of its subsidiaries, nor does Ionis have any knowledge of any tax deficiencies that would, in the aggregate, have a Material Adverse Effect.

3.24 Environmental Laws. Ionis and each of its subsidiaries (i) are, and at all times prior hereto were, in compliance with all laws, regulations, ordinances, rules, orders, judgments, decrees, permits or other legal requirements of any Governmental Authority, including without limitation any international, national, state, provincial, regional, or local authority, relating to the protection of human health or safety, the environment, or natural resources, or to hazardous or toxic substances or wastes, pollutants or contaminants ("***Environmental Laws***") applicable to such entity, which compliance includes, without limitation, obtaining, maintaining and complying with all permits and authorizations and approvals required by Environmental Laws to conduct their respective businesses, and (ii) have not received written notice of any actual or alleged violation of Environmental Laws, or of any potential liability for or other obligation concerning the presence, disposal or release of hazardous or toxic substances or wastes, pollutants or contaminants, except in the case of clause (i) or (ii) where such non-compliance, violation, liability, or other obligation would not, in the aggregate, have a Material Adverse Effect. Except as described in the SEC Documents, (A) there are no proceedings that are pending, or known to be contemplated, against Ionis or any of its subsidiaries under Environmental Laws in which a Governmental Authority is also a party, other than such proceedings regarding which it is reasonably believed no monetary sanctions of $250,000 or more will be imposed, (B) Ionis and its subsidiaries are not aware of any issues regarding compliance with Environmental Laws, or liabilities or other obligations under Environmental Laws or concerning hazardous or toxic substances or wastes, pollutants or contaminants, that would have a Material Adverse Effect, and (C) none of Ionis and its subsidiaries anticipates material capital expenditures relating to Environmental Laws.

3.25 Insurance. Except such as are described in the SEC Documents, Ionis and each of its subsidiaries carry, or are covered by, insurance from insurers of recognized financial responsibility in such amounts and covering such risks as, based on Ionis's internal assessments, is adequate for the conduct of their respective businesses and the value of their respective properties and as is customary for companies engaged in similar businesses in similar industries. All policies of insurance of Ionis and its subsidiaries are in full force and effect. Ionis and its subsidiaries are in compliance with the terms of such policies in all material respects; and neither Ionis nor any of its subsidiaries has received notice from any insurer or agent of such insurer that capital improvements or other expenditures are required or necessary to be made in order to continue such insurance; there are no claims by Ionis or any of its subsidiaries under any such policy or instrument as to which any insurance company is denying liability or defending under a reservation of rights clause; and neither Ionis nor any such subsidiary has any reason to believe that it will not be able to renew its existing insurance coverage as and when such coverage expires or to obtain similar coverage from similar insurers as may be necessary to continue its business at a cost that would not have a Material Adverse Effect.

3.26 AML. The operations of Ionis and its subsidiaries are and have been conducted at all times in compliance with applicable financial recordkeeping and reporting requirements of the Currency and Foreign Transactions Reporting Act of 1970, as amended, the money laundering statutes of all jurisdictions, the rules and regulations thereunder and any related or similar rules, regulations or guidelines, issued, administered or enforced by any Governmental Authority (collectively, the "***Money Laundering Laws***") and no action, suit or proceeding by or before any Governmental Authority involving Ionis or any of its subsidiaries with respect to the Money Laundering Laws is pending or, to the knowledge of Ionis, threatened, except, in each case, as would not have a Material Adverse Effect.

3.27 OFAC. Neither Ionis nor any of its subsidiaries nor, to the knowledge of Ionis, any director, officer, agent, employee or affiliate of Ionis or any of its subsidiaries is currently subject to any U.S. sanctions administered by the Office of Foreign Assets Control of the U.S. Treasury Department (***"OFAC"***); and Ionis will not directly or indirectly use the proceeds of sale of Shares, or lend, contribute or otherwise make available such proceeds to any subsidiary, joint venture partner or other person or entity, for the purpose of financing the activities of any person currently subject to any U.S. sanctions administered by OFAC.

3.28 FCPA. Neither Ionis nor any of its subsidiaries, nor, to the knowledge of Ionis, any director, officer, agent, employee or other person acting on behalf of Ionis or any of its subsidiaries, has (i) used any corporate funds for any unlawful contribution, gift, entertainment or other unlawful expense relating to political activity; (ii) made any direct or indirect unlawful payment to any foreign or domestic government official or employee from corporate funds; (iii) violated or is in violation of any provision of the U.S. Foreign Corrupt Practices Act of 1977 or the U.K. Bribery Act; or (iv) made any bribe, rebate, payoff, influence payment, kickback or other unlawful payment.

3.29 Sarbanes-Oxley. There is and has been no failure on the part of Ionis or any of Ionis's directors or officers, in their capacities as such, to comply in all material respects with the provisions of the U.S. Sarbanes-Oxley Act of 2002 and the rules and regulations promulgated in connection therewith.

Section 4. Representations and Warranties of Novartis

Except as otherwise specifically contemplated by this Agreement, Novartis hereby represents and warrants to Ionis and Akcea that:

4.1 Authorization; Enforcement. Novartis has the requisite corporate power and authority to enter into this Agreement and to consummate the transactions contemplated hereby and to purchase the Shares in accordance with the terms hereof. Novartis has taken all necessary corporate action to authorize the execution, delivery and performance of this Agreement (including the purchase of the Shares). This Agreement has been duly executed by Novartis and constitutes a legal, valid and binding obligation of Novartis enforceable against Novartis in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, or moratorium or similar laws affecting creditors' and contracting parties' rights generally and except as enforceability may be subject to general principles of equity and except as rights to indemnity and contribution may be limited by state or federal securities laws or public policy underlying such laws.

4.2 No Conflicts; Government Consents and Permits.

(a) The execution, delivery and performance of this Agreement by Novartis and the consummation by Novartis of the transactions contemplated hereby (including the purchase of the Shares) will not (i) conflict with or result in a violation of any provision of Novartis' Certificate of Incorporation or Bylaws, (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which Novartis is a party, or (iii) result in a violation of any law, rule, regulation, order, judgment or decree (including United States federal and state securities laws and regulations and regulations of any self-regulatory organizations) applicable to Novartis, except in the case of clauses (ii) and (iii) only, for such conflicts, breaches, defaults, and violations as would not have a Material Adverse Effect on Novartis or result in a liability for Ionis or Akcea.

(b) Novartis is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory or self-regulatory agency in order for it to execute, deliver or perform any of its obligations under this Agreement in accordance with the terms hereof, or to purchase the Shares in accordance with the terms hereof other than such as have been made or obtained except for the expiration or termination of any waiting period required under the HSR Act.

4.3 Investment Purpose. Novartis is purchasing the Shares for its own account and not with a present view toward the public distribution thereof and has no arrangement or understanding with any other persons regarding the distribution of such Shares except as would not result in a violation of the Securities Act. Novartis will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) any of the Shares except in accordance with the Securities Act and to the extent permitted by Section 7.1 and Section 7.2.

4.4 Reliance on Exemptions. Novartis understands that Ionis and Akcea intend for the Shares to be offered and sold to Novartis in reliance upon specific exemptions from the registration requirements of United States federal and state securities laws and that Ionis and Akcea are relying upon the truth and accuracy of, and Novartis' compliance with, the representations and warranties of Novartis set forth herein in order to determine the availability of such exemptions and the eligibility of Novartis to acquire the Shares.

4.5 Accredited Investor; Access to Information. Novartis is an "accredited investor" as defined in Regulation D under the Securities Act and is knowledgeable, sophisticated and experienced in making, and is qualified to make decisions with respect to investments in shares presenting an investment decision like that involved in the purchase of the Shares. Novartis has been furnished with materials relating to the offer and sale of the Shares, that have been requested by Novartis, including, without limitation, Ionis's SEC Documents, and Novartis has had the opportunity to review the SEC Documents. Novartis has been afforded the opportunity to ask Ionis and Akcea questions. Neither such inquiries nor any other investigation conducted by or on behalf of Novartis or its representatives or counsel will modify, amend or affect Novartis' right to rely on the truth, accuracy and completeness of the SEC Documents and Ionis's and Akcea's representations and warranties contained in this Agreement.

4.6 Governmental Review. Novartis understands that no United States federal or state agency or any other government or governmental agency has passed upon or made any recommendation or endorsement of the Shares or an investment therein.

Section 5. NOTICE OF INTENT TO ACQUIRE AKCEA SHARES

5.1 From the Subsequent Closing and so long as Novartis is required to report its ownership of Akcea Common Stock pursuant to Regulation 13D-G under the Securities Exchange Act of 1934, Novartis agrees to notify Akcea (which may be via email to the Chief Executive Officer of Akcea) 10 days prior to its direct acquisition, agreement to acquire or public offering to acquire, additional shares of Akcea's Common Stock in a single transaction, that represent more than an additional 1.0% of Akcea's total outstanding Common Stock, on an issued and outstanding basis without giving effect to any convertible securities; *provided that* Akcea agrees that such notification will be subject to the confidentiality provisions (but not the non-use provisions) applicable to Novartis' Confidential Information under Article 12 of the Collaboration Agreement until publicly disclosed by Novartis. For purposes of determining the number of outstanding shares of Akcea Common Stock for purposes of this Section 5, Novartis may rely on the number of outstanding shares of Akcea Common Stock as reflected in Akcea's most recent Annual Report on Form 10-K, Quarterly Report on Form 10-Q, Current Report on Form 8-K or other public filing with the SEC. For the avoidance of doubt, this Section 5 shall not apply to the purchase of any of Akcea's Common Stock (i) pursuant to Section 2 of this Agreement, (ii) by any of Novartis's executive officers or directors for his or her personal account or (iii) by an employee benefit plan in any diversified index, mutual or pension fund managed by an independent advisor, which fund in-turn holds, directly or indirectly, securities of Akcea.

Section 6. AKCEA VOTING AGREEMENT

6.1 Voting Agreement.

(a) If the Proxyholder instructs (or otherwise requests) that Novartis vote in favor of, or against, any matter, action, ratification or other event, other than as permitted by Section 6.1(b) with respect to Extraordinary Matters, for which approval of the holders of Akcea's stock is sought (either by vote or written consent) or upon which such holders are otherwise entitled to vote, including but not limited to the election of directors (collectively, a "Stockholder Matter"), then Novartis will (i) after receiving proper notice of any meeting of stockholders related to such Stockholder Matter (or, if no notice is required or such notice is properly waived, after notice from the Proxyholder is given), be present, in person or by proxy, as a holder of Akcea Shares at all such meetings and be counted for the purposes of determining the presence of a quorum at such meetings and (ii) vote (in person, by proxy or by action by written consent, as applicable) all Akcea Shares as to which Novartis has beneficial ownership or as to which Novartis otherwise exercises voting or dispositive authority in the manner directed by the Proxyholder; *provided, however*, that the Proxyholder may only instruct or otherwise request that Novartis vote in a manner that is consistent with the recommendation of the board of directors of Akcea.

(b) Extraordinary Matters. Novartis may vote or execute a written consent with respect to, any or all of the voting securities of Akcea as to which they are entitled to vote or execute a written consent, as it may determine in its sole discretion, with respect to the following matters, if presented to Akcea's stockholders for approval (each such matter being an "***Extraordinary Matter***"):

(i) any transaction which would result in a Change of Control of Akcea;

(ii) any issuance of Common Stock that represents more than 20% of the then outstanding Akcea Common Stock;

(iii) the entry into any licensing, partnering, partnership, collaboration, research and development, joint venture or other commercial agreement;

(iv) the payment of any dividends to any class of stockholders of Akcea; and

(v) any liquidation or dissolution of Akcea.

(c) Appointment of Proxy. To secure Novartis' obligations to vote the Akcea Shares in accordance with this Agreement and to comply with the other terms hereof, Novartis hereby appoints the Proxyholder, or its designees, as Novartis' true and lawful proxy and attorney, with the power to act alone and with full power of substitution, to vote or act by written consent with respect to all of Novartis' Akcea Shares in accordance with the provisions set forth in this Agreement, and to execute all appropriate instruments consistent with this Agreement on behalf of Novartis. The proxy and power granted by Novartis pursuant to this Section 6 are coupled with an interest and are given to secure the performance of Novartis' duties under this Agreement. Each such proxy and power will be irrevocable for the term hereof. The proxy and power will survive the merger, consolidation, conversion or reorganization of Novartis or any other entity holding any Akcea Shares.

(d) No Revocation. The voting agreement contained herein is coupled with an interest and may not be revoked during the term of this Agreement.

(e) Termination. Novartis's obligations pursuant to this Section 6 will expire (i) with respect to shares of Akcea Common Stock transferred by Novartis in an arm's length transfer to a non-Affiliate in compliance with this Agreement, immediately prior to such transfer, and (ii) upon the date on which Novartis beneficially owns less than 7.5% of Akcea's outstanding Common Stock on an issued and outstanding basis without giving effect to any convertible securities.

Section 7. TRANSFER, RESALE, LEGENDS.

7.1 Transfer or Resale. Novartis understands that:

(a) the Shares have not been and are not being registered under the Securities Act or any applicable state securities laws and, consequently, Novartis may have to bear the risk of owning the Shares for an indefinite period of time because the Shares may not be transferred unless (i) the resale of the Shares is registered pursuant to an effective registration statement under the Securities Act; (ii) Novartis has delivered to Ionis or Akcea, as applicable, an opinion of counsel (in form, substance and scope customary for opinions of counsel in comparable transactions) to the effect that the Shares to be sold or transferred may be sold or transferred pursuant to an exemption from such registration; or (iii) the Shares are sold or transferred pursuant to Rule 144;

(b) any sale of the Shares made in reliance on Rule 144 may be made only in accordance with the terms of Rule 144 and, if Rule 144 is not applicable, any resale of the Shares under circumstances in which the seller (or the person through whom the sale is made) may be deemed to be an underwriter (as that term is defined in the Securities Act) may require compliance with some other exemption under the Securities Act or the rules and regulations of the SEC thereunder; and

(c) except as provided under Section 9, neither Ionis, Akcea nor any other person is under any obligation to register the resale of the Shares under the Securities Act or any state securities laws or to comply with the terms and conditions of any exemption thereunder.

7.2 Agreement to Hold Akcea Shares. Novartis agrees that it will hold and will not sell the Akcea Shares (or otherwise make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale of the Shares) until the earliest of the (A) three-year anniversary of the Execution Date (the ***"Holding Period"***) or (B) sixth month following a decision from Akcea to discontinue for any reason the Pre-Option development activities for AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx} as contemplated in Section 1.2.1 of the Collaboration Agreement. In addition, after the expiration of the Holding Period, in any single trading day Novartis will not sell Akcea Shares in an amount that is more than 10% of the daily trading volume of Akcea's Common Stock for such trading day.

7.3 Legends. Novartis understands the certificates representing the Akcea Shares will bear a restrictive legend in substantially the following form (and a stop-transfer order may be placed against transfer of the certificates for such Akcea Shares):

THE SHARES EVIDENCED HEREBY ARE SUBJECT TO AN AGREEMENT TO VOTE THESE SHARES IN THE MANNER SET FORTH IN THE STOCK PURCHASE AGREEMENT DATED _____ AMONG IONIS PHARMACEUTICALS, INC., AKCEA THERAPEUTICS INC. AND NOVARTIS PHARMA AG.

THE SALE, PLEDGE, HYPOTHECATION OR TRANSFER OF THE SECURITIES REPRESENTED BY THIS CERTIFICATE IS SUBJECT TO THE TERMS AND CONDITIONS OF A STOCK PURCHASE AGREEMENT DATED _____ AMONG IONIS PHARMACEUTICALS, INC., AKCEA THERAPEUTICS INC. AND NOVARTIS PHARMA AG.

Novartis may request that Akcea remove, and Akcea agrees at its own expense to authorize and instruct (including by causing any required legal opinion to be provided) the removal of any legend from the Shares promptly following the expiration of the obligations set forth in Section 6 or Section 7, as applicable.

7.4 Legend Removal. Each of Ionis and Akcea agree that at such time as any legend set forth in Section 7.3 or otherwise applicable to such Shares, is no longer required, Ionis or Akcea, as applicable, shall, at its own expense and no later than three (3) trading days following a written request from Novartis, instruct its Transfer Agent to remove the applicable legend from the book entry stock record representing such Shares that is free from such legend. Neither Ionis nor Akcea may make any notation on its records or give instructions to its transfer agent that expand the restrictions on transfer set forth in this Section 7.

Section 8. CONDITIONS TO CLOSING

8.1 Conditions to Obligations of Ionis and Akcea. Ionis's and Akcea's (as applicable) obligation to complete the issuance and sale of the Shares and deliver such stock to Novartis is subject to the fulfillment or waiver of the following conditions at or prior to the applicable Closing:

(a) Receipt of Funds. Ionis and Akcea (as applicable) will have received immediately available funds in the full amount of the Purchase Price for the Shares being purchased at the applicable Closing.

(b) Representations and Warranties. The representations and warranties made by Novartis in Section 4 will be true and correct in all material respects as of the applicable Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct in all material respects as of such other date.

(c) Collaboration Agreement. Novartis shall have duly executed and delivered to Akcea the Collaboration Agreement, and there shall have been no termination of the Collaboration Agreement that, as of the Closing, is effective.

8.2 Conditions to Purchaser's Obligations at the Closing. Novartis' obligation to complete the purchase and sale of the Shares is subject to the fulfillment or waiver of the following conditions at or before the applicable Closing:

(a) Representations and Warranties. In the case where Novartis is purchasing Ionis Common Stock under Section 1.1, the representations and warranties made by Ionis in Section 3 will be true and correct as of the applicable Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct as of such other date. In the case where Novartis is purchasing Akcea Common Stock, Akcea will have delivered to Novartis a certificate signed by an authorized officer certifying that the representations and warranties made by Akcea in warranties made by Akcea in the underwriting agreement signed by Akcea in connection with the Qualified Initial Public Offering, are true and correct as of the Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct as of such other date. Novartis shall be entitled to rely upon the representations and warranties made by Akcea in the underwriting agreement signed by Akcea in connection with the Qualified Initial Public Offering as if made to Novartis (a copy of such underwriting agreement shall be delivered to Novartis as an exhibit to such certificate).

(b) Collaboration Agreement Representations and Warranties. The representations and warranties in Section 9.2 of the Collaboration Agreement shall be true and correct as of the applicable Closing Date. Akcea will have delivered to Novartis a certificate signed by an authorized officer certifying that the representations and warranties in Section 9.2 of the Collaboration Agreement are true and correct.

(c) Transfer Agent Instructions. Ionis or Akcea, as applicable, will have delivered to its transfer agent irrevocable written instructions to issue the Shares to Novartis and deliver such Shares (which may be done by book-entry).

(d) Listing Qualification. The Shares will be duly authorized for listing by NYSE or Nasdaq, subject to official notice of issuance, to the extent required by the rules of NYSE or Nasdaq.

(e) No Material Adverse Effect. From and after the date of this Agreement until the Closing Date, there shall have occurred no event that has caused or would cause a Material Adverse Effect that is continuing as of the applicable Closing Date.

(f) Collaboration Agreement. Akcea shall have duly executed and delivered to Novartis the Collaboration Agreement, and there shall have been no termination of the Collaboration Agreement that, as of the Closing, is effective.

8.3 Mutual Conditions to Closing. The obligations of Novartis on the one hand, and Ionis and Akcea (as applicable) on the other hand, to consummate the Closing are subject to the fulfillment as of the Closing Date of the following conditions:

(a) HSR Act Qualification. The filings required under the HSR Act in connection with this Agreement shall have been made and the required waiting period shall have expired or been terminated as of the Closing Date.

(b) Absence of Litigation. No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or delay the applicable Closing, will have been instituted or be pending before any court, arbitrator, governmental body, agency or official.

(c) No Governmental Prohibition. The sale of the Shares by Ionis or Akcea as applicable, and the purchase of the Shares by Novartis will not be prohibited by any applicable law or governmental order or regulation. Any applicable waiting periods under the HSR Act will have expired or terminated.

(d) Representations and Warranties. In the case where Novartis is purchasing Ionis Common Stock under Section 2.2, the representations and warranties made by Ionis in Section 3 will be true and correct as of the applicable Closing Date, except to the extent such representations and warranties are made as of another date, in which case such representations and warranties will be true and correct as of such other date.

Section 9. **REGISTRATION RIGHTS; LOCKUP AGREEMENT**

9.1 **Registration Rights; Most Favored Registration Rights**. If Novartis purchases Akcea Common Stock pursuant to Section 2.1, Novartis will have the same registration rights as Akcea has granted to Ionis pursuant to Section 5 of the Investor Rights Agreement dated December 18, 2015 between Ionis and Akcea, *mutatis mutandis*. If Akcea grants any registration rights to any Person that are otherwise superior to the registration rights granted to Novartis under this Section 9.1, then any such superior registration rights granted to other Persons shall (as a whole and not in part) replace Novartis' registration rights under this Agreement and shall be deemed to be incorporated into this Agreement.

9.2 **IPO lockup**. If Novartis purchases Akcea Common Stock pursuant to Section 2.1, Novartis agrees that it will sign a customary lockup agreement requested by the underwriters in Akcea's Qualified Initial Public Offering, including but not limited to an agreement not to sell, transfer, make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale, any Akcea Common Stock held by Novartis (other than those included in the registration) during the 180-day period following the effective date of the Qualified Initial Public Offering; *provided*, that all of Akcea's officers and directors and all persons or entities who hold Akcea's Common Stock (or securities convertible into Common Stock) in an amount that is greater than 1% of Akcea's then issued and outstanding Common Stock are bound by and have entered into similar agreements.

9.3 **Follow-on Lockup**. In addition, if Novartis purchases Akcea Common Stock pursuant to Section 2.1, so long as Novartis beneficially owns 5% or more of Akcea's outstanding Common Stock on an issued and outstanding basis without giving effect to any convertible securities, and provided that Novartis participates in such follow-on offering as a selling stockholder, Novartis will sign a customary lockup agreement requested by the underwriters in any follow-on offering of Akcea's Common Stock, including but not limited to an agreement not to sell, transfer, make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale, any Akcea Common Stock held by Novartis (other than those included in the registration) during the 90-day period following the effective date of the follow-on offering; *provided*, that all of Akcea's officers and directors and all persons or entities who hold Akcea's Common Stock (or securities convertible into Common Stock) in an amount that is greater than 5% of Akcea's on an issued and outstanding basis without giving effect to any convertible securities are bound by and have entered into similar agreements.

9.4 **Equal Treatment Under Lockups**. In the event that any party subject to any lockup agreement under Section 9.2 or 9.3 receives any discretionary waiver or termination of any of the restrictions of such lockup agreement by Akcea or the underwriters (all such released parties, the "***Released Parties***"), Novartis shall automatically be released from its obligations with respect to the same percent of Akcea Common Stock as the percent of Akcea Common Stock held by all Released Parties that are subject to the waiver or termination, with such percentage calculated by reference to the aggregate number of Akcea Common Stock beneficially owned by such Released Parties. For the avoidance of doubt, Akcea agrees to promptly notify Novartis of any such waiver or termination by Akcea or the underwriters.

Section 10. GOVERNING LAW; HSR; TERMINATION; MISCELLANEOUS.

10.1 Governing Law; Jurisdiction. This Agreement will be governed by and interpreted in accordance with the laws of the State of Delaware without regard to the principles of conflict of laws.

10.2 HSR Clearance Cooperation.

(a) Each of Novartis, Ionis and Akcea shall use commercially reasonable efforts to provide or cause to be provided promptly all assistance and cooperation to allow Novartis, Ionis and Akcea to prepare and submit any filings or submissions under the HSR Act, including providing to Novartis, Ionis and Akcea any information that it may require for the purpose of any filing, notification, application or request for further information made in respect of any such filing.

(b) Each of Novartis, Ionis, and Akcea shall, in connection with the Agreement contemplated hereby, with respect to actions taken on or after the date of this Agreement, without limitation: (1) promptly notify the other of, and if in writing, furnish the other with copies of (or, in the case of oral communications, advise the other of) any communications from or with any Governmental Authority with respect to the Agreement, (2) permit the other to review and discuss in advance, and consider in good faith the view of the other in connection with, any proposed written or oral communication with any Governmental Authority, (3) not participate in any substantive meeting or have any substantive communication with any Governmental Authority unless it has given the other party a reasonable opportunity to consult with it in advance and, to the extent permitted by such Governmental Authority, gives the other the opportunity to attend and participate therein, (4) furnish the other party's outside legal counsel with copies of all filings and communications between it and any such Governmental Authority with respect to the Agreement; *provided* that neither Party will be required to provide the other Party with its Board of Directors or internal committee materials; and such material may be redacted as necessary (I) to comply with contractual arrangements, (II) to address good faith legal privilege or confidentiality concerns and (III) to comply with applicable law, (5) furnish the other party's outside legal counsel with such necessary information and reasonable assistance as the other party's outside legal counsel may reasonably request in connection with its preparation of necessary submissions of information to any such Governmental Authority, and (6) use commercially reasonable efforts to respond as soon as practicable to requests for information by any Governmental Authority.

10.3 Termination. This Agreement will automatically terminate upon termination of the Collaboration Agreement.

10.4 Effect of Termination. Sections 7.3, 7.4, 9 and Section 10 hereof shall survive any termination of this Agreement.

10.5 Counterparts; Signatures by Facsimile. This Agreement may be executed in two counterparts, both of which are considered one and the same agreement and will become effective when the counterparts have been signed by each party and delivered to the other party hereto. This Agreement, once executed by a party, may be delivered to the other party hereto by electronic PDF or facsimile transmission (including pdf or any electronic signature complying with the U.S. federal ESIGN Act of 2000, *e.g.*, www.docusign.com) of a copy of this Agreement bearing the signature of the party so delivering this Agreement.

10.6 Headings. The headings of this Agreement are for convenience of reference only, are not part of this Agreement and do not affect its interpretation.

10.7 Severability. If any provision of this Agreement should be held invalid, illegal or unenforceable in any jurisdiction, the parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

10.8 Entire Agreement; Amendments. This Agreement (including any schedules and exhibits hereto) and the Collaboration Agreement constitutes the entire agreement between the parties hereto with respect to the subject matter hereof and thereof. There are no restrictions, promises, warranties or undertakings, other than those set forth or referred to herein or therein. This Agreement supersedes all prior agreements and understandings between the parties hereto with respect to the subject matter hereof. No provision of this Agreement may be amended other than by an instrument in writing signed by all three parties. No provision of this Agreement may be waived other than by an instrument in writing signed by the party(ies) who has the right to enforce the waived provision. Any amendment or waiver effected in accordance with this Section 10.8 will be binding upon Novartis, Ionis and Akcea.

10.9 Notices. All notices required or permitted hereunder will be in writing and will be deemed effectively given: (a) upon personal delivery to the party to be notified, (b) when sent by facsimile if sent during normal business hours of the recipient, if not, then on the next business day of the recipient, or (c) three days after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. The addresses for such communications are:

If to Ionis, addressed to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: 760-918-3592

with a copy to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
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. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to Novartis, addressed to:	Novartis Pharma AG Lichtstrasse 35 4002, Basel, Switzerland Attention: General Counsel Fax: +41613247399
with a copy to:	Novartis Pharma AG Lichtstrasse 35 4002, Basel, Switzerland Attention: Head Global Business Development & Licensing Fax: +41613247399

10.10 Successors and Assigns. This Agreement is binding upon and inures to the benefit of the parties and their successors and assigns. Each party will not assign this Agreement or any rights or obligations hereunder without the prior written consent of the other parties; *provided, however*, that Novartis may assign this Agreement together with all of the Shares it then owns (subject to Section 5.1, Section 7.2 and Section 9) to any Affiliate and any such assignee may assign the Agreement together with all of the Shares it then owns (subject to Section 5.1, Section 7.2 and Section 9) to Novartis or any other Affiliate of Novartis, in any such case, without such consent provided that the assignee agrees to assume Novartis' obligations under Section 5.1, Section 7.2 and Section 9 of this Agreement.

10.11 Third Party Beneficiaries. This Agreement is intended for the benefit of the parties hereto, their respective permitted successors and assigns, and is not for the benefit of, nor may any provision hereof be enforced by, any other person.

10.12 Further Assurances; Each party will do and perform, or cause to be done and performed, all such further acts and things, and will execute and deliver all other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby. **No Strict Construction.** The language used in this Agreement is deemed to be the language chosen by the parties to express their mutual intent, and no rules of strict construction will be applied against a party.

10.13 Equitable Relief; Specific Performance. Each of Novartis, Ionis and Akcea recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at law may prove to be inadequate relief to the other parties. Each of Novartis, Ionis and Akcea therefore agrees that the other parties are entitled to seek temporary and permanent injunctive relief or specific performance in any such case.

10.14 Expenses. Each party is liable for, and will pay, their own expenses incurred in connection with the negotiation, preparation, execution and delivery of this Agreement, including, without limitation, attorneys' and consultants' fees and expenses.

10.15 Dispute Escalation.

(a) General. The parties recognize that a dispute may arise out of or relate to this Agreement (***"Dispute"***). Any Dispute among the parties or their respective Affiliates will be resolved in accordance with this Section 10.15 and Section 10.16.

(b) Continuance of Rights and Obligations during Pendency of Dispute Resolution. If there are any Disputes in connection with this Agreement, all rights and obligations of the parties will continue until such time as any Dispute has been resolved in accordance with the provisions of this Section 10.15 and Section 10.16.

(c) Escalation. Any claim, Dispute, or controversy as to the breach, enforcement, interpretation or validity of this Agreement will be referred to the Novartis Pharmaceuticals Division Chief Executive Officer and to the Chief Operating Officer of Ionis (the ***"Executives"***) for attempted resolution. If the Executives are unable to resolve such Dispute within 30 days of such Dispute being referred to them, then, upon the written request of any party to the other parties, the Dispute will be subject to mediation in accordance with Section 10.15(d).

(d) Mediation. In the event the parties cannot resolve any Dispute as set forth above, either party may require the matter to be subject to non-binding mediation under the Commercial Rules and auspices of the International Chamber of Commerce ("***ICC***"), by a single mediator selected in accordance with the rules of the ICC. If the dispute is not resolved within thirty (30) days after mediation commences, the Dispute will be subject to Section 10.16.

10.16 Submission to Jurisdiction.

(a) Any action brought, arising out of, or relating to this Agreement shall be brought in the Court of Chancery of the State of Delaware. Each party hereby irrevocably submits to the exclusive jurisdiction of said Court in respect of any claim relating to the validity, interpretation and enforcement of this Agreement, and hereby waives, and agrees not to assert, as a defense in any action, suit or proceeding in which any such claim is made that it is not subject thereto or that such action, suit or proceeding may not be brought or is not maintainable in such courts, or that the venue thereof may not be appropriate or that this agreement may not be enforced in or by such courts. The parties hereby consent to and grant the Court of Chancery of the State of Delaware jurisdiction over such parties and over the subject matter of any such claim and agree that mailing of process or other papers in connection with any such action, suit or proceeding in the manner provided in Section 10.9 or in such other manner as may be permitted by law, shall be valid and sufficient thereof.

(b) EACH PARTY HERETO WAIVES: (1) ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY, (2) WITH THE EXCEPTION OF RELIEF MANDATED BY STATUTE, ANY CLAIM TO PUNITIVE, EXEMPLARY, MULTIPLIED, INDIRECT, CONSEQUENTIAL OR LOST PROFITS/REVENUES DAMAGES, AND (3) ANY CLAIM FOR ATTORNEY FEES, COSTS AND PREJUDGMENT INTEREST.

In Witness Whereof, Novartis and Ionis have caused this Agreement to be duly executed as of the date first above written.

Novartis Pharma AG

By: /s/ Paul Hudson

Its: Novartis Pharma CEO

Novartis Pharma AG

By: /s/ Nigel Sheail

Its: Head of Business Development & Licensing

Ionis Pharmaceuticals, Inc.

By: /s/ B. Lynne Parshall

Its: Chief Operating Officer

Akcea Therapeutics Inc.

By: /s/ Paula Soteropoulos

Its: President & CEO

APPENDIX 1

DEFINED TERMS

"Affiliate" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***AKCEA-APO(a)-L$_{Rx}$***" means the oligonucleotide known as ISIS 681257 (also known as IONIS-APO(a)-L$_{Rx}$) having the following sequence and chemistry: 5'-THA-AH$_{P=O}$^{Me}UG$_{P=O}$^{Me}C$_{P=O}$^{Me}U$_{P=O}$^{Me}C$_{P=O}$^{Me}CGTTGGTG^{Me}CT^{Me}U$_{P=O}$G$_{P=O}$^{Me}U^{Me}U^{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 oligonucleotide 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 structure and the choice for the symbol depends on whether the sugar is 2′-deoxy-D-ribose or D-ribose. The $_{P=O}$ designates the location of a phosphate diester linkage. Each of the other internucleoside linkages is a phosphorothioate diester linkage. AH designates the location of the aminohexyl linker and THA is 5-N-{tris[(6-(2-acetamido-3,4,6-tri-O-acetyl-β-D-galactopyranosyloxy)hexylamino)-3-oxopropoxymethyl]methyl}amino-5-oxopentanoyl.

"***AKCEA-APOCIII-L$_{Rx}$***" means the oligonucleotide known as ISIS 678354 (also known as IONIS-APOCIII-L$_{Rx}$) having the following sequence and chemistry: 5'-THA-AH$_{P=O}$AG^{Me}C^{Me}U^{Me}U^{Me}CTTGT^{Me}C^{Me}CAG^{Me}C^{Me}U^{Me}U^{Me}UA^{Me}U-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 oligonucleotide 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 structure and the choice for the symbol depends on whether the sugar is 2′-deoxy-D-ribose or D-ribose. The $_{P=O}$ designates the location of a phosphate diester linkage. Each of the other internucleoside linkages is a phosphorothioate diester linkage. AH designates the location of the aminohexyl linker and THA is 5-N-{tris[(6-(2-acetamido-3,4,6-tri-O-acetyl-β-D-galactopyranosyloxy)hexylamino)-3-oxopropoxymethyl]methyl}amino-5-oxopentanoyl.

"Change of Control" means with respect to a party, any (a) direct or indirect acquisition of all or substantially all of the assets of such party, (b) direct or indirect acquisition by a Person, or group of Persons acting in concert, of 50% or more of the voting equity interests of a party, (c) tender offer or exchange offer that results in any Person, or group of Persons acting in concert, beneficially owning 50% or more of the voting equity interests of a party, or (d) merger, consolidation, other business combination or similar transaction involving a party, pursuant to which any Person owns all or substantially all of the consolidated assets, net revenues or net income of a party, taken as a whole, or which results in the holders of the voting equity interests of a party immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold 50% or more of the combined voting power of the surviving, purchasing or continuing entity immediately after such merger, consolidation, other business combination or similar transaction, in all cases where such transaction is to be entered into with any person other than the other party to this Agreement or its Affiliates. For the avoidance of doubt, the Qualified Initial Public Offering of Akcea shall not be deemed a Change of Control.

"Common Stock" means the Ionis Common Stock or the Akcea Common Stock, as the case may be.

"Exchange Act" means the Securities Exchange Act of 1934, as amended, and the rules and regulations of the SEC thereunder.

"GAAP" means generally accepted accounting principles in the United States of America.

"Material Adverse Effect" means a material adverse change in or affecting the general affairs, condition (financial or otherwise), results of operations, stockholders' equity, properties, business, management or prospects of Ionis, Akcea or Novartis and its respective subsidiaries taken as a whole, or on the performance by such party of its obligations under this Agreement or the consummation of any of the transactions contemplated hereby or thereby.

"Nasdaq" means The Nasdaq Global Select Market or Nasdaq Global Market.

"NYSE" means the New York Stock Exchange.

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

"Proxyholder" means Akcea Therapeutics Inc. and its Chief Executive Officer and/or Chief Operating Officer, in their capacities as such officers of Akcea Therapeutics Inc.

"Qualified Initial Public Offering" means the closing of the sale of shares of Akcea Common Stock to the public at a price in a firm-commitment underwritten public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended, resulting in (i) a listing of Akcea Common Stock on either the NYSE or Nasdaq, (ii) at least $100,000,000 of gross proceeds to Akcea and (iii) an initial market capitalization of Akcea of at least $500 million.

"SEC" means the United States Securities and Exchange Commission or any successor entity.

"Securities Act" means the Securities Act of 1933, as amended, and the rules and regulations of the SEC thereunder.

CONFIDENTIAL TREATMENT REQUESTED

UNDER 17 C.F.R.§§ 200.80(B)4, AND 240.24B-2

Exhibit 10.3

Execution Copy

AMENDMENT #1

TO THE LICENSE AGREEMENT, DATED MAY 1ST, 2015

This AMENDMENT #1 ("***Amendment #1***") is entered into as of February 10, 2017 (the "***Amendment Date***") by and between **Ionis Pharmaceuticals, Inc.** (formerly named Isis Pharmaceuticals, Inc.), a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010, USA ("***Ionis***"), and **Bayer AG** (upon assignment by Bayer Pharma AG effective January 1, 2017), a company organized under the Laws of Germany, whose office is situated at Muellerstraße 178, 13353 Berlin, Germany ("***Bayer***").

Ionis and Bayer shall also each individually be referred to herein as a "***Party***", and shall be referred to collectively as the "***Parties***". Capitalized terms used in this Amendment #1, whether used in the singular or the plural, have the meaning ascribed to them in the Agreement (defined below), unless expressly stated otherwise herein. All attached appendices and schedules are a part of this Amendment #1.

WHEREAS:

(A) Ionis and Bayer have entered into a License Agreement dated May 1, 2015, as amended (the "***Agreement***") in respect of ISIS-FXI$_{Rx}$, including option rights to a Factor XI follow-on compound and a [***] compound;

(B) Under the Agreement, Ionis has completed certain clinical and non-clinical studies for ISIS-FXI$_{Rx}$, including the "*Isis Completion Activities*" and has identified and designated a follow-on Development Candidate targeting Factor XI incorporating Ionis' liver-targeted Conjugate Technology, [***];

(C) The Agreement provides for an Option for Bayer to license ISIS-FXI$_{Rx}$-2 upon the designation of a Development Candidate and Bayer is exercising its Option to ISIS-FXI$_{Rx}$-2 to obtain the license to ISIS-FXI$_{Rx}$-2 in accordance with this Amendment #1; and

(D) To expedite the Development of ISIS-FXI$_{Rx}$ and ISIS-FXI$_{Rx}$-2, Ionis will conduct the Ionis Development Activities described in this Amendment #1.

NOW, THEREFORE, the Parties hereto agree, in accordance with Section 13.12 of the Agreement, to amend the Agreement solely with respect to ISIS-FXI_{Rx} and ISIS-FXI_{Rx}-2 as follows:

1. DEFINITIONS - Appendix 1 of the Agreement shall be amended by adding or amending the definitions as set forth in Appendix 1A attached hereto this Amendment #1.

2. ARTICLE 1

2.1 Sections 1.1 through 1.4 of the Agreement

Sections 1.1 through 1.4 of the Agreement shall [***] Bayer has delivered to Ionis a Continuation Notice. Within [***] days following Bayer's delivery of a Continuation Notice to Ionis, Bayer will deliver to Ionis an updated Strategic Plan in accordance with the Agreement.

2.2 Section 1.6

In Section 1.6.1, the following wording shall be added at the end of sentence 1:

"…;*provided, however*, that until Bayer has delivered to Ionis a Continuation Notice, (i) Bayer shall [***] to Develop or Commercialize any Product under the Agreement, and (ii) with respect to ISIS-FXI_{Rx} and ISIS-FXI_{Rx}-2, Bayer's use of Commercially Reasonable Efforts to Develop and Commercialize either ISIS-FXI_{Rx} and/or ISIS-FXI_{Rx}-2 in accordance with the Agreement will be [***]."

2.3 New Section 1.7a

The following new Section 1.7a shall be added to the Agreement:

"1.7a **Ionis Development Activities**

1.7a(i) **Ionis Development Activities for ISIS-FXI_{Rx}**. Ionis will use Commercially Reasonable Efforts to Complete the phase IIb clinical trial set forth in Schedule 1.7A attached to this Amendment #1 for ISIS-FXI_{Rx} (such study, the "***CS5 Study***"), in accordance with the timelines specified therein. Ionis and Bayer will collaborate in the creation of a detailed protocol for the CS5 Study to be finalized no later than [***], *however*, Ionis will [***] regarding [***] of the CS5 Study and such [***] shall be consistent with Schedule 1.7A.

1.7a(ii) **Ionis Development Activities for ISIS-FXI_{Rx}-2**. Ionis will use Commercially Reasonable Efforts to Complete the [***], and [***] the Phase I Clinical Trial, in each case as expressly set forth in Schedule 1.7A to this Amendment #1 for ISIS-FXI_{Rx}-2 (such [***], collectively, the "***Non-Clinical Studies***" and such Phase I Clinical Trial, the "***CS1 Study***"). Ionis and Bayer will collaborate in the creation of detailed protocols for the Non-Clinical Studies and the CS1 Study no later than [***]; *however*, Ionis will [***] regarding [***] of the Non-Clinical Studies and the CS1 Study and such [***] shall be consistent with Schedule 1.7A.

1.7a(iii) **Amendment Data Package**. As soon as practicable following Completion of each of the Non-Clinical Studies, the CS1 Study and the CS5 Study (the CS1 Study and CS5 Study, collectively the "***Amendment-Clinical Studies***"), Ionis will deliver to Bayer, as applicable, [***]. All such information described in this paragraph collectively the "***Amendment Data Package***".

For purposes of this Amendment #1, with respect to the Non-Clinical Studies, "*Completion*" or "*Completes*" means the date the draft report(s) containing the data generated from such Non-Clinical Studies are available. Within [***] days after Ionis Completes the respective Non-Clinical Studies, CS1 Study and the CS5 Study, Ionis will provide Bayer [***]." In all other respects, Ionis Development Activities will be treated in the same manner as "*Isis Completion Activities*" under the Agreement.

For clarity, separate from the Amendment Data Package, Ionis will provide the information required under and in accordance with Section 1.5 of the Agreement for each of the Amendment-Clinical Studies.

1.7a(iv) **Information Exchange**. Prior to the Decision Deadline, Ionis shall keep Bayer regularly informed on the Ionis Development Activities. The Parties (including the appropriate clinical and non-clinical personnel of each Party) shall regularly meet in person or hold a telephone conference to share and discuss the progress of ongoing Ionis Development Activities as well as any available new data and results from ongoing or completed Ionis Development Activities, including but not limited to minutes of the Data and Safety Monitoring Board and/or any other relevant safety documentation. Each Party's Alliance Manager will facilitate and set the agenda for such meetings and otherwise coordinate such interactions between the Parties.

1.7a(v) **Bayer Development Activities**. For the avoidance of doubt, irrespective of the Ionis Development Activities and subject to payment by Bayer of the license fee pursuant to Section 7.3.1 of the Agreement (as amended by this Amendment #1), Bayer has the right to initiate at any time additional Development activities with regard to ISIS-FXI$_{Rx}$ and/or ISIS-FXI$_{Rx}$-2. Bayer shall consult and coordinate with Ionis prior to initiating any such Development activities. In setting up its Development activities, Bayer shall reasonably consider Ionis' comments and shall not conduct any Development activity that would have a material negative impact on the Completion of the Ionis Development Activities."

2.4 New Section 1.8.3

The following Section shall be added as Section 1.8.3:

Section 1.8.3 "Upon Bayer's delivery of a Continuation Notice to Ionis, the provisions set out in this Section 1.8 shall apply to ISIS-FXI$_{Rx}$ and/or ISIS-FXI$_{Rx}$-2 (as applicable) and, with respect to the territorial scope, applicability shall include all jurisdictions in which Amendment-Clinical Studies are conducted, *mutatis mutandis*."

2.5 Section 1.9

2.5.1 **Section 1.9.2(a)(ii)** – In the first sentence of Section 1.9.2(a)(ii) the words "*first [***]*" are deleted and replaced with the words "*first [***]*".

2.5.2 **New Section 1.9.2(c)** - The following Section shall be added as Section 1.9.2(c):

"1.9.2(c) **Supplies for the IONIS Development Activities**. Upon Ionis' request, Bayer will ([***]) provide Ionis with approximately [***] of API for ISIS-FXI$_{Rx}$ purchased by Bayer under Purchase Order No. [***], for Ionis' use in the CS5 Study and together with such API will provide Ionis with such minimum documentation related to Bayer's transport and storage of such API that Ionis reasonably requires to comply with Applicable Law (including GMP and GCP); for clarity and notwithstanding anything to the contrary, Ionis shall remain responsible for [***] of such API for use in the CS5 Study. In addition, [***], Bayer agrees that Ionis may use in the CS5 Study the Finished Drug Product in Ionis' possession (or the possession of Ionis' CMO) that was previously ordered by Bayer under Purchase Order No. [***], and Ionis will [***] for such Finished Drug Product.

2.5.3 Section 1.9.3 of the Agreement shall be deleted in its entirety and replaced with the following:

"1.9.3 **After Ionis Completes the CS5 Study**. After Ionis completes the CS5 Study, and upon Bayer's delivery of a Continuation Notice to Ionis, upon Bayer's request, Ionis will deliver to Bayer any inventory of cGMP API, Finished Drug Product and packaged Clinical Study material for ISIS-FXI$_{Rx}$ in Ionis' possession on the terms set forth on SCHEDULE 1.9.2(a) of the Agreement (except for any API Bayer delivered to Ionis for the CS5 Study, which will be returned to Bayer free of charge) and taking into account any amounts Bayer previously paid Ionis for any such material."

2.5.3 **New Section 1.9.4** - The following new Section 1.9.4 shall be added to the Agreement:

"1.9.4 **After Ionis Completes the Non-Clinical Studies and CS1 Study**. After Ionis completes the Non-Clinical Studies and the CS1 Study and upon Bayer's delivery of a Continuation Notice to Ionis, upon Bayer's request, Ionis will provide to Bayer any inventory of cGMP API, Finished Drug Product and packaged Clinical Study material for ISIS-FXI$_{Rx}$-2 in Ionis' possession on the terms set forth on SCHEDULE 1.9.2(A) of the Agreement."

2.5.4 The following new Section 1.9.5 shall be added to the Agreement:

"1.9.5 **Joint CMC Plan**. Following Completion of the Ionis Development Activities and Bayer's delivery of a Continuation Notice, Bayer will be responsible for supplying API and Finished Product for all future Development and Commercialization. To facilitate Bayer's efforts in that regard, within the first [***] days after the Amendment Date, the Parties' CMC teams will discuss and mutually agree on a joint CMC plan for technology transfer for API and Finished Drug Product Manufacturing for ISIS-FXI$_{Rx}$ and ISIS-FXI$_{Rx}$-2, *however*, Bayer will [***] to set up the CMC plan; *provided*, *further*, that such [***] will not permit Bayer to [***] to conduct any activity that [***]. Each Party will use Commercially Reasonable Efforts to conduct their respective activities under the mutually agreed CMC plan."

3. ARTICLE 2

With the exception of Section 2.2.2 and Section 2.6, Article 2 shall no longer apply to ISIS-FXI$_{Rx}$-2, and shall be deemed limited in scope to [***] only, *provided however*, that Section 2.4 shall apply with respect to Bayer's exercise of the Option to license ISIS-FXI$_{Rx}$-2 as follows:

"Bayer will have an exclusive option (the "***Option***") to obtain from Ionis the license set forth in Section 5.1.2 (as amended by this Amendment #1) which shall be deemed exercised by Bayer upon the Amendment Date or – if applicable – [***] Business Days following the date on which antitrust clearance for the exercise of the Option has been obtained (using the process described in Section 13.6, *mutatis mutandis*, under which the Parties will make the appropriate filings under the HSR Act within [***] days after signature of this Amendment)."

4. New ARTICLE 2A

The following new ARTICLE 2A shall be added to the Agreement:

"**ARTICLE 2A. ISIS-FXIRx-2 Decision**

2.A(i) Within [***] ([***]) days following Bayer's receipt of the last document required to constitute the Amendment Data Package (the ***"Decision Deadline***"), Bayer shall deliver written notice to Ionis indicating that Bayer will either (i) continue the Development and Commercialization of one or both of ISIS-FXI$_{Rx}$ and/or ISIS-FXI$_{Rx}$-2 in accordance with the Agreement (such notice, a "***Continuation Notice***"), or (ii) terminate the Agreement either (x) in its entirety or (y), subject to Bayer having delivered to Ionis a Drug Discovery Request Notice regarding [***] prior to delivering the notice of termination, with respect to ISIS-FXI$_{Rx}$ and ISIS-FXI$_{Rx}$-2 only (such notice, a "***Termination Notice***").

2.A(ii) If, by the Decision Deadline, Bayer delivers a Continuation Notice to Ionis, then on the earlier of (i) [***] ([***]) days following Bayer's delivery of such Continuation Notice, or (ii) Initiation by Bayer of a Clinical Study of ISIS-FXI$_{Rx}$-2 following delivery of the Continuation Notice, Bayer shall pay to Ionis within [***] days following receipt of an invoice from Ionis a milestone payment of $[***].

2.A(iii) If, by the Decision Deadline, Bayer delivers a Termination Notice to Ionis, then the Agreement will automatically terminate, as the case may be, either (i) with respect to ISIS-FXI$_{Rx}$ and ISIS-FXI$_{Rx}$-2 or (ii) in its entirety, the provisions of Section 11.3 of the Agreement will apply and all rights to ISIS-FXI$_{Rx}$, ISIS-FXI$_{Rx}$-2 and, as the case may be, [***] will revert back to Ionis.

5. ARTICLE 3

5.1 Section 3.3.3 shall no longer apply to ISIS-FXI$_{Rx}$-2.

5.2 The following Section 3.3.4 shall be added to the Agreement:

"3.3.4 **Ionis Development Activities**. Ionis will be responsible for all costs associated with the Ionis Development Activities under SCHEDULE 1.7A, including any costs associated with changes to the Amendment-Clinical Studies required by a Regulatory Authority."

5.3 **New Section 3.5** - The following Section 3.5 shall be added to the Agreement:

"In accordance with Section 2.2.2 of the Agreement, Bayer understands and agrees that the [***] technology under the agreement with [***] listed as [***] on Appendix 4 of the Agreement is incorporated into ISIS-FXI$_{Rx}$-2 and accordingly is "*Bayer Opt-In Technology*" in accordance with Section 2.2.2; *provided however*, that Ionis will [***] only for any payment due under such [***] agreement that is due [***] the date Bayer delivers to Ionis a Continuation Notice.

6. ARTICLE 5

6.1 Section 5.1.2 shall be amended to read as follows:

"**Section 5.1.2 ISIS-FXIRx-2 Development, Manufacture and Commercialization License**. Subject to the terms and conditions of this Agreement, effective upon Bayer's payment of the license fee pursuant to Section 7.3.1 of the Agreement (as amended by this Amendment #1), Ionis grants to Bayer a worldwide, exclusive, royalty-bearing license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured and Commercialize ISIS-FXI$_{Rx}$-2 in the Field."

6.2 Section 5.2.1 shall be amended to no longer refer to the milestone payment for Completion of the CS IV Study, but to the milestone payment following delivery of a Continuation Notice by Bayer pursuant to Article 2.A(ii). The following sentence shall be added at the end of Section 5.2.1:

"This Section 5.2.1 shall equally apply to both, ISIS-FXI$_{Rx}$ and ISIS-FXI$_{Rx}$-2. Therefore, where it says "ISIS-FXI$_{Rx}$", this shall be read as meaning "ISIS-FXI$_{Rx}$ and/or ISIS-FXI$_{Rx}$-2".

6.3 Section 5.2.2 shall no longer apply to ISIS-FXI$_{Rx}$-2 and will be limited in scope to [***].

7. ARTICLE 7

7.1 Section 7.2 shall no longer apply to ISIS-FXI$_{Rx}$-2, and Section 7.2.1 is deleted in its entirety.

7.2 Section 7.3.1 shall be deleted in its entirety and replaced by the following:

"Section 7.3.1 **License Fee for ISIS-FXIRx-2**. In consideration of the license under Section 5.1.2 of the Agreement for ISIS-FXI$_{Rx}$-2, and, if applicable, provided antitrust clearance for ISIS-FXI$_{Rx}$-2 has been obtained (using the process described in Section 13.6, *mutatis mutandis*, then, within [***] days following Bayer's receipt of an invoice from Ionis, Bayer will pay to Ionis a license fee of $[***]."

7.3 Section 7.4 – The first sentence of Section 7.4 shall be deemed amended to read as follows:

"**Milestone Payments for Achievement of Development Milestone Events by ISIS-FXIRx or ISIS-FXIRx-2**. Bayer will pay to Ionis within [***] days following Bayer's receipt of an invoice from Ionis, the milestone payments as set forth in TABLE 1 below when a development milestone event listed in TABLE 1 is first achieved by either ISIS-FXI$_{Rx}$ or ISIS-FXI$_{Rx}$-2."

The second development milestone event "[***]" listed in TABLE 1 of Section 7.4 of the Agreement is hereby deleted and replaced with "[***]" such that such development milestone event may be achieved [***] and such milestone payment is [***] $[***] to $[***]. For clarity, the milestone will be paid only once.

7.4 Section 7.5 shall be deleted in its entirety.

8. New Article 9A

A new Article 9A shall be added to the Agreement to include the additional representation and warranties as of the Amendment Date, as follows:

"Article 9A. ADDITIONAL REPRESENTATION AND WARRANTIES AS OF THE AMENDMENT DATE

9.1A Representations and Warranties of Both Parties. Each Party hereby represents and warrants as of the Amendment Date to the other Party that:

9.1.1A it has the power and authority and the legal right to enter into Amendment #1 and perform its obligations hereunder, and that it has taken all necessary action on its part required to authorize the execution and delivery of Amendment #1 and the performance of its obligations hereunder;

9.1.2.A Amendment #1 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;

9.1.3A all necessary consents, approvals and authorizations of all Regulatory Authorities and other parties required to be obtained by such Party in connection with the execution and delivery of Amendment #1 and the performance of its obligations hereunder have been obtained;

9.1.4A the execution and delivery of Amendment #1 and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the certificate of incorporation, bylaws or any similar instrument of such Party, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent not already obtained under, any contractual obligation or court or administrative order by which such Party is bound; and

9.1.5A all employees, consultants, or (sub)contractors (except academic collaborators or Third Parties under material transfer agreements) of such Party or Affiliates performing development activities hereunder on behalf of such Party will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to such Party or Affiliate, respectively, as the sole owner thereof.

9.2A Representations and Warranties of Ionis. Ionis hereby represents and warrants to Bayer as of the Amendment Date, that:

9.2.1A Ionis is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to Bayer with respect to the Licensed Technology under the Agreement for ISIS-FXI$_{Rx}$-2 as it exists on the Amendment Date;

9.2.2A all Licensed Patents Covering ISIS-FXI$_{Rx}$-2 that are owned by Ionis ("Ionis Owned Patents") have been filed and maintained properly and correctly in all material respects;

9.2.3A Ionis has not previously entered into any agreement, whether written or oral, with respect to, or otherwise assigned, transferred, licensed, conveyed or otherwise encumbered its right, title or interest in or to, the Licensed Technology (including by granting any covenant not to sue with respect thereto) in such a way as to make the representation set forth in Section 9.2.1A not true;

9.2.4A each of the Ionis Owned Patents that are Isis Product-Specific Patents Covering ISIS-FXI$_{Rx}$-2 properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent Right is issued or such application is pending;

9.2.5A to Ionis' Knowledge, each of the Ionis Owned Patents that are Isis Core Technology Patents Covering ISIS-FXI$_{Rx}$-2 properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent Right is issued or such application is pending;

9.2.6A Ionis has not received any written claim alleging that any of the Licensed Technology Covering ISIS-FXI$_{Rx}$-2 is invalid or unenforceable, including any Ionis Owned Patents required in order for Ionis to perform the Ionis Development Activities;

9.2.7A Ionis has not received any written claim alleging that any of Ionis' activities relating to ISIS-FXI$_{Rx}$-2 infringes any intellectual property rights of a Third Party;

9.2.8A to Ionis' Knowledge, (i) the licenses granted to Ionis under the Isis In-License Agreements relevant to ISIS-FXI$_{Rx}$-2 are in full force and effect, (ii) Ionis has not received any written notice, and is not aware, of any breach by any party to such Isis In-License Agreements, and (iii) Ionis' performance of its obligations under this Amendment (including the Ionis Development Activities) will not constitute a breach of Ionis' obligations under the Isis In-License Agreements and the licenses granted to Ionis thereunder;

9.2.9A to Ionis' Knowledge, in respect of the pending United States patent applications included in the Ionis Owned Patents relevant to ISIS-FXI$_{Rx}$-2, Ionis has submitted all material prior art of which it is aware in accordance with the requirements of the United States Patent and Trademark Office;

9.2.10A to Ionis' Knowledge, neither Ionis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Amendment Date that would be necessary in order for Bayer to further Develop or Commercialize ISIS-FXI$_{Rx}$-2 contemplated as of the Amendment Date;

9.2.11A except for the activities Ionis is obligated to conduct under the Prior Agreements as in effect on the Amendment Date, Ionis does not conduct any activities which would violate Article 4 of the Agreement;

9.2.12A to Ionis' Knowledge, Bayer's performance of its rights and obligations under this Amendment relating to ISIS-FXI$_{Rx}$-2 does not infringe any of Ionis' or Third Party's Patent Rights, Know-How or other intellectual property rights; *provided*, Bayer cannot assert a claim against Ionis for breach of this Section 8.2.12 related to any Third Party Patent Rights Bayer has Knowledge of as of the Amendment Date; and

9.2.13A all preclinical and clinical studies and trials conducted by Ionis on ISIS-FXI$_{Rx}$ and ISIS-FXI$_{Rx}$-2, have been conducted in accordance with Applicable Law and, as applicable, GLP and GCP, and to Ionis' Knowledge no claim for injury, loss or damage has been initiated or received in respect of any such studies or trials.

9.3A DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 9A, BAYER 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 BAYER AND IONIS EACH SPECIFICALLY DISCLAIM ANY 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 PATENT RIGHTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES."

9. ARTICLE 11

9.1 Section 11.2.1 shall be deleted in its entirety and replaced by the following:

"**Bayer's Termination for Convenience**. At any time following payment by Bayer of (i) the payment under Section 7.1, (ii) the license fee for ISIS-FXI$_{Rx}$-2 under Section 7.3.1, and (iii) the milestone payment for the first development milestone event under TABLE 1 of Section 7.4, subject to Sections 11.3.1, 11.3.2 and 11.3.3 below, Bayer may terminate this Agreement on a Product-by-Product basis for convenience by providing 90 days written notice to Ionis of such termination."

10. Article 13

10.1 13.8. Notices. For notices Ionis delivers to Bayer, the company shall be Bayer AG, having an address at Müllerstr. 178, 13353 Berlin. Section 13.8 shall be deemed amended accordingly.

11. Appendix 5 (Isis Core Technology Patents) and Appendix 7 (Isis Product-Specific Patents) shall be deleted in their entirety and replaced by Appendix 5A (Ionis Core Technology Patents) and Appendix 7A (Ionis Product-Specific Patents) attached hereto this Amendment.

12. Miscellaneous

12.1 All provisions of the Agreement not altered by this Amendment shall remain in force unaltered. All provisions of the Agreement altered by this Amendment shall only be altered as far as expressly stated in this Amendment.

12.2 The miscellaneous clauses as set out in Section 13 of the Agreement shall apply *mutatis mutandis* to this Amendment.

[The signature page follows]

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed and hereby represent and warrant that their respective signatures below indicate that each have been duly authorized by all necessary and appropriate corporate action to execute this Amendment.

Berlin, Feb 13, 2017	Carlsbad, CA USA February 10, 2017
(Place) (Date)	(Place) (Date)
Bayer AG	Ionis Pharmaceuticals, Inc.
ppa. /s/ Julio Triana	/s/ B. Lynne Parshall
Name: Julio Triana	Name: B. Lynne Parshall
Function/Title: Chief Financial Officer	Function/Title: Chief Operating Officer
i. V. /s/ Xin Ma	
Name: Dr. Xin Ma	
Function/Title: Head of New Product Commercialization & Portfolio Strategy	

APPENDIX 1A

Definitions

1. "***Amendment-Clinical Studies***" has the meaning set forth in Section 2.3 above.

2. "***Amendment Data Package***" has the meaning set forth in Section 2 above.

3. "***Continuation Notice***" has the meaning set forth in Section 4 above.

4. "***CS1 Study***" has the meaning set forth in Section 2.3 above.

5. "***CS5 Study***" has the meaning set forth in Section 2.3 above.

6. "***Decision Deadline***" has the meaning set forth in Section 4 above.

7. "***Ionis Development Activities***" has the meaning set forth in Section 2.3 above.

8. "***ISIS-FXI$_{Rx}$-2***" means the Compound known as [***] having the following sequence and chemistry:

   [***]

9. "***ISIS-FXI$_{Rx}$-2 Decision***" has the meaning set forth in Section 4 above.

10. "***Non-Clinical Studies***" has the meaning set forth in Section 2.3 above.

11. "***Termination Notice***" has the meaning set forth in Section 4 above.

APPENDIX 5A

Ionis Core Technology Patents

[***]

APPENDIX 7A

Ionis Product-Specific Patents

[***]

SCHEDULE 1.7A

Ionis Development Activities

[***]

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 9, 2017

/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 9, 2017

/s/ ELIZABETH L. HOUGEN

Elizabeth L. Hougen
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 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, 2017, 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 9, 2017

/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.