Current Agreements

Dealdoc

Collaboration and option agreement for AKCEA-APO(a)-L and AKCEA-APOCIII-L

Ionis Pharmaceuticals
Akcea Therapeutics
Novartis

Feb 16 2017

Collaboration and option agreement for AKCEA-APO(a)-L and AKCEA-APOCIII-L

Companies:	Ionis Pharmaceuticals Akcea Therapeutics Novartis
Announcement date:	Feb 16 2017
Amendment date:	Feb 25 2019
Deal value, US$m:	225 : sum of upfront and equity payments
Related contracts:	First amendment to collaboration and option agreement for AKCEA-APO(a)-L and AKCEA-APOCIII-L

Details

Announcement date:	Feb 16 2017
Amendment date:	Feb 25 2019
Start date:	Jan 05 2017
Industry sectors:	Bigpharma Pharmaceutical
Compound name:	AKCEA-APO(a)-LRx, AKCEA-APOCIII-LRx, TQJ230
Exclusivity:	Exclusive
Asset type:	Compound
Therapy areas:	Cardiovascular » Coronary artery disease
Technology types:	Small molecules
Deal components:	Collaborative R&D Option
Stages of development:	Phase I Phase II
Geographic focus:	Worldwide

Financials

Deal value, US$m:	225 : sum of upfront and equity payments
Upfront, US$m:	75 : upfront payment 150 : licensing fee
Milestones, US$m:	n/d : development, regulatory and commercial milestone payments
Royalty rates, %:	19 : tiered royalties in the mid-teens to low twenty percent range on net sales of each drug
Semi-quant royalties:	Mid teens Low twenties
Equity, US$m:	100 : equity investment
Loan, US$m:	50 : further equity investment

Termsheet

February 2019

Akcea Therapeutics and Ionis Pharmaceuticals announced that Novartis has exercised its option to license AKCEA-APO(a)-LRx, a drug to treat patients with elevated levels of lipoprotein(a), or Lp(a), and established cardiovascular disease (CVD).

AKCEA-APO(a)-LRx, referred to by Novartis as TQJ230, was discovered by Ionis and co-developed by Akcea and Ionis.

Based on the strategic collaboration agreement between Akcea and Novartis, Akcea will receive a $150 million license fee that will be split equally with Ionis.

Akcea will settle its $75 million obligation to Ionis in Akcea common stock.

February 2017

Ionis Pharmaceuticals and Akcea Therapeutics have closed on their exclusive, worldwide option and collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx following clearance under the Hart-Scott-Rodino Antitrust Improvements Act.

Following this approval and closing of the transaction, Novartis will pay Ionis and Akcea a $75 million up-front payment and make a $100 million equity investment in Ionis, which equates to 1,631,435 shares at $61.30 per share.

Novartis has an obligation to make a further equity investment of $50 million in the next 18 months in either Ionis at the same premium as the initial investment or in Akcea.

Ionis and Akcea are also eligible to receive a license fee as well as development, regulatory and commercial milestone payments for each drug as it advances.

In addition, Ionis and Akcea are eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of each drug.

Lp(a) is considered a key driver for cardiovascular disease due to its association with an increased risk of coronary heart disease.

Lp(a) is a lipoprotein particle that is assembled in the liver and consists of the apolipoprotein(a) protein covalently linked to LDL-cholesterol.

AKCEA-APOCIII-LRx is currently being evaluated in a Phase 1/2a study in healthy volunteers with elevated triglycerides.

Press Release

February 2019

AKCEA-APO(a)-LRx Advances as Leading Pharmaceutical Company Exercises Option to License

Akcea earns $150M license fee

BOSTON and CARLSBAD, Calif., Feb. 25, 2019 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), an affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced that Novartis has exercised its option to license AKCEA-APO(a)-LRx, a drug to treat patients with elevated levels of lipoprotein(a), or Lp(a), and established cardiovascular disease (CVD). AKCEA-APO(a)-LRx, referred to by Novartis as TQJ230, was discovered by Ionis and co-developed by Akcea and Ionis.

Elevated Lp(a) is an independent genetic risk factor for CVD that cannot be managed by lifestyle modifications, including diet or exercise, or with treatment using existing cholesterol-lowering therapies1,2. It is estimated that there are more than eight million patients living with CVD and elevated levels of Lp(a).

“We are very pleased that Novartis, an established global leader in drug development and commercialization, will now shepherd this landmark therapy through late-stage clinical development and toward the market,” said Paula Soteropoulos, chief executive officer at Akcea. “The Phase 2 study results presented last year at AHA showed that AKCEA-APO(a)-LRx significantly reduced Lp(a) levels below the recognized threshold for cardiovascular risk in patients living with cardiovascular disease and elevated Lp(a) levels with a favorable safety and tolerability profile. AKCEA-APO(a)-LRx is the first and only medicine to do this. We believe that this therapy has the potential to be a significant advance for millions of people affected by cardiovascular disease around the world.”

Novartis will assume responsibility for all future development activities for AKCEA-APO(a)-LRx, including a planned global Phase 3 cardiovascular outcomes study and, pending regulatory approval, global commercialization activities.

AKCEA-APO(a)-LRx is an antisense drug developed based on Ionis’ proprietary LIgand Conjugated Antisense, or LICA, technology platform. Ionis’ proprietary LICA technology platform has the potential to produce new drugs that can be used at lower doses and with less frequent administration compared to non-LICA antisense drugs. AKCEA-APO(a)-LRx is designed to inhibit production of apolipoprotein(a), or Apo(a) protein, thereby reducing systemic levels of Lp(a).

“The Ionis LICA platform is a game-changing breakthrough for our antisense technology. AKCEA-APO(a)-LRx, our most advanced LICA medicine, is a particularly exciting and important new medicine because of its potential to treat millions of patients with cardiovascular disease. This treatment represents one of many important new medicines within our LICA pipeline and illustrates our continued commitment to innovation and in bringing transformative medicines to patients in great need,” said Brett Monia, chief operating officer at Ionis.

Based on the strategic collaboration agreement between Akcea and Novartis, Akcea will receive a $150 million license fee that will be split equally with Ionis. Akcea will settle its $75 million obligation to Ionis in Akcea common stock.

ABOUT AKCEA-APO(a)-LRx AND THE PHASE 2 STUDY AKCEA-APO(a)-LRx is an antisense drug that uses Ionis’ advanced LIgand Conjugated Antisense, or LICA, technology. AKCEA-APO(a)-LRx inhibits the production of apolipoprotein(a), or Apo(a), protein, thereby reducing Lp(a).

The Phase 2 study was designed to evaluate the safety and tolerability of AKCEA-APO(a)-LRx and to determine the appropriate dose and dose regimen for a planned Phase 3 cardiovascular outcomes study. The randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study included 286 patients with established CVD and high Lp(a) levels (baseline mean of 100mg/dL [250 nmol/L]- more than three times the upper limit of normal). Results from the study showed statistically significant dose-dependent reductions of Lp(a) compared to placebo at all dose levels, including low monthly doses of AKCEA-APO(a)-LRx. In the phase 2 study, 98% of patients in the 20mg weekly cohort and 81% of patients in the 60mg every 4 week cohort achieved clinically significant reductions in Lp(a) levels bringing them below the recommended threshold of risk for CVD events (<50 mg/dL). Treatment with AKCEA-APO(a)-LRx was associated with decreases in LDL-C, apoB, OxPL-apoB, OxPL-apo(a). Most adverse events were mild. The most frequent adverse events were injection site reactions (ISRs). ISRs occurred in 26% of patients and were mostly mild and one patient discontinued due to an ISR. There were no safety concerns related to platelet counts, liver function or renal function. Approximately 90% of patients completed treatment and the rate of discontinuation was comparable between the active and placebo groups. All patients were treated for at least six months, with some patients treated up to one year.

ABOUT Lp(a) Lipoprotein(a), or Lp(a), is made up of apo(a) protein bound to LDL cholesterol and contains oxidized phospholipids, resulting in an atherogenic, pro-inflammatory and thrombogenic lipoprotein. Elevated Lp(a) is recognized as an independent, genetic cause of cardiovascular disease present in approximately 20-30% of the population. Lp(a) levels are determined at birth and, therefore, lifestyle modifications, including diet and exercise, do not impact Lp(a) levels.

For additional information about Lp(a), please see the Lipoprotein(a) Foundation at http://www.lipoproteinafoundation.org/.

About Akcea Therapeutics, Inc. Akcea Therapeutics, Inc., an affiliate of Ionis Pharmaceuticals, Inc., is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious and rare diseases. Akcea is advancing a mature pipeline of six novel drugs, including TEGSEDI™ (inotersen), WAYLIVRA™ (volanesorsen), AKCEA-APO(a)-LRx, AKCEA-ANGPTL3-LRx, AKCEA-APOCIII-LRx, and AKCEA-TTR-LRx, all with the potential to treat multiple diseases. All six drugs were discovered by and are being co-developed with Ionis, a leader in antisense therapeutics, and are based on Ionis’ proprietary antisense technology. TEGSEDI is approved in the U.S., E.U. and Canada. WAYLIVRA is under regulatory review for the treatment of familial chylomicronemia syndrome, or FCS, and is currently in Phase 3 clinical development for the treatment of people with familial partial lipodystrophy, or FPL. Akcea is building the infrastructure to commercialize its drugs globally. Akcea is a global company headquartered in Boston, Massachusetts. Additional information about Akcea is available at www.akceatx.com and you can follow us on twitter at @akceatx.

About Ionis Pharmaceuticals As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, proprietary antisense technology platform with the potential to treat diseases where no other therapeutic approaches have proven effective. Our drug discovery platform has served as a springboard for actionable promise and realized hope for patients with unmet needs – such as children and adults with spinal muscular atrophy (SMA). We created SPINRAZA® (nusinersen)* and are proud to have brought new hope to the SMA community by developing the first and only approved treatment for this disease. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 drugs with the potential to treat patients with cardiovascular disease, rare diseases, neurological diseases, infectious diseases and cancer. We created TEGSEDI™ (inotersen), the world’s first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adult patients with hereditary transthyretin (TTR) amyloidosis (ATTR) that our affiliate Akcea Therapeutics is commercializing. Together with Akcea, we are also bringing new medicines to patients with cardiometabolic lipid disorders.

February 2017

CARLSBAD, Calif. and CAMBRIDGE, Mass., Feb. 16, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) and Akcea Therapeutics, a wholly-owned subsidiary of Ionis Pharmaceuticals, Inc., announced today they have closed on their exclusive, worldwide option and collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx following clearance under the Hart-Scott-Rodino Antitrust Improvements Act. Following this approval and closing of the transaction, Novartis will pay Ionis and Akcea a $75 million up-front payment and make a $100 million equity investment in Ionis, which equates to 1,631,435 shares at $61.30 per share. Novartis has an obligation to make a further equity investment of $50 million in the next 18 months in either Ionis at the same premium as the initial investment or in Akcea. Ionis and Akcea are also eligible to receive a license fee as well as development, regulatory and commercial milestone payments for each drug as it advances. In addition, Ionis and Akcea are eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of each drug.

ABOUT Lp(a) Lp(a) is considered a key driver for cardiovascular disease due to its association with an increased risk of coronary heart disease. Lp(a) is a lipoprotein particle that is assembled in the liver and consists of the apolipoprotein(a) protein covalently linked to LDL-cholesterol. Diet and lifestyle changes have little impact on Lp(a) levels and current therapies are not able to adequately reduce elevated levels of Lp(a) to acceptable levels in patients who have severely elevated Lp(a). Additional information is available through Lipoprotein (a) Foundation at www.lipoproteinafoundation.org.

Filing Data

In January 2017, we initiated a strategic collaboration with Novartis for the development and commercialization of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx. In February 2019, Novartis exercised its option to license AKCEA-APO(a)-LRx. Novartis initiated a Phase 3 study of AKCEA-APO(a)-LRx in patients with CVD and elevated levels of Lp(a). Novartis is now responsible for all future development and commercialization activities for AKCEA-APO(a)-LRx. We are eligible to receive tiered, double-digit royalties in the mid-teens to low twenty percent range on sales of AKCEA-APO(a)-LRx from Novartis and milestone payments if and when it meets the development, regulatory and sales milestones specified in our agreement. In connection with Novartis' exercise of its option to exclusively license AKCEA-APO(a)-LRx, we and Novartis established a more definitive framework under which we may negotiate the co-commercialization of AKCEA-APO(a)-LRx between the two companies in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-LRx in exchange for Novartis paying us increased commercial milestone payments based on sales of AKCEA-APO(a)-LRx. We will share any milestone payments and royalties equally with Ionis.

In December 2019, Novartis made a strategic portfolio decision not to exercise its option and to terminate its rights to AKCEA-APOCIII-LRx and, consequently, we now retain the rights to AKCEA-APOCIII-LRx. In January 2020, we reported positive Phase 2 top line results from this program in the treatment of patients with hypertriglyceridemia who are at risk for, or have established, CVD. We and Ionis plan to initiate a Phase 3 program in FCS for this medicine in 2020 and we are evaluating development in additional rare and common diseases that are associated with high triglyceride levels. AKCEA-APOCIII-LRx also has the potential to favorably impact numerous other risk factors independently associated with CVD.

Under our Novartis agreement, we received $75.0 million in an upfront option payment in February 2017, of which we retained $60.0 million and paid Ionis a $15.0 million sublicense fee, and Novartis purchased $100.0 million of Ionis' common stock at a premium. We also received a $150.0 million license fee when Novartis exercised its option to license AKCEA-APO(a)-LRx in February 2019, for which we issued 2,837,373 shares of our common stock to Ionis in March 2019, as payment for a $75.0 million sublicense fee. In addition to the upfront payment and license fee we are eligible to receive up to $675.0 million in milestone payments from Novartis for AKCEA-APO(a)-LRx, including $25.0 million for the achievement of a development milestone, up to $290.0 million for the achievement of regulatory milestones and up to $360.0 million for the achievement of commercialization milestones. We are also eligible to receive tiered, double-digit royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-LRx, and Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. We will share any milestone payments and royalties equally with Ionis.

If Novartis stops developing or commercializing AKCEA-APO(a)-LRx and we subsequently commercialize the medicine on our own or with another party, we are required to negotiate in good faith and mutually agree with Novartis the terms of a royalty payable to Novartis on the returned medicine.

The agreement with Novartis will continue until the expiration of all payment obligations under the agreement. In addition, the agreement as a whole or with respect to any medicine under the agreement may terminate early under the following situations:

• Novartis may terminate the agreement as a whole or with respect to any medicine at any time by providing written notice to us;

• Either we or Novartis may terminate the agreement with respect to any medicine by providing written notice to the other party in good faith that we or Novartis have determined that the continued development or commercialization of the medicine 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 medicine by providing written notice to the other party upon the other party's uncured failure to perform a material obligation related to the medicine 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 or Ionis' patents.

Under certain circumstances, the agreement with Novartis provides a mechanism to ensure that patients who were being treated with AKCEA-APO(a)-LRx prior to such termination or who desire access to AKCEA-APO(a)-LRx can continue to have access to AKCEA-APO(a)-LRx while the regulatory and commercial responsibilities for AKCEA-APO(a)-LRx are transitioned from Novartis to us. Additionally, in January 2017, we and Ionis entered into a Stock Purchase Agreement, or SPA, with Novartis. Under the SPA, in July 2017, Novartis purchased $50.0 million of our common stock in a separate private placement concurrent with the completion of our IPO at a price per share equal to the IPO price.

Contract

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)-LRx and AKCEA-APOCIII-LRx, based on Akcea's and Ionis' knowledge, experience and intellectual property rights to both antisense technology and to AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx;

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)-LRx and AKCEA-APOCIII-LRx;

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)-LRx and AKCEA-APOCIII-LRx 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)-LRx and AKCEA-APOCIII-LRx 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)-LRX AND AKCEA-APOCIII-LRX

1.1. Overview. The intent of the (A) pre-Option Exercise Collaboration is (i) for Akcea to develop AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx 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)-LRx and AKCEA-APOCIII-LRx 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)-LRx and AKCEA-APOCIII-LRx, which options are exercisable after the End of Phase 2b Meeting for each of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx, 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)-LRx and

AKCEA-APOCIII-LRx. 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)-LRx and AKCEA-APOCIII-LRx Pre-Option Responsibilities. Akcea will use Commercially Reasonable Efforts to develop each of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx 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)-LRx and AKCEA-APOCIII-LRx 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

* ***Confidential Treatment Requested

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

* ***Confidential Treatment Requested

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

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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 [***]

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[***] 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)-LRx and AKCEA-APOCIII-LRx 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

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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)-LRx and AKCEA-APOCIII-LRx [***].

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-LRx 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-LRx. 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

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“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)-LRx and AKCEA-APOCIII-LRx.

(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.

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(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)-LRx and AKCEA-APOCIII-LRx 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

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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 [***]

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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").

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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

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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.

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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:

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(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 [***] 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

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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)-LRx Development, Manufacture and Commercialization License. Subject to the terms and conditions of this Agreement, upon Novartis' exercise of the Option for AKCEA-APO(a)-LRx 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)-LRx.

5.1.2. AKCEA-APOCIII-LRx Development, Manufacture and Commercialization License. Subject to the terms and conditions of this Agreement, upon Novartis' exercise of the Option for AKCEA-APOCIII-LRx 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-LRx.

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:

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(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

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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)-LRx or AKCEA-APOCIII-LRx (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

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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

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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,

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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

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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

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[***] 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'

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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

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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

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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)-LRx 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-LRx 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)-LRx:

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-LRx:

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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)-LRx:

TABLE 3

Sales Milestone Event for AKCEA-APO(a)-LRx

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-LRx:

TABLE 4

Sales Milestone Event for AKCEA-APOCIII-LRx

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

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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-

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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 [***], (ii) the [***], and (iii) the [***] (such royalty period, the "Initial Payment Period").

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(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.

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(e) [***]. The Parties may [***] a [***] 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 [***].

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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 [***]

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[***] 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

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[***], (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

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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

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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

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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

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(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

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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

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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

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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

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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

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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

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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

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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

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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.

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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);

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(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)-LRx and AKCEA-APOCIII-LRx, 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

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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)-LRx and AKCEA-APOCIII-LRx, 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)-LRx or AKCEA-APOCIII-LRx 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

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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

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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.

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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

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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).

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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

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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

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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

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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

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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

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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

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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

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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:

Ionis Pharmaceuticals, Inc.

(so long as Ionis and

2855 Gazelle Court

Akcea are Affiliates)

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

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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]

* - * - * - *

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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 Soteropoulos

Name:

Paula Soteropoulos

Titl

President & CEO

SIGNATURE PAGE TO STRATEGIC COLLABORATION, OPTION AND LICENSE AGREEMENT

List of Appendices and Schedules

APPENDIX 1 — Definitions

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

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SCHEDULE 1.3.1 — API Supply Terms

SCHEDULE 1.3.2 — Manufacturing Transition Strategy and Pre-Option Novartis Activities

SCHEDULE 2.1.1 — CSC Representatives

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SCHEDULE 7.8.2(F) — Royalty Calculation Examples

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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.

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“AKCEA-APO(a)-LRx” means the Oligonucleotide known as ISIS 681257 (also known as IONIS-APO(a)-LRx) having the following sequence and chemistry: 5’-THA-AHP=OMeUGP=OMeCP=OMeUP=OMeCP=OMeCGTTGGTGMeCTMeUP=OGP=OMeUMeUMeC-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. MeU 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-LRx” means the Oligonucleotide known as ISIS 678354 (also known as IONIS-APOCIII-LRx) having the following sequence and chemistry: 5’-THA-AHP=OAGMeCMeUMeUMeCTTGTMeCMeCAGMeCMeUMeUMeUAMeU-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. MeU 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

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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.

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“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(d).

“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

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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.

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“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.

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“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)-LRx and AKCEA-APOCIII-LRx 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)-LRx, and/or (ii) AKCEA-APOCIII-LRx.

“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′-AGMeCMeUMeUMeCTTGTMeCMeCAGMeCMeUMeUMeUAMeU-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

[***]

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APPENDIX 3

Akcea In-License Agreements

1. [***]

2. [***]

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APPENDIX 4

Akcea Core Technology Patents

[***]

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APPENDIX 5

Akcea Manufacturing and Analytical Patents

[***]

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APPENDIX 6

Akcea Product-Specific Patents

(Relevant to AKCEA-APO(a)-LRx)

[***]

(Relevant to AKCEA-APOCIII-LRx)

[***]

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APPENDIX 7

Prior Agreements

1. [***]

2. [***]

3. [***]

4. [***]

5. [***]

6. [***]

7. [***]

8. [***]

9. [***]

10. [***]

11. [***]

12. [***]

13. [***]

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14. [***]

15. [***]

16. [***]

17. [***]

18. [***]

19. [***]

SCHEDULE 1.3.1

API Supply Terms

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

For the supply of AKCEA-APO(a)-LRx API, Novartis will pay Akcea US$[***] per gram for such API. Total supply of AKCEA-APO(a)-LRx 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-LRx API, Novartis will pay Akcea US$[***] per gram for such API. Total supply of AKCEA-APOCIII-LRx 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

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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)-LRx and AKCEA-APOCIII-LRx, 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).

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SCHEDULE 1.3.2

Manufacturing Transition Activities And Pre-Option Novartis Activities

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SCHEDULE 2.1.1

Collaboration Steering Committee

CSC Representatives

Akcea

[***]

[***]

[***]

Novartis

[***]

[***]

[***]

JDCC

[***]

[***]

[***]

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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 [***].

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SCHEDULE 7.8.2(F)

Royalty Calculation Examples

Example of the application of royalty payments to Akcea under the following assumptions:

[***]

[***]

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Exhibit X

Novartis' Form of Invoice

[***]

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