

15,625,000 Shares



## Common Stock

This is an initial public offering of shares of common stock by Akcea Therapeutics, Inc. We are offering 15,625,000 shares of our common stock. The initial public offering price is \$8.00 per share.

Prior to this offering, there has been no market for our common stock. Our common stock has been approved for listing on the Nasdaq Global Select Market under the symbol "AKCA."

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, we have elected to comply with certain reduced public company reporting requirements for this prospectus and future filings.

	<i>Per share to public</i>	<i>Per share to Ionis(1)</i>	<i>Total</i>
Initial public offering price	\$ 8.00	\$ 8.00	\$125,000,000
Underwriting discounts and commissions(1)(2)	\$ 0.56	\$ 0.00	\$ 7,000,000
Proceeds to Akcea, before expenses	\$ 7.44	\$ 8.00	\$118,000,000

- (1) Shares purchased by Ionis Pharmaceuticals, Inc. are not subject to underwriting discounts and commissions. See below for additional information.  
 (2) See "Underwriting" for a description of the compensation payable to the underwriters.

We have granted the underwriters an option for a period of 30 days to purchase up to 2,343,750 additional shares of common stock.

Novartis Pharma AG, our strategic collaborator, has agreed to purchase \$50.0 million of our common stock in a separate private placement concurrent with the completion of this offering at a price per share equal to the initial public offering price. The sale of shares in the concurrent private placement will not be registered under the Securities Act of 1933, as amended. The closing of this offering is not conditioned upon the closing of the concurrent private placement. The shares of common stock purchased in the concurrent private placement will not be subject to any underwriting discounts or commissions.

Ionis Pharmaceuticals, Inc., or Ionis, has agreed to purchase 3,125,000 shares of common stock in this offering at the initial public offering price. The underwriters will not receive any underwriting discounts or commissions on the shares purchased by Ionis. Ionis will own approximately 70.8% of the total number of shares of our common stock outstanding after the completion of this offering and will be able to determine the outcome of all corporate actions requiring stockholder approval.

**Investing in our common stock involves a high degree of risk. See "Risk Factors" beginning on page 17.**

**Neither the Securities and Exchange Commission nor other regulatory body has approved or disapproved of these securities or passed on the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.**

The underwriters expect to deliver shares of common stock to purchasers on July 19, 2017.

*Joint Book-running Managers*

**Cowen**

**Stifel**

**Wells Fargo Securities**

*Lead Manager*

**BMO Capital Markets**

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We have not, and the underwriters have not, authorized anyone to provide any information or to make any representations other than those contained in this prospectus, or in any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus or in any applicable free writing prospectus is current only as of its date, regardless of its time of delivery or any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

**Through and including August 7, 2017 (25 days after the commencement of this offering), all dealers that effect transactions in shares of our common stock, whether or not participating in this offering, may be required to deliver a prospectus. This delivery is in addition to a dealer's obligation to deliver a prospectus when acting as an underwriter and with respect to their unsold allotments or subscriptions.**

For investors outside the United States: We have not, and the underwriters have not, done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the shares of common stock and the distribution of this prospectus outside the United States.

## PROSPECTUS SUMMARY

*This summary highlights selected information contained elsewhere in this prospectus. This summary does not contain all the information you should consider before investing in our common stock. You should read the entire prospectus carefully, including “Risk factors,” “Management’s discussion and analysis of financial condition and results of operations” and our consolidated financial statements and notes to those consolidated financial statements, before making an investment decision. Unless the context requires otherwise: (1) references to “Akcea,” our “company,” “we,” “us” or “our” refer to Akcea Therapeutics, Inc., a Delaware corporation and its subsidiaries, Akcea Therapeutics UK Ltd., Akcea Intl Ltd. and Akcea Therapeutics Canada, Inc. and (2) references to “Ionis” or “Ionis Pharmaceuticals” refer to Ionis Pharmaceuticals, Inc., a Delaware corporation.*

### Overview

We are a late-stage biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. Our goal is to become the premier company offering treatments for inadequately treated lipid disorders. We are advancing a mature pipeline of four novel drugs with the potential to treat multiple diseases. Our drugs, volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, are all based on antisense technology developed by Ionis Pharmaceuticals, Inc., or Ionis. Our most advanced drug, volanesorsen, has completed a Phase 3 clinical program for the treatment of familial chylomicronemia syndrome, or FCS, and is currently in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. FCS and FPL are both severe, rare, genetically defined lipid disorders characterized by extremely elevated levels of triglycerides. Both diseases have life-threatening consequences and the lives of patients with these diseases are impacted daily by the associated symptoms. In our clinical program, we have observed consistent and substantial (>70%) decreases in triglycerides and improvements in other manifestations of FCS, including pancreatitis attacks and abdominal pain. We believe the safety and efficacy data from the volanesorsen program demonstrate a favorable risk-benefit profile for patients with FCS. In the third quarter of 2017, we plan to file for marketing authorization for volanesorsen to treat patients with FCS.

We are assembling the infrastructure to commercialize our drugs globally with a focus on lipid specialists as the primary call point. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed lipid disorders will allow us to partner efficiently and effectively with the specialized medical community that supports these patients.

To maximize the commercial potential of two of the drugs in our pipeline, we initiated a strategic collaboration with Novartis Pharma AG, or Novartis, for the development and commercialization of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. As part of our collaboration, we received \$75.0 million in an upfront option payment, of which we retained \$60.0 million and paid \$15.0 million to Ionis as a sublicense fee. After we complete Phase 2 development of each of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, if, on a drug by drug basis, Novartis exercises its option to license a drug and pays us the \$150.0 million license fee to do so, Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize each such licensed drug worldwide. We plan

to co-commercialize any licensed drug commercialized by Novartis in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen. Overall, we are eligible to receive significant license fees, milestone payments and royalties on sales of each drug Novartis licenses if and when it meets the development, regulatory and sales milestones specified in our agreement. We will share any license fees, milestone payments and royalties equally with Ionis.

Cardiometabolic disease, which includes cardiovascular diseases and metabolic diseases is the number one cause of death globally. According to the American Heart Association, or AHA, cardiovascular disease, or CVD, alone accounts for 17.3 million deaths per year globally, a number that the AHA expects to grow to more than 23.6 million by 2030. Further, between 2010 and 2030, total direct medical costs of CVD in the United States alone are projected to triple from \$272.5 billion to \$818.1 billion, according to the AHA. In addition, the number of individuals with metabolic diseases, including diabetes, is rising dramatically. According to a 2010 study published in *Population Health Metrics*, the number of people in the United States with diabetes is projected to grow from approximately 20 million in 2010 to between 46 million and 87 million by 2050. Cardiometabolic risk factors include metabolic syndrome, dyslipidemia, hypertension, obesity and insulin resistance. Lipid risk factors driven by abnormalities in lipid molecules or the processing of lipid molecules contribute to cardiometabolic diseases, with elevated low density lipoprotein cholesterol, or LDL-C, being the most widely recognized. Despite the availability of powerful drugs to lower LDL-C, many people remain at significant risk due to other lipid disorders that are not adequately addressed with current therapies. We believe this treatment gap represents a significant commercial opportunity both in rare and in broader patient populations.

Our clinical pipeline contains novel drugs with the potential to treat inadequately addressed lipid disorders beyond elevated LDL-C that are contributing to the dramatic increase in the incidence of cardiometabolic disease, such as elevated triglycerides, oxidized phospholipids and other lipoproteins such as lipoprotein(a), or Lp(a). Each of the four drugs in our pipeline targets the specific ribonucleic acid, or RNA, that encodes for a unique protein associated with lipid dysfunction, robustly and selectively inhibiting the production of such protein. These drugs were designed and developed at Ionis, and use Ionis' proprietary antisense technology, which is a potent and specific way of reducing disease-causing proteins. Specifically, our drugs utilize Ionis' generation 2.0+ antisense technology, which is designed for increased potency and enhanced safety characteristics relative to Ionis' generation 2.0 technology. Additionally, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> utilize Ionis' advanced Ligand Conjugated Antisense, or LICA, technology. We believe the enhancements offered by Ionis' LICA technology can provide greater patient convenience by allowing for significantly lower doses and less frequent administration. Our current pipeline includes drugs with the potential to treat patients with a wide range of lipid disorders associated with cardiometabolic disease that other technologies, such as small molecules and antibodies, have not been able to adequately address.

The following figure illustrates our pipeline:

Drug <sup>(1)</sup>	Preclinical	Phase 1	Phase 2	Phase 3	Preparing Filings	Planned Next Milestone
<b>Volanesorsen</b>	Familial Chylomicronemia Syndrome (FCS)					Filings Q3:17
	Familial Partial Lipodystrophy (FPL)					Phase 3 Data 2019
<b>AKCEA-APO(a)-L<sub>Rx</sub><sup>(2)</sup></b>	Hyperlipoproteinemia(a) with CV Risk					Phase 2b Data Mid 18
<b>AKCEA-ANGPTL3-L<sub>Rx</sub></b>	Rare Hyperlipidemias					Phase 2 start H2:17
	NAFLD/Metabolic complications					Phase 2 start H2:17
<b>AKCEA-APOCIII-L<sub>Rx</sub><sup>(2)</sup></b>	Hypertriglyceridemia with CV risk					Phase 1/2 Data H2:17

(1) We have used alternate names for our drugs:

- Volanesorsen also has been known as IONIS-APOCIII<sub>Rx</sub>, ISIS-APOCIII<sub>Rx</sub> and ISIS 304801.
- AKCEA-APO(a)-L<sub>Rx</sub> also has been known as IONIS-APO(a)-L<sub>Rx</sub>, ISIS-APO(a)-L<sub>Rx</sub> and ISIS 681257.
- AKCEA-ANGPTL3-L<sub>Rx</sub> also has been known as IONIS-ANGPTL3-L<sub>Rx</sub>, ISIS-ANGPTL3-L<sub>Rx</sub> and ISIS 703802.
- AKCEA-APOCIII-L<sub>Rx</sub> also has been known as IONIS-APOCIII-L<sub>Rx</sub>, ISIS-APOCIII-L<sub>Rx</sub> and ISIS 678354.

(2) We have initiated a strategic collaboration with Novartis for AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>.

Note: The arrows designate the current phase of development for each drug and indication, and do not represent the extent of completion of the activities we are currently conducting within the phase.

Note: The “L” designation indicates drugs that use Ionis’ LICA technology.

## Clinical Pipeline

### *Volanesorsen for the treatment of FCS and FPL*

We are developing volanesorsen to treat patients with FCS and FPL, orphan diseases characterized by extremely elevated triglyceride levels and a high risk of life-threatening pancreatitis. Patients with FCS and FPL live with daily and chronic manifestations of their disease that negatively affect their lives. Volanesorsen acts to reduce triglyceride levels by inhibiting the production of apolipoprotein C-III, or ApoC-III, a protein that is a key regulator of triglyceride clearance. People who have low levels of ApoC-III or reduced ApoC-III function have lower levels of triglycerides and a lower incidence of CVD.

We estimate there are 3,000 to 5,000 FCS patients and an additional 3,000 to 5,000 FPL patients globally. Volanesorsen has been granted orphan drug status in both the United States and the European Union for the treatment of FCS. Volanesorsen has also been granted orphan drug status in the European Union for the treatment of FPL, and we are in the process of applying for orphan drug status for FPL in the United States. An orphan disease is defined as having a

population of less than 200,000 patients in the United States and a population of less than 5 in 10,000 individuals in the European Union.

Patients with FCS and FPL share certain common disease characteristics, particularly elevated triglyceride levels, or hypertriglyceridemia, but are quite distinct physically and genetically. As a consequence of their elevated triglyceride levels, both patient populations are at risk of debilitating and potentially life-threatening pancreatitis. In addition, both patient populations are susceptible to recurrent abdominal pain after eating. Other shared disease symptoms are chronic fatigue, abnormal enlargement of the liver or spleen, and insulin resistance and type 2 diabetes. Therapy for both diseases includes a strict, extremely low fat diet on a lifelong basis to manage abdominal pain and risk of pancreatitis. However, even this diet typically does not bring triglyceride levels into the normal range and most patients still suffer from chronic manifestations of their disease and remain at high risk for pancreatitis.

Despite the similarities, triglyceride levels are generally more elevated in FCS patients compared to FPL patients, although levels in both groups are many times above the normal range and well above the risk threshold for acute pancreatitis. While insulin resistance and type 2 diabetes are common in both groups, a much higher proportion of FPL patients have these complications. FPL is a disease of abnormal fat storage and distribution, whereas FCS is a disease of abnormal fat clearance. This leads to an important difference between these patient populations: the quite distinct physical appearance in FPL, which is marked by the absence of subcutaneous fat in the buttocks and extremities and localization of subcutaneous fat in the head and neck. FPL patients also have significant fat deposits in and around major internal organs such as liver and heart. As a consequence, cardiovascular and peripheral vascular disease are common findings in the FPL patient population, and may cause premature death.

ApoC-III is a validated therapeutic target in both diseases and the therapeutic intent of targeting ApoC-III with volanesorsen is to substantially reduce triglyceride levels. Based on our volanesorsen clinical development program to date, including our completed pivotal study in patients with FCS, treatment with volanesorsen significantly reduces triglyceride levels and has shown evidence of reducing the risk of pancreatitis and abdominal pain. We believe that the totality of evidence supports the potential for significant clinical benefit in patients suffering from both debilitating diseases, FCS and FPL.

We recently completed the Phase 3 program for volanesorsen to treat patients with FCS and are planning to file for regulatory approval in this indication in the third quarter of 2017. The Phase 3 program consisted of two studies, the APPROACH study and the COMPASS study. The APPROACH study, a one year randomized, placebo-controlled study in 66 patients with FCS (average incoming triglycerides of 2,209 mg/dL), achieved its primary endpoint of reduction in triglycerides at three months, with a 77% mean reduction in triglycerides, which translated into a 1,712 mg/dL mean absolute triglyceride reduction in volanesorsen-treated patients. We observed 50% of treated patients achieved triglyceride levels below 500 mg/dL, a commonly accepted threshold for pancreatitis risk. In addition, in the APPROACH study, treatment with volanesorsen was associated with a statistically significant reduced rate of pancreatitis attacks in the group of patients who had the highest incidence of pre-study pancreatitis, and reduced abdominal pain in patients reporting pain before treatment in the study. The triglyceride lowering effects we observed were maintained throughout the 12 month study period. The COMPASS study, a six month randomized placebo-controlled study in 113 patients with very high triglycerides (>500 mg/dL), also achieved its primary endpoint of reduction in triglycerides at three months, with a 71% mean reduction in triglycerides. In the COMPASS study, treatment with volanesorsen was associated with a statistically significant reduction in pancreatitis attacks. The data from the COMPASS and APPROACH studies



is consistent with and supports the robust triglyceride lowering we observed in the Phase 2 program for volanesorsen.

The most common adverse event in the studies was injection site reactions, which were mostly mild. In addition, declines in platelet counts were observed in many patients. These platelet declines were not clinically significant in most patients and were generally well managed with monitoring and dose adjustment. Five patients discontinued participation in the APPROACH study due to platelet count declines and four patients discontinued due to other non-serious adverse events, including one case each of sweating and chills, severe fatigue, rash and injection site reaction. In the volanesorsen program as a whole, which included approximately 280 individuals who received volanesorsen, there were five treatment-related or potentially treatment-related serious adverse events, or SAEs. Two of the SAEs were described by the investigators as serum sickness-like reaction and serum sickness, respectively, and both patients fully recovered. The other three SAEs were serious platelet events (grade 4 thrombocytopenia), which resolved without complication after cessation of dosing. We believe our current regimen of platelet monitoring is designed to adequately identify any such potential event to provide patient safety. There have been no deaths and no treatment-related cardiovascular events in any volanesorsen clinical study. The ongoing Phase 3 study of volanesorsen in patients with FPL, called BROADEN, is currently enrolling and we plan to report data from this study in 2019. If the data are positive, in 2019 we plan to file for marketing authorization for volanesorsen to treat patients with FPL. If approved, we plan to globally commercialize volanesorsen ourselves for both FCS and FPL.

#### *AKCEA-APO(a)-L<sub>Rx</sub> for the treatment of CVD driven by hyperlipoproteinemia(a)*

We are developing AKCEA-APO(a)-L<sub>Rx</sub> for patients who are at significant risk of CVD because of their elevated levels of Lp(a). AKCEA-APO(a)-L<sub>Rx</sub> inhibits the production of the apolipoprotein(a), or Apo(a), protein, thereby reducing Lp(a). Apo(a) is a form of low density lipoprotein, or LDL, that is very atherogenic (promoting the formation of plaques in the arteries) and very thrombogenic (promoting the formation of blood clots). Elevated Lp(a) is recognized as an independent, genetic cause of coronary artery disease, heart attack, stroke and peripheral arterial disease. Inhibiting the production of Apo(a) in the liver reduces the level of Lp(a) in blood, potentially slowing down or reversing cardiovascular disease in patients with hyperlipoproteinemia(a), a condition in which individuals have levels of Lp(a) greater than 60 mg/dL. Lp(a) is difficult to inhibit using other technologies, such as small molecules and antibodies; there are multiple genetically-determined forms of the Apo(a) molecule and creating a small molecule or antibody that can interact with multiple targets is difficult. We believe antisense technology is particularly well suited to address hyperlipoproteinemia(a) because it specifically targets the RNA that codes for all forms of the Apo(a) molecule. As a result, it can stop the production of all of the forms of the protein. Furthermore, we believe addressing elevated Lp(a) is the next important horizon in lipid-focused therapy and, through our collaboration with Novartis, we plan to develop AKCEA-APO(a)-L<sub>Rx</sub> to treat patients with established cardiovascular disease in whom hyperlipoproteinemia(a) plays a causal role.

We have completed a Phase 1/2 study with AKCEA-APO(a)-L<sub>Rx</sub> in patients with hyperlipoproteinemia(a) and we reported the results at the AHA meeting in November 2015. In this clinical study, we observed significant and sustained reductions in Lp(a) of up to 97% with a mean reduction of 79% after only a single, small volume dose of AKCEA-APO(a)-L<sub>Rx</sub>. With multiple doses of AKCEA-APO(a)-L<sub>Rx</sub>, we observed even greater reductions of Lp(a) of up to 99% with a mean reduction of 92%. Based on these results, we have started a Phase 2b dose-ranging study of AKCEA-APO(a)-L<sub>Rx</sub> in patients with hyperlipoproteinemia(a) and established CVD. We have initiated a strategic collaboration with Novartis for this drug. In this collaboration, we intend to complete the above-referenced Phase 2b study. Following completion of this study, Novartis has an option to license the drug. If Novartis exercises its option to license AKCEA-APO(a)-L<sub>Rx</sub>, Novartis plans to

conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize AKCEA-APO(a)-L<sub>Rx</sub> worldwide.

#### *AKCEA-ANGPTL3-L<sub>Rx</sub> for the treatment of multiple lipid disorders*

We are developing AKCEA-ANGPTL3-L<sub>Rx</sub> to treat multiple lipid disorders. Studies have shown that elevated levels of the angiotensin-like 3, or ANGPTL3, protein are associated with an increased risk of premature heart attacks, increased arterial wall thickness and multiple metabolic disorders, such as insulin resistance. In contrast, people with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels and thus lower risk of heart attacks and multiple metabolic disorders. In preclinical studies, an analog of AKCEA-ANGPTL3-L<sub>Rx</sub> inhibited the production of the ANGPTL3 protein in the liver, inhibiting liver fat accumulation and lowering blood levels of triglycerides, LDL-C and very low density lipoprotein cholesterol, or VLDL-C. In addition, our preclinical data and initial Phase 1 data suggest that inhibiting the production of ANGPTL3 could improve other lipid parameters, including triglyceride levels and total cholesterol.

We are conducting a Phase 1/2 program for AKCEA-ANGPTL3-L<sub>Rx</sub> in people with elevated triglycerides. We reported results for the initial cohort from this study at the AHA meeting in November 2016. We observed that the people with elevated triglycerides achieved dose-dependent, statistically significant mean reductions in ANGPTL3 of up to 83%. Treatment with AKCEA-ANGPTL3-L<sub>Rx</sub> was also associated with statistically significant mean reductions in triglycerides of up to 66%, in LDL-C of up to 35% and in total cholesterol of up to 36%. In this study, AKCEA-ANGPTL3-L<sub>Rx</sub> was reported to be well tolerated. The most common adverse events in the AKCEA-ANGPTL3-L<sub>Rx</sub> treated group of patients were mild headaches and dizziness that were approximately equal to the rate observed in the placebo group. In the second half of 2017, we plan to begin a study of AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with hyperlipidemia with metabolic complications including insulin resistance and fatty liver, in which we plan to include patients with nonalcoholic fatty liver disease, or NAFLD, or nonalcoholic steatohepatitis, or NASH. Further, in the second half of 2017, we also plan to study AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with rare hyperlipidemias, including patients with FCS. If we find that AKCEA-ANGPTL3-L<sub>Rx</sub> can effectively lower triglyceride levels in patients with rare hyperlipidemias, including patients with FCS, through a different mechanism of action from volanesorsen, it may represent an opportunity to expand our FCS franchise. Additional potential indications for which we may consider developing AKCEA-ANGPTL3-L<sub>Rx</sub> include other rare hyperlipidemias and lipodystrophies.

#### *AKCEA-APOCIII-L<sub>Rx</sub> for the treatment of CVD driven by high triglycerides*

We are developing AKCEA-APOCIII-L<sub>Rx</sub> to inhibit the production of ApoC-III, the same protein inhibited by volanesorsen, for the broad population of patients who have cardiometabolic disease due to their elevated triglyceride levels. ApoC-III impacts triglyceride levels and may also increase inflammatory processes. This combination of effects makes ApoC-III a promising target for patients with LDL-C already controlled on statin therapy, but for whom triglycerides remain poorly controlled. We believe that the enhancements offered by Ionis' LICA technology can provide greater patient convenience by allowing for significantly lower doses and less frequent administration, compared to volanesorsen. We are conducting a Phase 1/2 study of AKCEA-APOCIII-L<sub>Rx</sub> in people with elevated triglycerides and plan to report results from this study in the second half of 2017. We have initiated a strategic collaboration with Novartis for this drug. In this collaboration, we intend to complete the Phase 2 program required to define the appropriate dose and regimen to support a planned cardiovascular outcome study. We plan to initiate a Phase 2b dose-ranging study of AKCEA-APOCIII-L<sub>Rx</sub> in patients with hypertriglyceridemia and established CVD in the second half of 2017 and plan to report data from this study in 2019. At the completion of Phase 2 development, Novartis has an option to license the drug. If Novartis exercises its option to license AKCEA-APOCIII-L<sub>Rx</sub>,



Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize AKCEA-APOCIII-L<sub>Rx</sub> worldwide.

### **Commercial Approach**

We plan to commercialize volanesorsen ourselves globally, with a specialized and comprehensive patient-centric approach. Our orphan-focused commercial model will include a small, highly focused salesforce in each country that we are targeting, complemented by medical affairs and patient and healthcare provider services. We plan to provide high touch patient and healthcare provider support through reimbursement assistance, partnerships with specialty pharmacies, injection training, routine platelet monitoring and dietary counseling, which we believe will enable strong integration with treating physicians and facilitate patient uptake and compliance. We plan to include dedicated case managers as part of our support team who will work directly with patients, caregivers and healthcare providers to help patients start and stay on therapy. Our global commercial organization is initially focused on our nearest term opportunities with volanesorsen to treat patients with FCS and FPL. Our initial plan is to focus on lipid specialists, specialized endocrinologists and pancreatologists as our primary call points. At the outset, we plan to focus our commercial efforts in the United States, Canada and Europe, and intend to expand over time to other relevant geographies. We are also focused on disease education and market access, with the goal of ensuring that identified patients can most effectively obtain our drugs once commercialized. We plan to commercialize by ourselves any approved drugs with a rare disease or specialty focus. We may enter into additional strategic relationships to commercialize certain of our drugs, particularly in indications with large patient populations, as evidenced by our collaboration with Novartis. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. We also plan to co-commercialize any such drug in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen.

Our commercial organization is focused on the following priorities to prepare for the launch of volanesorsen:

- Improve diagnosis by working with a small number of specialist physician experts to advance the understanding of the signs and symptoms of FCS and FPL, and then communicate that simplified clinical diagnosis criteria to the broader physician and patient community.
- Build a database of patients by working with physicians and patient organizations and through improved diagnosis and referrals. We add patients to our database through communication with physicians, patient organizations, and other tools, such as electronic medical record database searches. We plan to use our database to help us engage with physicians who may have patients who could potentially benefit from our drugs. In order to protect patient confidentiality, we do not include patient-specific information in the database.
- Build an integrated high-touch patient support team to help patients start and stay on therapy. We plan to provide reimbursement assistance, injection training, platelet monitoring and dietary support, as well as establish partnerships with specialty pharmacies, to help patients remain on therapy over the long term. We plan to include dedicated case managers as part of our support team who will work directly with patients, caregivers and healthcare providers to help patients start and stay on therapy.
- Prepare for successful market access through payors and other reimbursement authorities by establishing and quantifying the burden of disease associated with living with FCS and FPL.

We have made significant strides in our commercialization priorities, in particular with respect to identifying FCS patients and advancing the understanding of the burden of this debilitating disease. In addition to the patients from our overall clinical program, we have made substantial progress in finding additional FCS patients globally, including the approximately 170 patients identified in an FCS survey that we commissioned called IN-FOCUS. The goal of this survey was to further our understanding of the profile of FCS, and an interim analysis on the first 60 respondents supports that patients with FCS have a significant disease burden. Our survey found that patients suffer from pain, fatigue, cognitive issues such as brain fog and depression, managing highly-controlled restrictive diets and chronic and acute pancreatitis (and resulting hospitalizations), among other consequences. These effects, and the associated fear and anxiety, impact FCS patients' quality of life and employment.

### **Our Strategy**

Our goal is to become the premier company offering treatments for previously inadequately treated lipid disorders. The critical components of our business strategy to achieve this goal include the following:

- Successfully complete development, obtain regulatory approvals and commercialize volanesorsen in two orphan indications.
- Pursue indications that drive the greatest near and long term value.
- Advance multiple novel clinical-stage drugs to commercialization and further grow our pipeline.
- Build a leading, fully integrated, independent development and commercialization organization with a specialized and focused global team centered around a high touch patient and physician experience through services including case management, reimbursement assistance, injection training, platelet monitoring and dietary support, as well as through partnerships with specialty pharmacies.
- Create value through strategic collaborations, such as our collaboration with Novartis, to drive drugs to their fullest potential in indications with large target patient populations.

### **Our Relationship with Ionis**

We founded our operations in 2015 as a wholly owned subsidiary of Ionis to develop and commercialize Ionis' drugs to treat lipid disorders. Ionis has funded our expenses to date. We are becoming an independent company building a focus and excellence in development and commercialization. We expect Ionis to remain our principal stockholder for the foreseeable future. Through our relationship with Ionis, we benefit in the following ways:

- We have access to Ionis' innovative generation 2.0+ antisense and LICA technologies for use in our drugs. These technologies allow for precise specificity, favorable dosing properties and no anticipated drug-to-drug interactions.
- We obtained exclusive rights to globally commercialize a robust, mature pipeline of drugs, including volanesorsen, AKCEA-APO(a)-L<sub>RX</sub> and our other drugs in development. Our licensed rights also include access to Ionis' intellectual property and expertise to develop, manufacture and commercialize these drugs.
- We have a joint development program that provides us access to Ionis' development and regulatory organization, which has significant expertise in developing drugs to treat patients with lipid disorders. Ionis also provides resources to support our nonclinical and clinical studies.
- We contract with Ionis for support in areas such as legal, finance and human resources, which allows us to be more capital efficient than a typical company of our size and stage of

development. This support allows us to focus our efforts and resources on developing and preparing to commercialize our drugs.

- We are not required to make any upfront or pre-commercialization payments to Ionis for drugs we are developing under our development, commercialization and license agreement, as would be typical in a drug license. Our agreement allows us to more efficiently invest our capital in developing and preparing to commercialize our drugs, as we are only required to make milestone and royalty payments post-commercialization or if we grant a sublicense to Ionis' technology.
- As a result of our relationship with Ionis, we may have the opportunity to evaluate additional antisense drugs that may complement our efforts in becoming the premier lipid disease company. For example, Ionis has granted us a right of first negotiation with respect to Ionis development candidates that are designed to treat a rare cardiometabolic disease or a rare inherited metabolic disease.

While we and Ionis intend our relationship to enhance our capabilities, certain terms of our relationship may limit our ability to achieve this expected benefit, including:

- Some of our directors and officers may have a conflict of interest because of their positions with Ionis.
- A Joint Steering Committee, or JSC, sets the development and regulatory strategy for our drugs by mutual agreement. If the JSC cannot come to a mutual agreement, it could delay our ability to develop and commercialize our drugs in development.
- We will need to mutually agree with Ionis on the terms of any additional sublicense to a third party for our drugs in development. If we cannot mutually agree, it could delay or prevent our ability to develop and commercialize our drugs.
- Our agreements prevent Ionis from developing and commercializing drugs targeting ApoC-III, Apo(a) or ANGPTL3 RNA. However, our agreements do not prevent Ionis from developing and commercializing other drugs to pursue the same indications we are pursuing with our drugs.

Immediately following the completion of this offering, Ionis will own 70.8% of our outstanding common stock. Ionis has advised us that it does not have any current plans to sell or distribute to its stockholders the shares of our common stock that it beneficially owns, although it may elect to do so in the future.

### **Concurrent Private Placement**

In connection with our strategic collaboration agreement with Novartis, Novartis has agreed to purchase \$50.0 million of our common stock in a separate private placement concurrent with the completion of this offering at a price per share equal to the initial public offering price. Immediately following the completion of this offering, Novartis will own approximately 9.7% of the total number of shares of our common stock outstanding.

### **Risks Associated with Our Business**

Our business is subject to numerous risks and uncertainties, including those highlighted in the section entitled "Risk Factors" immediately following this prospectus summary. These risks include, among others, the following:

- We have a limited operating history, have incurred losses since our inception and may never become profitable.

- We will require substantial additional funding to achieve our goals. If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.
- Even if our drugs are successful in preclinical and earlier-stage clinical studies, the drugs may not be successful in later-stage clinical studies.
- If the FDA or another regulatory authority believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, the regulatory authority will not approve the specific drug or will require additional studies. For example, since three of the patients in the Phase 3 program for volanesorsen experienced serious platelet events (grade 4 thrombocytopenia), a condition in which the patient has very low platelet levels, and five patients discontinued participation in the APPROACH study due to platelet count declines, the FDA or another regulatory authority may require us to conduct additional studies before considering an application for marketing authorization.
- If we or our partners fail to obtain regulatory approval for our drugs, including volanesorsen and our other drugs in development, we or our partners cannot sell them in the applicable markets.
- If we cannot establish effective marketing and sales capabilities or enter into agreements with third parties to market and sell our drug products, we may not generate product revenue.
- If government or other third-party payors fail to provide adequate coverage and payment rates for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, our revenue and prospects for profitability will be limited.
- We have granted Novartis an option to exclusively license AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. If Novartis exercises its option, we will depend on Novartis to develop and commercialize these drugs. If Novartis does not exercise its option, we will have to seek additional sources for funding cardiovascular outcome studies and may have to delay or reduce our development and commercialization plans for AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>. Similarly, if Novartis exercises its option but does not adequately develop and commercialize these drugs, it could adversely affect our development and commercialization plans and potential revenue from these drugs.
- We depend on third parties to conduct our clinical studies for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.
- Ionis controls the direction of our business, and the concentrated ownership of our common stock will prevent you and other stockholders from influencing significant decisions.
- The resources Ionis provides us under our development, commercialization and license agreement and services agreement may not be sufficient for us to operate as a standalone company, and we may experience difficulty in separating our resources from Ionis.
- If we cannot protect our patents or our other proprietary rights, others may compete more effectively against us.

### **Corporate and Other Information**

We were initially incorporated in December 2014 in Delaware as a wholly owned subsidiary of Ionis and founded our operations in 2015.

Our principal executive offices are located at 55 Cambridge Parkway, Cambridge, Massachusetts. Our telephone number is (617) 207-0202. Our website address is [www.akceatx.com](http://www.akceatx.com). The information contained on, or that can be accessed through, our website is not incorporated by reference into this prospectus, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our common stock.

“Akcea,” the Akcea logo, and other trademarks or service marks of Akcea Therapeutics, Inc. appearing in this prospectus are the property of Akcea Therapeutics, Inc. This prospectus contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this prospectus may appear without the ® or TM symbols.

### **Implications of Being an Emerging Growth Company**

We qualify as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. An emerging growth company may take advantage of specified reduced reporting and other burdens that are otherwise applicable generally to public companies. These provisions include:

- a requirement to have only two years of audited financial statements and only two years of related selected financial data and management’s discussion and analysis of financial condition and results of operations disclosure;
- an exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting pursuant to the Sarbanes-Oxley Act of 2002;
- reduced disclosure about the emerging growth company’s executive compensation arrangements; and
- no requirement to seek nonbinding advisory votes on executive compensation or golden parachute arrangements.

We may take advantage of some or all of these provisions until we are no longer an emerging growth company. We will remain an emerging growth company until the earlier to occur of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of this offering, (b) in which we have total annual gross revenue of at least \$1.07 billion or (c) in which we are deemed to be a “large accelerated filer” under the rules of the Securities and Exchange Commission, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the prior June 30th and (2) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

We are choosing to “opt out” of the provision of the JOBS Act that permits emerging growth companies to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies and, as a result, we will comply with new or revised accounting standards as required when they are adopted. This decision to opt out of the extended transition period is irrevocable.

We have elected to adopt certain of the reduced disclosure requirements available to emerging growth companies. As a result of these elections, the information that we provide in this prospectus may be different than the information you may receive from other public companies in which you hold equity interests. In addition, it is possible that some investors will find our common stock less attractive as a result of these elections, which may result in a less active trading market for our common stock and higher volatility in our stock price.

## THE OFFERING

Common stock offered by us . . . . . 15,625,000 shares

Common stock to be outstanding  
immediately after this offering, the  
concurrent private placement and the  
conversion of outstanding  
indebtedness to Ionis. . . . . 64,197,879 shares

Option to purchase additional shares . . We have granted the underwriters an option, exercisable for 30 days after the date of this prospectus, to purchase up to an additional 2,343,750 shares from us.

Use of proceeds . . . . . We estimate that we will receive net proceeds from this public offering of approximately \$115.0 million, based on the initial public offering price of \$8.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. Our net proceeds from the concurrent private placement will be approximately \$50.0 million. We intend to use the aggregate net proceeds to advance the development of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> through additional clinical studies and to support the launch and initial commercialization of volanesorsen, if approved. We also intend to use a portion of the net proceeds for development personnel expenses, other development activities, working capital and other general corporate purposes. We are also undertaking this offering in order to create a public market for our common stock and thereby facilitate access to the public equity markets, increase our visibility in the marketplace, obtain additional capital and increase our liquidity. Further, we may use a portion of the net proceeds to acquire complementary businesses, products, or technologies, although we have no present commitments or agreements for any specific acquisitions. These expectations are subject to change. See "Use of Proceeds" for a more complete description of the intended use of proceeds from this offering.

Risk factors . . . . . See "Risk factors" and the other information included in this prospectus for a discussion of factors you should carefully consider before deciding to invest in our common stock.

Nasdaq Global Select Market symbol . . "AKCA"

Ionis has agreed to purchase 3,125,000 shares of common stock in this offering at the initial public offering price. The underwriters will not receive any underwriting discounts or commissions on the shares purchased by Ionis.



The number of shares of our common stock that will be outstanding after this offering, the concurrent private placement and the conversion of outstanding indebtedness to Ionis is based on 28,884,540 shares of common stock outstanding as of March 31, 2017, and excludes:

- 5,063,585 shares of common stock issuable upon the exercise of options outstanding as of March 31, 2017, at a weighted-average exercise price of \$6.48 per share;
- 3,436,415 shares of common stock reserved for future issuance under our 2015 equity incentive plan, as amended, of which 1,678,661 shares of common stock are issuable upon exercise of options granted subsequent to March 31, 2017; and
- 500,000 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, which will become effective upon the closing of this offering.

Unless otherwise indicated, all information contained in this prospectus, and the number of shares of common stock outstanding as of March 31, 2017:

- reflects the conversion of all our outstanding Series A convertible preferred stock into an aggregate of 28,884,540 shares of common stock in connection with the closing of this offering;
- reflects the issuance of 13,438,339 shares of common stock to Ionis upon the automatic conversion, in connection with the closing of this offering, of \$106.0 million of outstanding principal, together with accrued interest, pursuant to our line of credit agreement, based on the initial public offering price of \$8.00 per share, and which are referred to in this prospectus as the Ionis Conversion Shares;
- reflects the issuance of 6,250,000 shares of common stock to Novartis in the concurrent private placement, based on the initial public offering price of \$8.00 per share, and which are referred to in this prospectus as the Novartis Private Placement Shares;
- assumes no exercise by the underwriters of their option to purchase up to an additional 2,343,750 shares of our common stock;
- assumes no issuance or exercise of options after March 31, 2017;
- assumes the filing of our amended and restated certificate of incorporation and the adoption of our amended and restated bylaws immediately prior to the closing of this offering; and
- reflects a one-for-2.555 reverse stock split of our common stock effected on June 19, 2017.

## SUMMARY CONSOLIDATED FINANCIAL DATA

The following tables set forth our historical consolidated financial data as of and for the periods indicated. The summary consolidated financial data for the years ended December 31, 2014, 2015 and 2016 have been derived from our audited consolidated financial statements included elsewhere in this prospectus. The summary consolidated financial data for the three months ended March 31, 2016 and 2017 and as of March 31, 2017 have been derived from our unaudited financial statements included elsewhere in this prospectus. We have prepared the unaudited financial statements on the same basis as the audited financial statements, and the unaudited financial data include, in our opinion, all adjustments, consisting only of normal recurring adjustments, that we consider necessary for a fair presentation of our financial position and results of operations for these periods. Our historical operating results are not necessarily indicative of future operating results and results for the three months ended March 31, 2017 are not necessarily indicative of the results for the full year. We have derived the consolidated financial statements we present in this registration statement by carving out the expenses associated with our drugs from Ionis' consolidated financial statements in accordance with applicable accounting standards and Securities and Exchange Commission regulations.

The following data should be read together with our consolidated financial statements and the related notes thereto, as well as the sections entitled "Selected Consolidated Financial Data" and

“Management’s Discussion and Analysis of Financial Condition and Results of Operations,” included elsewhere in this prospectus.

(in thousands, except share and per share amounts)	Years Ended December 31,			Three Months Ended March 31,	
	2014	2015	2016	2016	2017
<b>Consolidated statement of operations data:</b>					
Research and development revenue under collaborative agreements . . . . .	—	—	—	—	\$ 9,597
Research and development expenses . . . . .	\$ 29,028	\$ 50,885	\$ 68,459	\$ 11,796	\$ 64,794
General and administrative expenses . . . . .	\$ 995	\$ 10,553	\$ 15,053	\$ 4,253	\$ 4,676
Net loss . . . . .	\$ (30,023)	\$ (61,422)	\$ (83,217)	\$ (15,962)	\$ (60,353)
Net loss per share of preferred stock, basic and diluted(1) . .	\$ (1.04)	\$ (2.13)	\$ (2.88)	\$ (0.55)	\$ (2.09)
Weighted-average shares of preferred stock outstanding, basic and diluted(1) . . . . .	28,884,540	28,884,540	28,884,540	28,884,540	28,884,540
Pro forma net loss per share, basic and diluted (unaudited)(1)(2) . . . . .			\$ (2.88)		\$ (2.09)
Pro forma weighted-average shares of common stock outstanding, basic and diluted (unaudited)(1)(2) . . . . .			28,884,540		28,884,540

- (1) See note 1, *Organization and significant accounting policies*, to our consolidated financial statements appearing elsewhere in this prospectus for further detail on the calculation of basic and diluted net loss per share.
- (2) Pro forma basic and diluted net loss per share represents net loss divided by the pro forma weighted-average shares of common stock outstanding. Pro forma weighted-average shares of common stock outstanding reflects the conversion of all outstanding shares of preferred stock into common stock as though the conversion had occurred on the first day of the relevant period.

(in thousands)	As of March 31, 2017		
	Actual	Pro forma(1)	Pro forma as adjusted(2)
	(unaudited)		
<b>Consolidated balance sheet data:</b>			
Cash, cash equivalents and short-term investments . . . . .	\$ 124,522	\$ 124,522	\$ 290,799
Working capital(3) . . . . .	51,922	51,922	231,922
Total assets . . . . .	132,981	132,981	297,371
Payable to Ionis . . . . .	15,000	15,000	—
Line of credit with Ionis(4) . . . . .	91,541	91,541	—
Series A convertible preferred stock . . . . .	100,000	—	—
Common stock . . . . .	—	29	64
Additional paid-in capital . . . . .	60,116	160,087	432,559
Accumulated deficit . . . . .	(235,015)	(235,015)	(235,981)
Stockholders' (deficit) equity . . . . .	(74,942)	(74,942)	196,599

- (1) Pro forma consolidated balance sheet data reflects the automatic conversion of all outstanding shares of preferred stock into common stock immediately prior to the closing of this offering.
- (2) Pro forma as adjusted consolidated balance sheet data reflects (i) the pro forma items described immediately above, (ii) payment of our \$15.0 million payable to Ionis which was paid in May 2017, (iii) the sale of 15,625,000 shares of common stock in this offering at the initial public offering price of \$8.00 per share, after deducting the underwriting discounts and commissions and estimated unpaid offering expenses payable by us, (iv) \$15.0 million of additional borrowing under our line of credit with Ionis in May 2017, (v) the issuance of 13,438,339 Ionis Conversion Shares, based on the initial public offering price of \$8.00 per share, in full satisfaction of our obligations to Ionis pursuant to our line of credit and (vi) the issuance of 6,250,000 Novartis Private Placement Shares, based on the initial public offering price of \$8.00 per share.
- (3) We define working capital as current assets less current liabilities. See our consolidated financial statements included elsewhere in this prospectus for further details regarding our current assets and current liabilities.
- (4) As of March 31, 2017, we borrowed \$91.0 million under our line of credit with Ionis. In May 2017, we borrowed an additional \$15.0 million under our line of credit with Ionis. As of the date of this prospectus, we have borrowed \$106.0 million under our line of credit with Ionis. The outstanding principal and accrued interest under our line of credit will convert into 13,438,339 Ionis Conversion Shares, based on the initial public offering price of \$8.00 per share. The pro forma as adjusted information set forth above reflects this conversion.

## RISK FACTORS

*Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below, together with all of the other information in this prospectus, including our consolidated financial statements and related notes, before deciding whether to purchase shares of our common stock. If any of the following risks are realized, our business, operating results and prospects could be materially and adversely affected. In that event, the price of our common stock could decline, and you could lose part or all of your investment. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may also adversely affect our business.*

### **Risks Related to Our Financial Condition and Need for Additional Capital**

#### ***We have a limited operating history and may never become profitable.***

Ionis Pharmaceuticals, Inc., or Ionis, incorporated us as a Delaware corporation in December 2014, and we have operated as a wholly owned subsidiary of Ionis since that time. As such, we have limited experience as a company, and no experience operating independently from Ionis, and have not yet demonstrated that we can successfully overcome many of the risks and uncertainties frequently encountered in new and rapidly evolving fields, particularly the biotechnology and pharmaceutical fields.

As a company, we have never obtained regulatory approval for, or commercialized, any product. Our ability to generate substantial revenue and achieve profitability depends on our ability, alone or with strategic partners, to successfully develop our drugs, and obtain the regulatory approvals necessary to commercialize our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development. We do not anticipate generating revenue from product sales for at least the next few years, if ever. Even if we achieve profitability in the future, we may not sustain profitability in subsequent periods. Our ability to generate revenue from product sales depends heavily on our and our current and future strategic partners' success in:

- completing clinical development of volanesorsen for one or more indications and nonclinical and clinical development of AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>;
- seeking and obtaining regulatory and marketing authorization for our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide the amount and quality of products and services we need to continue to develop and, if approved, commercialize volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- launching and commercializing volanesorsen and AKCEA-ANGPTL3-L<sub>Rx</sub> by establishing a sales, marketing and distribution infrastructure;
- launching and co-commercializing AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> through our collaboration with Novartis Pharma AG, or Novartis, under terms that we plan to negotiate with Novartis in the future;
- educating physicians about our target patient populations, including patients with familial chylomicronemia syndrome, or FCS, and patients with familial partial lipodystrophy, or FPL;
- obtaining market acceptance of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development as viable treatment options;

- obtaining and maintaining adequate coverage and reimbursement from third-party payors for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, to ultimately operate without reliance on Ionis;
- negotiating favorable terms in any partnership, licensing or other arrangements into which we may enter;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, product trademarks and know-how;
- developing and commercializing volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development without infringing others' intellectual property rights; and
- attracting, hiring and retaining qualified personnel.

We may not successfully develop any products, generate product revenue or achieve profitability. If we cannot achieve or maintain profitability, it would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. If the market price of our common stock declined, you could lose all or part of your investment.

***We have incurred losses since our inception.***

Because drug discovery and development require substantial lead-time and funding prior to commercialization, we have incurred expenses while generating limited revenue from our operating activities since our formation. Our net losses were \$30.0 million, \$61.4 million and \$83.2 million for the years ended December 31, 2014, December 31, 2015 and December 31, 2016, respectively. Our net losses were \$16.0 million and \$60.4 million for the three months ended March 31, 2016 and 2017, respectively. As of March 31, 2017, we had an accumulated deficit of approximately \$235.0 million. Most of the losses resulted from costs incurred in connection with our development programs and from general and administrative costs associated with our operations. We expect to incur additional operating losses for the foreseeable future, and these losses may increase if we cannot generate substantial revenue.

***We will require substantial additional funding to achieve our goals. If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.***

All of our drugs are undergoing clinical studies. All of our drug programs will require additional nonclinical and/or clinical testing and/or marketing authorization prior to commercialization. We will need to spend significant additional resources to conduct these activities. Our expenses could increase beyond expectations if the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory authorities require us to perform clinical studies and other studies in addition to those that we currently anticipate. As of March 31, 2017, we had cash, cash equivalents and short-term investments equal to \$124.5 million. Our research and development expenses were \$29.0 million, \$50.9 million and \$68.5 million for the years ended December 31, 2014, December 31, 2015 and December 31, 2016, respectively. Our research and development expenses were \$11.8 million and \$64.8 million for the three months ended March 31, 2016 and 2017, respectively.

We have funded our operating activities through a \$100.0 million cash contribution we received from Ionis in 2015, \$75.0 million we received from initiating our collaboration with Novartis, which we received in the first quarter of 2017 and \$106.0 million in drawdowns under our line of credit with Ionis which we received in the first and second quarters of 2017. We entered into our line of credit agreement with Ionis in January 2017 and it allows us to borrow up to \$150.0 million. We will no



longer have access to the line of credit following the closing of this offering and we do not have any firm commitment from Ionis to fund our cash flow deficits or provide other direct or indirect financial assistance to us following the closing of this offering. Based on our existing cash, cash equivalents and short-term investments and expected net proceeds from this offering and the concurrent private placement, we will need to raise additional funding to continue developing the drugs in our pipeline and to seek regulatory approval for and to commercialize volanesorsen and other drugs in our pipeline.

Even if we obtain marketing authorizations to sell volanesorsen or AKCEA-ANGPTL3-L<sub>Rx</sub>, we will incur significant costs to commercialize the approved product. Even if we generate revenue from the sale of any approved products, we may not become profitable and would need to obtain additional funding to continue operations.

### **Risks Related to Clinical Development, Regulatory Review and Approval of Our Drugs**

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

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

If any of our drugs in clinical studies, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, do not show sufficient safety and efficacy in patients with the targeted indication, it would negatively affect our development and commercialization goals for the drug and we would have expended significant resources with little or no benefit to us.

***Even if our drugs are successful in preclinical and earlier-stage clinical studies, the drugs may not be successful in later-stage clinical studies.***

Successful results in preclinical or initial clinical studies, including the results of earlier studies for our drugs in development, may not predict the results of subsequent clinical studies, including the Phase 3 study of volanesorsen for the treatment of FPL. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on people in the study;
- we or our partners may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- we or our partners may not identify, recruit and train suitable clinical investigators at a sufficient number of study sites;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- enrollment in our clinical studies may be slower than we anticipate;
- patients who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;

- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- we or our partners may require additional capital to fund the clinical study; and
- the supply or quality of our drugs or other materials necessary to conduct the clinical studies may be insufficient, inadequate or delayed.

In addition, volanesorsen and AKCEA-APOCIII-L<sub>Rx</sub> have the same mechanism of action, and all of our current drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, are chemically similar to each other and the drugs Ionis and other companies are developing separately. As a result, a safety observation we, Ionis or other companies encounter with one of our or their drugs could have or be perceived by a regulatory authority to have an impact on a different drug we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our drugs or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our drugs: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. Similarly, we have an ongoing Phase 3 study of volanesorsen in patients with FPL and an ongoing open label extension study of volanesorsen in patients with FCS. Adverse events or results from these studies could negatively impact our planned marketing approval applications for volanesorsen in patients with FCS or the commercial opportunity for volanesorsen.

Any failure or delay in the clinical studies for any of our drugs in development could reduce the commercial potential or viability of our drugs.

***We may not have appropriately designed the planned and ongoing clinical studies for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development to support submission of a marketing application to the FDA and foreign regulatory authorities or demonstrate safety or efficacy at the level required by the FDA and foreign regulatory authorities for product approval.***

We recently completed a Phase 3 clinical program for volanesorsen for the treatment of FCS and have an ongoing Phase 3 study of volanesorsen in patients with FPL. We are also conducting or plan to conduct clinical studies for AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>.

Even if we achieve positive results on the endpoints for these clinical studies or any future clinical studies, the FDA or foreign regulatory authorities may believe the clinical studies do not show the appropriate balance of safety and efficacy in the indication being sought or may interpret the data differently than we do, and deem the results insufficient to demonstrate the appropriate balance of safety and efficacy at the level required for product approval. For example, the FDA or foreign regulatory authorities could claim that we have not tested volanesorsen in a sufficient number of patients to demonstrate volanesorsen is safe and effective in patients with FCS or FPL to support an application for marketing authorization. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and delay these development programs. These risks are more likely to occur since we are developing our drugs against therapeutic targets or to treat diseases in which there is little or no clinical experience. In addition, these risks may be more likely to occur for volanesorsen since three of the patients in the Phase 3 program experienced serious platelet events (grade 4 thrombocytopenia), a condition in which the patient has very low platelet levels, and additional patients experienced other adverse

events in the program, including five patients who discontinued participation in the APPROACH study due to platelet count declines.

We may make modifications to the clinical study protocols or designs of our ongoing clinical studies that delay enrollment or completion of such clinical studies and could delay regulatory approval of volanesorsen and our other drugs in development. Any failure to obtain approval for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development on the timeline that we currently anticipate, or at all, would have a material and adverse impact on our business, prospects, financial condition and results of operations and could cause our stock price to decline.

***If we or our partners fail to obtain regulatory approval for our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, we or our partners cannot sell them in the applicable markets.***

We cannot guarantee that any of our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, will be safe and effective, or will be approved for commercialization. We and our partners must conduct time-consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, before they can be approved for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We or our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. It is possible that regulatory authorities will not approve any of our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, for marketing. If the FDA or another regulatory authority believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, the authority will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm our ability to successfully commercialize the drug. For example, since three of the patients in the Phase 3 program for volanesorsen experienced serious platelet events (grade 4 thrombocytopenia), a condition in which the patient has very low platelet levels, and additional patients experienced other adverse events in the program, some of whom discontinued participation in the studies, including five patients who discontinued participation in the APPROACH study due to platelet count declines, the FDA or another regulatory authority may require us to conduct additional studies of volanesorsen before considering an application for marketing approval.

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

- such authorities may disagree with the design or implementation of our clinical studies;
- we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a drug is safe and effective for any indication;
- such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the United States;
- we or our partners may be unable to demonstrate that our drug's clinical and other benefits outweigh its safety risks to support approval;
- such authorities may disagree with the interpretation of data from preclinical or clinical studies;

- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers who manufacture clinical and commercial supplies for our drugs; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

Failure to successfully develop volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, or to receive marketing authorization for these drugs or delays in these authorizations would prevent or delay the commercial launch of the drug, and, as a result, would negatively affect our ability to generate revenue.

***We may not be able to benefit from orphan drug designation for volanesorsen, or any of our other drugs.***

The FDA and EMA have granted orphan drug designation to volanesorsen for the treatment of patients with FCS. The EMA has granted orphan drug designation to volanesorsen for the treatment of patients with FPL and we are in the process of applying for orphan drug status for FPL in the United States. In the United States, under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods.

We may lose orphan drug exclusivity if the FDA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable drug to meet the needs of patients with the rare disease or condition.

Even if we maintain orphan drug exclusivity for volanesorsen or obtain orphan drug exclusivity for our other drugs, the exclusivity may not effectively protect the drug from competition because regulatory authorities still may authorize different drugs for the same condition.

***We may expend our limited resources to pursue a particular drug or indication and fail to capitalize on drugs or indications that may be more profitable or for which there is a greater likelihood of success.***

We are dedicating a substantial amount of our resources to develop and seek regulatory approval for volanesorsen to treat patients with FCS and FPL. As a result, we may forego or delay pursuit of opportunities with our other drugs or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. Our spending on current and future research and development programs and drugs for specific indications may not yield any commercially viable drugs.

***Our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, could be subject to regulatory limitations following approval.***

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. Promotional communications regarding prescription drugs must be consistent with the information in the product's approved labeling. We and our partners may not obtain the labeling claims necessary or desirable to

successfully commercialize our drug products, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development.

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

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

In addition, if we or others identify side effects after any of our drug products are on the market, if manufacturing problems occur subsequent to regulatory approval, or if we, our manufacturers or our partners fail to comply with regulatory requirements, we or our partners could be subject to:

- restrictions on our ability to conduct clinical studies, including full or partial clinical holds on ongoing or planned clinical studies;
- restrictions on such products' manufacturing processes;
- changes to the product label;
- restrictions on the marketing of a product;
- restrictions on product distribution;
- requirements to conduct post-marketing clinical studies;
- Untitled or Warning Letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of regulatory approvals;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions; or
- imposition of civil or criminal penalties.

Any one or a combination of these events could prevent us from achieving or maintaining market acceptance of the affected drug product or could substantially increase the costs and expenses of commercializing such drug product, which in turn could delay or prevent us from generating any revenue or profit from the sale of the drug product.

### **Risks Related to Commercialization of Our Drugs**

***If we cannot establish effective marketing and sales capabilities or enter into agreements with third parties to market and sell our drug products, we may not generate product revenue.***

We currently have a limited commercial infrastructure to market, sell or distribute our drugs. If approved, to commercialize our products, we must build our marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. To commercialize volanesorsen and AKCEA-ANGPTL3-L<sub>Rx</sub> in the initial indications we plan to pursue, we plan to build a specialty sales force in each global region we

expect to market the applicable drug, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine platelet monitoring, dietary counseling and a medical affairs team. We may seek to further penetrate markets by expanding our sales force or through strategic partnerships with other pharmaceutical or biotechnology companies or third party sales organizations, such as our strategic collaboration with Novartis.

Even though certain members of our management team and other employees have significant experience commercializing drug products, as a company we have no prior experience marketing, selling or distributing drug products, and there are significant risks involved in building and managing a commercial infrastructure. It will be expensive and time consuming for us to build and establish our own sales force and related compliance protocols to market any drug products. We may never successfully develop this capability and any failure could delay or preclude a product launch. We and our partners, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel.

We will incur expenses prior to product launch to develop a marketing and sales infrastructure. If regulatory requirements or other factors cause a delay in the commercial launch of volanesorsen, or our other drugs in development, we would incur additional expenses for having developed these capabilities earlier than required and prior to realizing any revenue from sales of volanesorsen and our other drugs in development. Even if we can effectively hire a sales force and develop a marketing and sales infrastructure, our sales force and marketing teams may not successfully commercialize volanesorsen or our other drugs in development.

If we cannot hire a sales force or collaborate with a third-party marketing and sales organization to globally commercialize any approved drug product, our ability to generate product revenue may be limited. To the extent we rely on third parties to commercialize any drug products, such as would be the case if Novartis exercises its option for AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>, we may receive less revenue than if we commercialized these drug products ourselves. In addition, we would have less control over the sales efforts of any other third parties involved in our commercialization efforts.

***We plan to rely on third-party specialty channels to distribute volanesorsen, and our other drugs to patients. If we cannot effectively establish and manage this distribution process, it could harm or delay the commercial launch and sales of volanesorsen and our other drugs in development.***

We and our strategic partners may contract with, and rely on, third-party specialty pharmacies to distribute volanesorsen, and our other drugs to patients. A specialty pharmacy is a pharmacy that specializes in dispensing medications for complex or chronic conditions, a process that requires a high level of patient education and ongoing management. Our management team will need to devote a significant amount of its attention to building and managing this distribution network. If we cannot effectively build and manage this distribution process, the commercial launch and sales of volanesorsen and AKCEA-ANGPTL3-L<sub>Rx</sub> will be delayed or less successful, which would harm our results of operations.



In addition, the use of specialty pharmacies involves certain risks, including, but not limited to, risks that these organizations will:

- not provide us with accurate or timely information regarding their inventories, the number of patients who are using our drugs or complaints regarding our drugs;
- not effectively sell or support volanesorsen, AKCEA-ANGPTL3-L<sub>Rx</sub> and our other drugs;
- reduce or discontinue their efforts to sell or support volanesorsen, AKCEA-ANGPTL3-L<sub>Rx</sub> or our other drugs;
- not devote the resources necessary to sell volanesorsen, AKCEA-ANGPTL3-L<sub>Rx</sub> or our other drugs in the volumes and within the time frames that we expect;
- not satisfy financial obligations to us or others; or
- cease operations.

Any such events may result in decreased sales and lower revenue, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

***If the market does not accept our drugs, including volanesorsen and our other drugs in development, we are not likely to generate substantial product revenue or become profitable.***

Even if we or our strategic partners obtain a marketing authorization for volanesorsen and our other drugs in development, our success will depend upon the medical community, patients and third-party payors accepting our drugs as medically useful, cost-effective, safe and convenient. Even if the FDA or foreign regulatory authorities authorize our drugs for commercialization, doctors may not prescribe our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

Additionally, in many of the markets where we or our partners may sell our drugs in the future, if we cannot agree with the government or other third-party payors regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market. Similarly, cost control initiatives by governments or third-party payors could decrease the price received for our drugs or increase patient coinsurance to a level that makes commercializing volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development economically unviable.

The degree of market acceptance for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development depends upon a number of factors, including the:

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

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. For example, we expect volanesorsen's product label will require periodic platelet monitoring, which could negatively affect our ability to attract and retain patients for volanesorsen. Additionally, in the clinical setting, some patients discontinued treatment with volanesorsen, including five patients who discontinued participation in the APPROACH study due to platelet count declines. While we believe we can better maintain patients on volanesorsen through our patient-centric commercial approach where we plan

to have greater involvement with physicians and patients, if we cannot effectively maintain patients on volanesorsen, we may not be able to generate substantial revenue from volanesorsen sales.

***The patient populations suffering from FCS and FPL are small and have not been established with precision. If the actual number of patients is smaller than we estimate, or if we cannot raise awareness of these diseases and diagnosis is not improved, our revenue and ability to achieve profitability may be adversely affected.***

We estimate there are 3,000 to 5,000 FCS patients and an additional 3,000 to 5,000 FPL patients globally. Our estimates of the sizes of the patient populations are based on published studies as well as internal analyses. If the results of these studies or our analyses of them do not accurately reflect the number of patients with FCS and FPL, our assessment of the market potential for volanesorsen may be inaccurate, making it difficult or impossible for us to meet our revenue goals, or to obtain and maintain profitability. In addition, as is the case with most orphan diseases, if we cannot successfully raise awareness of these diseases and improve diagnosis, it will be more difficult or impossible to achieve profitability.

In addition, since the patient populations for FCS and FPL are small, the per-patient drug pricing must be high in order to recover our development and manufacturing costs, fund adequate patient support programs and achieve profitability. For these initial indications, we may not maintain or obtain sufficient sales volume at a price high enough to justify our product development efforts and our sales and marketing and manufacturing expenses.

***If we or our partners fail to compete effectively, volanesorsen and our other drugs in development will not contribute significant revenue.***

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

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

These competitive developments could make our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, obsolete or non-competitive. Further, all of our drugs are delivered by injection, which may render them less attractive to patients than non-injectable products offered by our current or future competitors.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies, in obtaining FDA and other regulatory authorizations and in commercializing pharmaceutical products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and many of our competitors will have greater marketing and sales capabilities than our capabilities.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of drugs in our development pipeline. For example, if approved, volanesorsen could face competition from drugs like metreleptin.

Metreleptin, produced by Novilion Therapeutics, Inc., is currently approved for use in generalized lipodystrophy patients. In September 2016, Arrowhead Pharmaceuticals, Inc. and Amgen Inc. announced a license and collaboration for development of Arrowhead's preclinical program which uses an RNAi conjugated with a GalNAc for the same target as AKCEA-APO(a)-L<sub>Rx</sub>. AKCEA-APOCIII-L<sub>Rx</sub> may compete with gemcabene, an oral small molecule that reduces ApoC-III, that Gemphire Therapeutics, Inc. is developing to treat patients with triglycerides above 500 mg/dL. If volanesorsen or the other drugs in our pipeline cannot compete effectively with these and other products with common or similar indications to the drugs in our pipeline, we may not be able to generate substantial revenue from our product sales.

***If government or other third-party payors fail to provide adequate coverage and payment rates for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, our revenue and prospects for profitability will be limited.***

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

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

***If we are found in violation of federal or state "fraud and abuse" laws or other healthcare laws and regulations, we may be required to pay a penalty and/or be suspended from participation in federal or state healthcare programs, which may adversely affect our business, financial condition and results of operation.***

We may be subject to various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws, among other things, make it

illegal for a prescription drug manufacturer to pay, or offer to pay, a healthcare provider to refer, purchase or prescribe a particular drug. Due to the breadth of the statutory and regulatory provisions, it is possible that government authorities and others might challenge our practices under anti-kickback or other fraud and abuse laws. Moreover, recent healthcare reform legislation has strengthened these laws. In addition, false claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment, to government third-party payors, including Medicare and Medicaid claims for reimbursed drugs that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Our activities relating to the sale and marketing of our products may be subject to scrutiny under these laws. If we violated fraud and abuse laws, we could face a combination of:

- criminal and civil sanctions, including fines and civil monetary penalties;
- the possibility of exclusion from federal healthcare programs, including Medicare and Medicaid; and
- corporate integrity agreements, which could impose rigorous operational and monitoring requirements on us.

Given the significant penalties and fines that the government can impose on companies and individuals if convicted, allegations of violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals may bring similar actions under the False Claims Act. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing focus on these laws by law enforcement authorities. To the extent we have access to protected health information we could be subject to federal and state health information privacy and security laws, including without limitation, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information. State health information privacy and security laws in certain circumstances are more stringent than HIPAA and many of the state laws differ from each other in significant ways and may not have the same effect, thus complicating compliance. Our failure to comply with applicable federal and state health information privacy and security laws could subject us to significant fines and multi-year corrective action plans. Once we have a commercialized drug, we will be required to report annually to Centers for Medicare and Medicaid Services certain information related to payments and other transfers of value we may provide to physicians and teaching hospitals. Further, an increasing number of state laws require manufacturers to make reports to states on pricing and marketing information. Many of these laws are unclear as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

Similar rigid restrictions related to anti-kickbacks and promoting and marketing medicinal products apply in the European Union and other countries. Authorities in these countries strictly enforce these restrictions. Even in those countries where we will not be directly responsible for promoting and marketing our products, inappropriate activity by any of our international commercialization partners we may have could harm us.

## Risks Related to Dependence on Third Parties

### ***We plan to substantially depend on our collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>.***

We have granted Novartis an exclusive option to exclusively license each of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> pursuant to our strategic collaboration, option and license agreement with Novartis. We plan to substantially depend on Novartis to develop and commercialize these drugs. We initiated this collaboration primarily to have Novartis:

- conduct the cardiovascular outcome studies that are likely to be required for approval of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>;
- seek and obtain regulatory approvals for AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>; and
- globally commercialize AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>.

If Novartis exercises its option to license one or both of these drugs, we would rely on Novartis to further develop, obtain regulatory approvals for, and commercialize the licensed drug. In general, we cannot control the amount and timing of resources that Novartis devotes to our strategic collaboration. If Novartis fails to use commercially reasonable effort to further develop, obtain regulatory approvals for, or commercialize these drugs, or if Novartis' efforts are not effective, our business may be negatively affected. Novartis could pursue other technologies or develop other drugs either on its own or in collaboration with others to treat the same diseases as we and Novartis plan to treat with AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>. Novartis could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>, and Novartis is not required to inform us of such activities.

Our strategic collaboration with Novartis may not continue for various reasons. Novartis can terminate our agreement at any time and is under no obligation to exercise the options we granted them. If Novartis does not exercise its option, or following option exercise stops developing or commercializing a drug, we will have to seek additional sources for funding and may have to delay or reduce our development and commercialization plans for AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>.

In addition, if Novartis exercises its option to license AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>, Novartis would be responsible for the long term supply of drug substance and finished drug product for the licensed drug.

Our strategic collaboration with Novartis may not result in the successful commercialization of AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>. If Novartis does not successfully develop, manufacture or commercialize AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>, we may receive limited or no revenues for these drugs.

### ***AKCEA-APOCIII-L<sub>Rx</sub> and AKCEA-ANGPTL3-L<sub>Rx</sub> may compete with volanesorsen, which could reduce our expected revenues for volanesorsen.***

Volanesorsen and AKCEA-APOCIII-L<sub>Rx</sub> both inhibit the production of the same protein. We believe the enhancements we incorporated into AKCEA-APOCIII-L<sub>Rx</sub> can provide greater patient convenience by allowing for significantly lower doses and less frequent administration compared to volanesorsen. As such, if Novartis exercises its option and successfully commercializes AKCEA-APOCIII-L<sub>Rx</sub> while we are commercializing volanesorsen, to the extent physicians and patients elect to use AKCEA-APOCIII-L<sub>Rx</sub> instead of volanesorsen, it will reduce the revenue we derive from



volanesorsen. In addition, while AKCEA-ANGPTL3-L<sub>Rx</sub> and volanesorsen use different mechanisms of action, if AKCEA-ANGPTL3-L<sub>Rx</sub> can effectively lower triglyceride levels in FCS patients, it may likewise reduce the revenue we derive from volanesorsen.

***If we cannot manufacture our drugs or contract with a third party to manufacture our drugs at costs that allow us to charge competitive prices to buyers, we will not be able to operate profitably.***

To successfully commercialize volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, we will need to establish large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. In addition, as our drug development pipeline matures, we will have a greater need for clinical study and commercial manufacturing capacity. We have no direct experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. We currently rely and expect to rely for the foreseeable future on Ionis' manufacturing capacity and efficiency to produce our oligonucleotide drugs, and our business could be negatively affected if Ionis ceased to provide us with this capability for any reason. In addition, there are a small number of suppliers for certain raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, if we cannot continue to acquire raw materials from these suppliers on commercially reasonable terms or at all, we may be required to find alternative suppliers, which could be expensive and time consuming and negatively affect our ability to develop or commercialize our drugs in a timely manner or at all. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

We do not have long-term supply agreements for our drugs. We cannot guarantee that we will have a steady supply of drug to complete clinical studies, make registration batches for approval or satisfy market demand if commercialized at prices that are commercially acceptable. In addition, if we need to change manufacturers for any reason, we will need to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with verifying a new manufacturer could negatively affect our ability to develop drugs in a timely manner or within budget.

Also, manufacturers must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. Our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorization for our drugs, including authorizations for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, or result in enforcement action after authorization that could limit the commercial success of our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development.

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

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct the clinical studies for our drugs and expect to continue to do so in the future. For example, we use clinical research organizations for the clinical studies for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for



ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan, approved protocols for the study and applicable regulations. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our drugs, including authorizations for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development.

***We may seek to form additional partnerships in the future with respect to volanesorsen, and our other drugs in development, and we may not realize the benefits of such partnerships.***

Although we intend to develop and commercialize volanesorsen for patients with FCS and FPL ourselves, we may form partnerships, create joint ventures or collaborations or enter into licensing arrangements with third parties for the development and commercialization of our drugs in development. For example, we have granted Novartis an exclusive option to exclusively license AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. We face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Any delays in entering into new strategic partnership agreements related to our drugs could delay the development and commercialization of our drugs and reduce their competitiveness even if they reach the market. Moreover, we may not be successful in our efforts to establish a strategic partnership or other collaborative arrangement for any additional drugs because the potential partner may consider that our development pipeline is not advanced enough to justify a collaborative effort, or that volanesorsen and our other drugs in development do not have the requisite potential to demonstrate safety and efficacy in the target populations. In addition, we will need to mutually agree with Ionis on the terms of any sublicense to a third party for volanesorsen and our other drugs in development. If we cannot mutually agree on terms for a sublicense to a third party or if Ionis does not agree to a sublicense at all, it could delay our ability to develop and commercialize volanesorsen and our other drugs in development. Even if we are successful in establishing such a strategic partnership or collaboration, we cannot be certain that, following such a strategic transaction or collaboration, we will be able to progress the development and commercialization of the applicable drugs as envisioned, or that we will achieve the revenue that would justify such transaction. If we do not accurately evaluate the commercial potential or target market for a particular drug, we may relinquish valuable rights to that drug through future collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights.

### **Risks Related to Our Relationship with Ionis**

***Ionis controls the direction of our business, and the concentrated ownership of our common stock will prevent you and other stockholders from influencing significant decisions.***

Immediately following the completion of this offering, Ionis will own 70.8% of the economic interest and voting power of our outstanding common stock, or 68.3% of the economic interest and voting power of our outstanding common stock if the underwriters exercise their option to purchase additional shares in full. As long as Ionis beneficially controls a majority of the voting power of our outstanding common stock, it will generally be able to determine the outcome of all corporate actions requiring stockholder approval, including the election and removal of directors. Even if Ionis were to control less than a majority of the voting power of our outstanding common stock, it may influence the outcome of such corporate actions so long as it owns a significant portion of our common stock. If Ionis continues to hold its shares of our common stock, it could remain our controlling stockholder for an extended period of time or indefinitely.

Ionis' interests may not be the same as, or may conflict with, the interests of our other stockholders. Investors in this offering will not be able to affect the outcome of any stockholder vote while Ionis controls the majority of the voting power of our outstanding common stock. As a result, Ionis can control, directly or indirectly and subject to applicable law, all matters affecting us, including:

- any determination with respect to our business strategy and policies, including the appointment and removal of officers and directors;
- any determinations with respect to mergers, business combinations or disposition of assets;
- our financing and dividend policy;
- compensation and benefit programs and other human resources policy decisions;
- termination of, changes to or determinations under our development, commercialization and license agreement, which we refer to as the license agreement, and services agreement with Ionis;
- changes to any other agreements that may adversely affect us; and
- determinations with respect to our tax returns.

Because Ionis' interests may differ from ours or from those of our other stockholders, actions that Ionis takes with respect to us, as our controlling stockholder, may not be favorable to us or our other stockholders.

***If Ionis sells a controlling interest in our company to a third party in a private transaction, you may not realize a change of control premium on shares of our common stock, and we may become subject to the control of a presently unknown third party.***

Following the completion of this offering, Ionis will continue to own a significant equity interest in our company. This means that Ionis could choose to sell some or all of its shares of our common stock in a privately negotiated transaction, which, if sufficient in size, could result in a change of control of our company.

Ionis' ability to privately sell its shares of our common stock, with no requirement for a concurrent offer to be made to acquire your shares of our common stock, could prevent you from realizing any change of control premium on your shares of our common stock that may otherwise accrue to Ionis on its private sale of our common stock. Additionally, if Ionis privately sells its significant equity interest in our company, we may become subject to the control of a presently unknown third party. Such third party may have conflicts of interest with those of other stockholders. In addition, if Ionis sells a controlling interest in our company to a third party, such a sale could negatively impact or accelerate any future indebtedness we may incur, and negatively impact any other commercial agreements and relationships, all of which may adversely affect our ability to run our business as described herein and may have a material adverse effect on our operating results and financial condition.

***Certain of our directors and officers may have actual or potential conflicts of interest because of their positions with Ionis.***

Following this offering, Stanley T. Croke, Chairman of the Board and Chief Executive Officer for Ionis, and B. Lynne Parshall, Chief Operating Officer for Ionis, will serve on our board of directors and retain their positions with Ionis. Similarly, Elizabeth L. Hougen, Chief Financial Officer for Ionis, will serve as our Chief Financial Officer and retain her position with Ionis. In addition, these individuals will own Ionis equity and Ionis equity awards. Ionis common stock, options to purchase Ionis common stock and other Ionis equity awards represent a significant portion of these individuals' net worth. Their position at Ionis and the ownership of any Ionis equity or equity awards creates, or

may create the appearance of, conflicts of interest when we ask these individuals to make decisions that could have different implications for Ionis than the decisions have for us. In addition, our certificate of incorporation will provide for the allocation of certain corporate opportunities between us and Ionis. Under these provisions, neither Ionis or its other affiliates, nor any of their officers, directors, agents or stockholders, will have any obligation to present to us certain corporate opportunities. For example, a director of our company who also serves as a director, officer or employee of Ionis or any of its other affiliates may present to Ionis certain acquisitions, in-licenses, potential development programs or other opportunities that may be complementary to our business and, as a result, such opportunities may not be available to us. To the extent attractive corporate opportunities are allocated to Ionis or its other affiliates instead of to us, we may not be able to benefit from these opportunities. See “Description of Capital Stock—Corporate Opportunities” for additional information.

***The resources Ionis provides us under the license agreement and the services agreement may not be sufficient for us to operate as a standalone company, and we may experience difficulty in separating our resources from Ionis.***

Because we have not operated separately from Ionis in the past, we may have difficulty doing so. We will need to acquire resources in addition to, and eventually in lieu of, those provided by Ionis to our company, and may also face difficulty in separating our resources from Ionis’ resources and integrating newly acquired resources into our business. In addition, Ionis may prioritize its own research, development, manufacturing and other needs ahead of the services Ionis has agreed to provide us, or Ionis employees who conduct services for us may prioritize Ionis’ interests over our interests. Our business, financial condition and results of operations could be harmed if we have difficulty operating as a standalone company, fail to acquire resources that prove to be important to our operations or incur unexpected costs in separating our resources from Ionis’ resources or integrating newly acquired resources.

***Our historical financial information is not necessarily representative of the results that we would have achieved as a separate, publicly traded company and may not be a reliable indicator of our future results.***

Some of the historical information about us in this prospectus refers to our business as operated by and integrated with Ionis. Our historical financial information is derived from the consolidated financial statements and accounting records of Ionis. Accordingly, the financial information included in this prospectus does not necessarily reflect the financial condition, results of operations or cash flows that we would have achieved as a separate, publicly traded company during the periods presented or those that we will achieve in the future primarily as a result of the factors described below:

- Prior to our formation as a separate subsidiary, Ionis operated our business as part of its broader corporate organization, rather than as an independent company. Ionis performed various corporate functions for our business, such as accounting, information technology, finance, business development and legal. Ionis currently provides some of these functions to us, as described in “Certain relationships and related person transactions.” Our historical financial results reflect allocations of corporate expenses from Ionis for such functions and are likely to be less than the expenses we would have incurred had we operated as a separate publicly traded company. We will need to make significant investments to replicate or outsource from other providers the facilities, systems, infrastructure and personnel we may no longer have access to as a result of our separation from Ionis. As we transition more and more of these functions away from Ionis so that we can develop our independent ability to operate without access to Ionis’ existing operational and administrative

infrastructure our costs will increase. We may not operate our business efficiently or at comparable costs, and our profitability may decline;

- We have been able to use Ionis' size and purchasing power in procuring various goods and services and shared economies of scope and scale in costs, employees, vendor relationships and other business relationships. Although we have the license agreement and services agreement with Ionis, these arrangements may not fully capture the benefits we previously enjoyed when we were integrated with Ionis and may result in us paying higher charges than in the past for these services. As a separate, independent company, we may not obtain goods and services at the prices and terms obtained prior to our separation, which could decrease our overall profitability. As a separate, independent company, we also may not successfully negotiate favorable tax treatments and credits with governmental entities. This could have an adverse effect on our results of operations and financial condition;
- Generally, our working capital requirements and capital for our general corporate purposes, including research and development and capital expenditures, were historically satisfied as part of Ionis' corporate-wide cash management policies. As a result of the separation, we may need to obtain additional financing from banks, through public offerings or private placements of debt or equity securities, strategic relationships or other arrangements; and
- The cost of capital for our business may be higher than Ionis' cost of capital prior to the separation.

Other significant changes may occur in our cost structure, management, financing and business operations as a result of operating as a company separate from Ionis. For additional information about the past financial performance of our business and the basis of presentation of the consolidated financial statements of our business, see "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes included elsewhere in this prospectus.

***We will incur incremental costs as a standalone company.***

We will need to replicate or replace the functions, systems and infrastructure to which we will no longer have the same access after this offering. We may also need to make investments or hire additional employees to operate without the same access to Ionis' existing operational and administrative infrastructure. These initiatives may be costly to implement. Due to the scope and complexity of the underlying projects relative to these efforts, the amount of total costs could be materially higher than our estimate, and the timing of the incurrence of these costs is subject to change.

Ionis currently performs or supports many important corporate functions for our company. Our consolidated financial statements reflect charges for these services on an allocation basis. Following this offering, our services agreement with Ionis will govern many of these services. Under the services agreement we will be able to use these Ionis services for a fixed term established on a service-by-service basis. However, we generally will have the right to terminate a service earlier if we give notice to Ionis. Partial reduction in the provision of any service requires Ionis' consent. In addition, either party will be able to terminate the agreement due to a material breach of the other party, upon prior written notice, subject to limited cure periods.

We will pay Ionis mutually agreed upon fees for these services, based on Ionis' costs of providing the services. Since we negotiated the services agreement in the context of a parent subsidiary relationship, the terms of the agreement, including the fees charged for the services, may be higher or lower than those that would be agreed to by parties bargaining at arm's length for similar services and may be higher or lower than the costs reflected in the allocations in our historical consolidated financial statements. Ionis will pass third party costs through to us at Ionis' cost. In addition, while Ionis provides us these services, our operational flexibility to modify or implement changes with respect to such services or the amounts we pay for them will be limited.

We may not be able to replace these services or enter into appropriate third-party agreements on terms and conditions, including cost, comparable to those that we will receive from Ionis under our services agreement. Additionally, after the agreement terminates, we may not sustain the services at the same levels or obtain the same benefits as when we were receiving such services and benefits from Ionis. When we begin to operate these functions separately, if we do not have our own adequate systems and business functions in place, or cannot obtain them from other providers, we may not operate our business effectively or at comparable costs, and our business may suffer. In addition, we have historically received informal support from Ionis, which may not be addressed in our services agreement. The level of this informal support will diminish and could end following this offering.

***We may not be able to fully realize the expected benefits of our license agreement with Ionis.***

We have a development, commercialization and license agreement with Ionis. Pursuant to the license agreement, subject to certain restrictions, we and Ionis will share development responsibilities for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development. We are paying for research and development costs and reimbursing Ionis for Ionis' employees supporting our development activities. Until we build or acquire our own capabilities to replace those Ionis is providing to us, particularly development, regulatory and manufacturing services, we will be heavily dependent on Ionis.

While we and Ionis intend the license agreement to bolster our capabilities, certain terms of the license agreement may limit our ability to achieve this expected benefit, including:

- a Joint Steering Committee, or JSC, comprising two senior members from our company and two senior members from Ionis, sets the development strategy for our drugs by mutual agreement. A Regulatory Sub-committee, established by the JSC and having equal membership from our company and Ionis, will set the regulatory strategy for each of our drugs by mutual agreement. If the JSC or the Regulatory Sub-committee cannot come to a mutual agreement, it could delay our ability to develop and commercialize volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- we will need to mutually agree with Ionis on the terms of any additional sublicense to a third party for volanesorsen and our other drugs in development. If we cannot mutually agree on terms for a sublicense to a third party or if Ionis does not agree to a sublicense at all, it could delay or prevent our ability to develop and commercialize volanesorsen and our other drugs in development;
- we will need to obtain Ionis' approval to in-license a product, acquire a product or acquire another company, until the earlier of (i) 5 years following this offering or (ii) when Ionis no longer is required to record its share of our profits and losses from an accounting perspective; and

- there is nothing in our agreements with Ionis to prevent Ionis from developing and commercializing drugs targeting RNAs that are not ApoC-III, Apo(a) or ANGPTL3 to pursue the same indications we are pursuing with our drugs.

Each of the foregoing terms and Ionis' other rights under the license agreement, could limit our ability to realize the expected benefits of the license agreement or otherwise limit our ability to pursue transactions or development efforts other stockholders may view as beneficial. Further, if Ionis does not continue to own a significant portion of our equity, Ionis' incentive to help us would be diminished. If we fail to achieve the expected benefits of our agreements with Ionis, it may be more difficult, time consuming or expensive for us to develop and commercialize volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, or may result in our drugs being later to market than those of our competitors or prevent them from ever getting to market. If these events cause delays in new product development we could lose the first in class products in a given therapeutic area.

For a summary description of the terms of the license agreement, see "Certain Relationships and Related Person Transactions."

### **Risks Related to Our Intellectual Property**

#### ***If we breach our obligations under our license agreement with Ionis, we could lose our rights to volanesorsen and our other drugs in development.***

We obtained our rights to volanesorsen and our other drugs in development under our license agreement with Ionis. If we breach our obligations under this license agreement and, as a result, Ionis subsequently exercises its right to terminate it, we generally would not be able to continue to develop or commercialize volanesorsen, and our other drugs in development that incorporate Ionis' intellectual property, and Ionis would receive a royalty-free, nonexclusive license to our improvements to those programs, meaning we would lose the benefits of our investment in these programs. If we breach our obligations under this license agreement with respect to AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub> and, as a result, Ionis exercises its right to terminate it, then our strategic collaboration with Novartis would convert into a direct strategic collaboration between Novartis and Ionis, and Ionis would receive all of the revenue and other benefits associated with that strategic collaboration. For a summary description of the license agreement, see "Certain Relationships and Related Person Transactions."

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

Our success depends to a significant degree upon whether we can continue to secure and maintain intellectual property rights that protect volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development. However, patents may not issue from any of our pending patent applications in the United States or in other countries and we may not be able to obtain, maintain or enforce our owned or licensed patents and other intellectual property rights which could impact our ability to compete effectively. In addition, the scope of any of our owned or licensed patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

Composition of matter patents on the active pharmaceutical ingredient for a product are generally considered to be the strongest form of intellectual property protection for pharmaceutical



products, as such patents provide protection without regard to any method of use. Our volanesorsen patent portfolio currently includes:

- issued patent claims to the specific antisense sequence and chemical composition of volanesorsen in the United States, Australia, and Europe;
- issued patent claims in the United States and Australia drawn to the use of antisense compounds complementary to an active region of human ApoC-III messenger ribonucleic acid, including the site targeted by volanesorsen;
- additional patent applications designed to protect the volanesorsen composition in Canada; and
- additional methods of use in jurisdictions worldwide for volanesorsen.

The natural term of the issued U.S. patent covering the volanesorsen composition of matter will expire in 2023, but we plan to seek to extend the U.S. patent expiration beyond 2023 based upon the development and regulatory review period in the United States. The natural term of the granted European and Australian patents covering volanesorsen will expire in 2024, but we plan to seek to extend each of these patents beyond 2024 based upon the development and regulatory review periods in Europe and Australia.

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

If we or any licensor partner loses or cannot obtain patent protection for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> or our other drugs in development it could have a material adverse impact on our business.

***Intellectual property litigation could cause us to spend substantial resources and prevent us from pursuing our programs.***

From time to time we may have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or

proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios.

***Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.***

Our commercial success depends upon our ability and the ability of our strategic partners to develop, manufacture, market and sell our drugs and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. Extensive litigation regarding patents and other intellectual property rights is common in the biotechnology and pharmaceutical industries. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our drugs and technology, including interference, derivation, reexamination, post-grant review, opposition, cancellation or similar proceedings before the U.S. PTO or its foreign counterparts. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. We may not be aware of all such intellectual property rights potentially relating to our drugs and their uses. If a third party claims that volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, our other drugs in development or our technology infringe its patents or other intellectual property rights, we or our partners may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain. Thus, we do not know with certainty that our drugs or our intended commercialization thereof, does and will not infringe or otherwise violate any third party's intellectual property.

***We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.***

Filing, prosecuting and defending patents on drugs in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those we could obtain in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products. In addition, competitors may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patent rights or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems

of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology. This could make it difficult for us to stop competitors from infringing our patent rights or misappropriating our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit our right to enforce our patent rights against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. We must ultimately seek patent protection on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

In addition, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patent rights at risk of being invalidated or interpreted narrowly, could put our owned or licensed patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

***If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent protection for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, our business may be materially harmed.***

Depending upon the timing, duration and specifics of the first FDA marketing authorization of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, a United States patent that we own or license may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments allow the owner of an approved product to extend patent protection for up to five years as compensation for patent term lost during product development and the FDA regulatory review process. During this period of extension, the scope of protection is limited to the approved product and approved uses.

Although we plan on seeking patent term restoration for our products, we may not succeed if, for example, we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we cannot obtain patent term restoration or the term of any such patent restoration is less than we request, our competitors may enter the market and compete against us sooner than we anticipate, and our ability to generate revenue could be materially adversely affected.

***Changes in United States patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.***

Recent United States Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the United States Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

***If we and our partners do not adequately protect the trademarks and trade names for our products, then we and our partners may not be able to build name recognition in our markets of interest and our business may be adversely affected.***

Our competitors or other third parties may challenge, infringe or circumvent the trademarks or trade names for our products. We and our partners may not be able to protect these trademarks and trade names. In addition, if the trademarks or trade names for one of our products infringe the rights of others, we or our partners may be forced to stop using the trademarks or trade names, which we need for name recognition in our markets of interest. If we cannot establish name recognition based on our trademarks and trade names, we and our partners may not be able to compete effectively and our business may be adversely affected.

***Intellectual property rights do not necessarily address all potential threats to our competitive advantage.***

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- others may make compounds that are similar to our drugs but that are not covered by the claims of the patents that we own or have exclusively licensed;
- we, or our license partners or current or future strategic partners, might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed;
- we, or our license partners or current or future strategic partners, might not have been the first to file patent applications covering our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- our pending licensed patent applications or those that we own in the future may not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business, results of operations and prospects.

### **Risks Related to Our Business and Industry**

***We will need to significantly increase the size of our organization, and we may experience difficulties in managing growth.***

We are currently a small company with 30 full-time employees as of March 31, 2017. To commercialize volanesorsen, and our other drugs in development that we are responsible for commercializing, we will need to increase our operations and expand our use of third-party contractors. We plan to continue to build our compliance, financial and operating infrastructure to ensure the maintenance of a well-managed company including hiring additional staff within our regulatory, clinical and medical affairs groups and an in-house commercial organization initially

focused on marketing and selling volanesorsen, if approved. We currently have limited sales and marketing capability and therefore intend to recruit a specialty sales force in anticipation of volanesorsen's potential approval.

Future growth will impose significant added responsibilities on our management, including the need to identify, recruit, maintain and integrate additional employees. In addition, to meet our obligations as a public company, we will need to increase our general and administrative capabilities. Our current management, personnel and systems may not be adequate to support this future growth. Our future financial performance and our ability to commercialize our drugs and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to:

- manage our clinical studies and the regulatory process effectively;
- manage the manufacturing of our drugs for clinical and commercial use;
- integrate current and additional management, administrative, financial and sales and marketing personnel;
- develop a marketing and sales infrastructure;
- hire new personnel necessary to effectively commercialize volanesorsen and our other drugs in development;
- develop our administrative, accounting and management information systems and controls;
- and
- hire and train additional qualified personnel.

Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and our management may be unable to successfully manage future market opportunities or our relationships with customers and other third parties.

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, when we anticipate filing an application for marketing authorization, or when we or our partners plan to commercially launch a drug. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development, the price of our securities could decrease.

***The loss of key personnel, or if we cannot attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.***

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

studies, obtain regulatory approvals or effectively commercialize drugs may make it more challenging to recruit and retain qualified personnel.

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

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development. We have clinical study insurance coverage and commercial product liability insurance coverage. In addition, Novartis has agreed to indemnify us against specific claims arising from Novartis' development and commercialization of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. However, this insurance coverage and indemnities may not be adequate to cover claims against us. Insurance may not be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenue. Thus, whether or not we are insured or indemnified, a product liability claim or product recall may result in losses that could be material.

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

Our development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We cannot completely eliminate the risk of contamination, which could cause:

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

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

***A variety of risks associated with operating our business and, following approval, marketing our drugs internationally could materially adversely affect our business.***

In addition to our U.S. operations, we plan to establish operations and, following approval, commercialize our products in Europe and other countries globally. We face risks associated with our current and planned international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Once we



establish international operations we will be subject to numerous risks associated with international business activities, including:

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

The UK's anticipated exit from the European Union could increase these risks.

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

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

We currently rely on Ionis to manufacture our clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment required to develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism may harm these facilities. If a disaster affects these facilities, our and our partners' development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to

cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, a shutdown of the U.S. government, including the FDA could harm or delay our development and commercialization activities.

***Our business and operations would suffer in the event of computer system failures.***

Despite the implementation of security measures, our internal computer systems, and those of our CROs, manufacturers and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If issues were to arise and cause interruptions in our operations, it could result in a material disruption of our drug programs. For example, the loss of clinical study data from completed or ongoing or planned clinical studies could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development could be delayed.

**Risks Related to Our Common Stock and This Offering**

***We are an “emerging growth company” and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.***

We are an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, and we intend to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including: not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We will remain an emerging growth company until the earlier to occur of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of this offering, (b) in which we have total annual gross revenue of at least \$1.07 billion or (c) in which we are deemed to be a “large accelerated filer” under the rules of the U.S. Securities and Exchange Commission, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the prior June 30th and (2) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

We have taken advantage of reduced reporting burdens in this prospectus. In particular, in this prospectus, we have not included all of the executive compensation related information that would be required if we were not an emerging growth company. We cannot predict whether investors will find our common stock less attractive than if we did not rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Even after we no longer qualify as an emerging growth company, we may still qualify as a “smaller reporting company” which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

***There has been no public market for our common stock prior to this offering, and you may not be able to resell our shares at or above the price you paid, or at all.***

Prior to this offering, there has been no public market for our common stock. We have applied to list our common stock on the Nasdaq Global Select Market, or Nasdaq, but an active trading market for our common stock may never develop or be sustained following this offering. Further, since Ionis will remain a significant stockholder after we complete this offering, it is more likely that an active trading market for our common stock may never develop or be sustained. If an active trading market for our common stock does not develop after this offering, the market price and liquidity of our common stock will be materially and adversely affected. You may not be able to sell your shares quickly or at the market price if trading in our common shares is not active. Negotiations between us and the underwriters will determine the offering price for our common stock and the offering price may bear no relationship to the market price for our common stock after this offering. An active trading market for our common stock may not develop and the market price of our common stock may decline below the offering price. Further, an inactive market may also impair our ability to raise capital by selling shares of our common stock and may impair our ability to enter into strategic partnerships or acquire companies or products by using our shares of common stock as consideration.

***The market price for our common stock may be volatile, which could contribute to the loss of your investment.***

Fluctuations in the price of our common stock could contribute to the loss of all or part of your investment. Prior to this offering, there has not been a public market for our common stock. Accordingly, the initial public offering price for the shares of our common stock may not be indicative of the price that will prevail in the trading market, if any, that develops following this offering. If an active market for our common stock develops and continues, the trading price of our common stock following this offering is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. Any of the factors listed below could have a material adverse effect on your investment in our common stock and our common stock may trade at prices significantly below the initial public offering price. In such circumstances the trading price of our common stock may not recover and may experience a further decline.

Factors affecting the trading price of our common stock may include:

- our failure to effectively develop and commercialize volanesorsen and our other drugs in development;
- Novartis' failure to exercise its option and/or effectively develop and commercialize AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> to the extent it exercises its option to license those drugs from us;
- changes in the market's expectations about our operating results;
- adverse results or delays in preclinical or clinical studies;

- our decision to initiate a clinical study, not to initiate a clinical study or to terminate an existing clinical study;
- adverse regulatory decisions, including failure to receive regulatory approval for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- success or failure of competitive products or antisense drugs more generally;
- adverse developments concerning our manufacturers or our strategic partnerships;
- inability to obtain adequate product supply for any drug for clinical studies or commercial sale or inability to do so at acceptable prices;
- the termination of a strategic partnership or the inability to establish additional strategic partnerships;
- unanticipated serious safety concerns related to the use of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- adverse safety or other clinical results, such as those that have occurred in the past or that may occur in the future, related to drugs being developed by Ionis or other companies that are or may be perceived to be similar to our drugs;
- our ability to effectively manage our growth;
- the size and growth, if any, of the targeted market;
- our operating results do not meet the expectation of securities analysts or investors in a particular period;
- actual or anticipated fluctuations in our quarterly financial results or the quarterly financial results of companies perceived to be similar to us;
- securities analysts do not publish reports about us or our business or publish negative reports;
- changes in financial estimates and recommendations by securities analysts concerning our company, our market opportunity, or the biotechnology and pharmaceutical industries in general;
- operating and stock price performance of other companies that investors deem comparable to us;
- overall performance of the equity markets;
- announcements by us or our competitors of acquisitions, new drugs or programs, significant contracts, commercial relationships or capital commitments;
- our and our strategic partners' ability to successfully market volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- changes in laws and regulations affecting our business, including but not limited to clinical study requirements for approvals;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain and maintain patent protection for volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development;
- commencement of, or involvement in, litigation involving our company, our general industry, or both;
- changes in our capital structure, such as future issuances of securities or the incurrence of additional debt;
- the volume of shares of our common stock available for public sale;
- additions or departures of key scientific or management personnel;
- any major change in our board or management;
- changes in accounting practices;
- ineffectiveness of our internal control over financial reporting;
- significant changes in our relationship with Ionis;

- sales of substantial amounts of common stock by our directors, executive officers or significant stockholders or the perception that such sales could occur; and
- general economic and political conditions such as recessions, interest rates, fuel prices, elections, drug pricing policies, international currency fluctuations and acts of war or terrorism.

Broad market and industry factors may materially harm the market price of our common stock irrespective of our operating performance. The stock market in general, and Nasdaq and the market for biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies which investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

***Raising additional funds through debt or equity financing could be dilutive and may cause the market price of our common stock to decline.***

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through cash received under our license agreement with Novartis, a combination of equity offerings and debt financings, and potentially through additional license and development agreements or strategic partnerships with third parties. If we raise additional capital by selling equity or convertible debt securities, these sales could substantially dilute your investment and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. Furthermore, if we issue additional securities, whether equity or debt, or if investors believe we may issue additional securities, the market price of our common stock could decline. Moreover, if we raise capital by issuing debt, we may need to dedicate a substantial portion of our operating cash flow to pay principal and interest on the debt and we would likely need to comply with restrictions on our operations, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely affect our ability to conduct our business. Additional funding may not be available to us on acceptable terms, or at all. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our drug development or commercialization programs.

***If securities analysts do not publish research or reports about our business or if they publish negative reports or downgrade our stock, the price of our common stock could decline.***

The trading market for our common stock will rely in part on the research and reports that industry or financial analysts publish about us, our business, our markets and our competitors. We do not control these analysts. If securities analysts do not cover our common stock after the closing of this offering, the lack of research coverage may adversely affect the market price of our common stock. Furthermore, if one or more of the analysts who do cover us downgrade our stock or if those analysts issue other unfavorable commentary about us or our business, our stock price would likely decline. If one or more of these analysts cease coverage of us or fails to regularly publish reports on us, we could lose visibility in the market and interest in our stock could decrease, which in turn could cause our stock price or trading volume to decline and may also impair our ability to expand our business with existing customers and attract new customers.



***Sales of a substantial number of shares of our common stock by our existing stockholders in the public market may cause our stock price to decline.***

Sales of our common stock in the public market after this offering, or the perception that these sales may occur, could cause the market price of our common stock to decline. Upon the closing of this offering, we will have 64,197,879 shares of common stock outstanding. Of these, only 12,500,000 shares of our common stock sold in this offering, plus any shares sold upon exercise of the underwriters' option to purchase additional shares, will be freely transferable without restriction or additional registration under the Securities Act of 1933, as amended, or the Securities Act. Novartis has agreed that it will not sell any of the Novartis Private Placement Shares until the earlier of January 5, 2020 or six months after we stop developing a drug under our agreement with Novartis. Thereafter, Novartis may only sell a limited number of shares each day. The remaining shares outstanding after this offering will be available for sale, upon the expiration of the 180-day lock-up period beginning from the date of this prospectus, if applicable, subject to volume and other restrictions as applicable under Rule 144 under the Securities Act. At its discretion, Cowen and Company, LLC may release any or all of these shares prior to expiration of the lock-up period. Immediately after the lock-up agreements expire, up to an additional 45,447,879 shares of common stock held by Ionis will be eligible for sale in the public market, all of which will be subject to volume limitations under Rule 144 under the Securities Act. In addition, 9,000,000 shares of common stock that are either subject to outstanding options or reserved for future issuance under our employee benefit plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules, the lock-up agreements and Rule 144 and Rule 701 under the Securities Act. To the extent the holders of these shares sell them into the market or our stockholders believe these sales might occur, the market price of our common stock could decline.

Immediately following the completion of this offering, Ionis will own approximately 70.8% of the total number of shares of our common stock outstanding. Subject to the restrictions described in the paragraph above, future sales of these shares in the public market will be subject to the volume and other restrictions of Rule 144 under the Securities Act for so long as Ionis is deemed to be our affiliate, unless we register the shares to be sold with the Securities and Exchange Commission, or SEC. We cannot predict with certainty whether or when Ionis will sell a substantial number of shares of our common stock. Ionis' sale of a substantial number of shares after this offering, or a perception that such sales could occur, could significantly reduce the market price of our common stock. Upon completion of this offering, except as otherwise described herein, all shares we are offering hereby will be freely tradable without restriction, assuming our affiliates do not hold the shares.

For a further description of restrictions affecting certain shares of our common stock immediately after this offering, see the section entitled "Share Eligible for Future Sale."

***Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.***

We expect we will need significant additional capital in the future to continue our planned operations, including expanded research and development activities, clinical studies, commercial activities and cover costs associated with operating a public company. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to the holders of our common stock, including shares of common stock sold in this offering.



Immediately following this offering, we intend to file a registration statement registering under the Securities Act the shares of our common stock reserved for issuance under the 2015 Akcea Equity Incentive Plan. If the holders of equity securities granted under the 2015 Akcea Equity Incentive Plan sell a large amount of these securities or it is perceived that the holders will sell these securities in the public market, the trading price of our common stock could decline substantially. These sales also could impede our ability to raise future capital.

***You will experience immediate and substantial dilution in the net tangible book value of the shares you purchase in this offering.***

If you purchase shares of our common stock in this offering, you will experience immediate and substantial dilution, as the initial public offering price of our common stock will be substantially greater than the net tangible book value per share of our common stock.

Based on the initial public offering price of \$8.00 per share, if you purchase our common stock in this offering, you will suffer immediate and substantial dilution of approximately \$4.96 per share. Further, giving effect to the same assumptions, investors other than Lonis purchasing common stock in this offering and the concurrent private placement will contribute approximately 39.4% of the total amount invested by stockholders since our inception, but will own only approximately 29.2% of the shares of common stock outstanding after giving effect to this offering, the concurrent private placement and the issuance of shares of common stock to Lonis pursuant to our line of credit. If the underwriters exercise their option to purchase additional shares, or if outstanding options to purchase our common stock are exercised, you will experience additional dilution. For a further description of the dilution that you will experience immediately after this offering, see the section entitled "Dilution."

***We have broad discretion in the use of net proceeds from this offering and the concurrent private placement and may not use them effectively.***

We currently intend to use the net proceeds from this offering and the concurrent private placement to advance the development of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> through additional non-clinical and clinical studies and to support the launch and commercialization of volanesorsen if approved, as well as for development personnel expenses, other development activities, working capital and other general corporate purposes. We may also use the proceeds to acquire and develop other products. For a further description of our use of proceeds from this offering and the concurrent private placement, see the section entitled "Use of Proceeds." Although we currently intend to use the net proceeds in such a manner, we will have broad discretion in the application of the net proceeds. If we do not use these funds effectively, it could harm our ability to continue to develop and commercialize volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development.

***We will incur significant increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.***

As a newly public company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act and rules of the SEC and those of Nasdaq have imposed various requirements on public companies including that we establish and maintain effective disclosure and financial controls. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must evaluate our systems and procedures, and test our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. In addition, we will be required to have our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting the later of our second annual report on Form 10-K or the first annual report on Form 10-K following the date on which we are no longer an emerging growth company. Our compliance with Section 404 of the Sarbanes-Oxley Act will require that we incur substantial accounting expense and expend significant management efforts. We currently do not have an internal audit group, and we will need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. If we do not comply with the requirements of Section 404 in a timely manner, or if we or our independent registered public accounting firm identify deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities, which would require additional financial and management resources.

To successfully implement our business plan and comply with Section 404, we must prepare timely and accurate financial statements. We expect that we will need to continue to improve existing procedures and controls, and implement new operational and financial systems, to manage our business effectively. Any delay in the implementation of, or disruption in the transition to, new or enhanced systems, procedures or controls, may cause our operations to suffer, and we may be unable to conclude that our internal control over financial reporting is effective and to obtain an unqualified report on internal controls from our auditors as required under Section 404 of the Sarbanes-Oxley Act. This, in turn, could have an adverse impact on trading prices for our common stock and could adversely affect our ability to access the capital markets.

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

***We do not expect to pay any cash dividends for the foreseeable future.***

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

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

As described above under “—Risks related to our financial condition and need for additional capital,” we have incurred net losses since our inception and anticipate that we will continue to incur

significant losses for the foreseeable future. Under the Internal Revenue Code of 1986, as amended, or the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under that provision, we can carry forward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits. The amounts of our unused carryovers of NOLs and tax credits as of December 31, 2016, and a description of the valuation allowance we have recorded with respect to those items, are set forth below under “Management’s discussion and analysis of financial condition and results of operations.”

If a corporation undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, Sections 382 and 383 of the Code limit the corporation’s ability to use carryovers of its pre-change NOLs, credits and certain other tax attributes to reduce its tax liability for periods after the ownership change. Our issuance of common stock pursuant to this offering may result in a limitation under Sections 382 and 383, either separately or in combination with certain prior or subsequent shifts in the ownership of our common stock. As a result, our ability to use carryovers of our pre-change NOLs and credits to reduce our future U.S. federal income tax liability may be subject to limitations. This could result in increased U.S. federal income tax liability for us if we generate taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase our state tax liability. The use of our tax attributes will also be limited to the extent that we do not generate positive taxable income in future tax periods.

***We could be subject to securities class action litigation.***

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and resources, which could harm our business.

***Provisions in our amended and restated certificate of incorporation, our amended and restated bylaws and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.***

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and bylaws include provisions that:

- authorize “blank check” preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- specify that only board of directors or holders of greater than 10% of our common stock can call special meetings of our stockholders;
- prohibit stockholder action by written consent once Ionis no longer holds a majority of our voting power;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;

- provide that a majority of directors then in office, even though less than a quorum, may fill vacancies on our board of directors;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated bylaws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated bylaws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management. Further, Novartis has agreed that until Novartis holds less than 7.5% of our outstanding common stock, Novartis will vote the Novartis Private Placement Shares consistent with the recommendation of our board of directors. Although Novartis has retained the right to vote the Novartis Private Placement Shares in its sole discretion in connection with certain enumerated matters, including any transaction which would result in our change of control, our agreement with Novartis may nevertheless delay or prevent changes in our management or board of directors.

In addition, because we are incorporated in the State of Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit your opportunity to receive a premium for your shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our bylaws designate the Court of Chancery of the State of Delaware and federal court within the State of Delaware as the exclusive forum for certain types of actions and proceedings that our stockholders may initiate, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our bylaws provide that, subject to limited exceptions, the Court of Chancery of the State of Delaware and federal court within the State of Delaware will be exclusive forums for any:

- derivative action or proceeding brought on our behalf;
- action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders;
- action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws; or
- other action asserting a claim against us that is governed by the internal affairs doctrine.

Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our bylaws described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

## SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This prospectus includes forward-looking statements, including in the sections entitled “Prospectus Summary,” “Risk Factors,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” and “Business.” These forward-looking statements include, without limitation, statements regarding our industry, business strategy, our future financial condition, and plans and objectives of management for future operations. Terminology such as “may,” “believes,” “intends,” “seeks,” “anticipates,” “plans,” “estimates,” “expects,” “should,” “assumes,” “continues,” “could,” “will,” “future,” “goal,” “potential,” “likely,” and the negative of these or similar terms and phrases are intended to identify forward-looking statements in this prospectus.

Forward-looking statements reflect our current expectations regarding future events, results or outcomes. These expectations may or may not be realized. Although we believe the expectations reflected in the forward-looking statements are reasonable, we can give you no assurance these expectations will be proven correct. Some of these expectations may be based upon assumptions, data or judgments that prove to be incorrect. Actual events, results and outcomes may differ materially from our expectations due to a variety of known and unknown risks, uncertainties and other factors. Although it is not possible to identify all of these risks and factors, they include, among others, the following:

- the success, cost, timing and potential indications of our drug development activities and clinical studies, including our ongoing and later studies of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>;
- our and our partners’ ability to obtain and maintain regulatory approval of our drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, in any of the indications for which we plan to develop them, and any related restrictions, limitations, and/or warnings in the label of an approved drug;
- the future results of ongoing or later clinical studies, including of volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-APOCIII-L<sub>Rx</sub> and AKCEA-ANGPTL3-L<sub>Rx</sub>;
- our ability to obtain orphan drug designation for AKCEA-ANGPTL3-L<sub>Rx</sub> or any of our other drugs, if applicable;
- Novartis’ exercise of its option to license AKCEA-APO(a)-L<sub>Rx</sub> and/or AKCEA-APOCIII-L<sub>Rx</sub> from us and/or Novartis’ ability to effectively develop and commercialize AKCEA-APO(a)-L<sub>Rx</sub> and/or AKCEA-APOCIII-L<sub>Rx</sub> to the extent it exercises its option to license each of these drugs from us;
- our ability to obtain funding for our operations, including funding necessary to complete the clinical studies of any of our drugs;
- our plans to research, develop and commercialize our drugs;
- our ability to attract and retain strategic partners with development, regulatory and commercialization expertise;
- the size and growth potential of the markets for our drugs, and our ability to identify target patient populations and serve those markets, especially for diseases with small patient populations;
- our and our strategic partners’ ability to successfully commercialize our drugs;
- the rate and degree of market acceptance of our drugs;
- our ability to grow our organization and increase the size of our facilities to meet our anticipated growth;
- our ability to develop and maintain sales and marketing capabilities, whether alone or with potential future strategic partners;



- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- the success of competing therapies that are or become available;
- our ability to attract and retain key scientific, commercial or management personnel;
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act;
- our use of the proceeds from this offering and the concurrent private placement;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our expectations regarding our ability to obtain and maintain intellectual property protection for our drugs and our ability to operate our business without infringing on the intellectual property rights of others;
- regulatory developments in the United States and foreign countries; and
- other risks and factors listed under “Risk factors” and elsewhere in this prospectus.

These risks are not exhaustive. Other sections of this prospectus may include additional factors that could adversely affect our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the effects of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

In light of these risks, uncertainties and other factors, the forward-looking statements contained in this prospectus might not prove to be accurate and you should not place undue reliance upon them. All forward-looking statements speak only as of the date made and we undertake no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this prospectus and the documents that we reference in this prospectus, and have filed as exhibits to the registration statement of which this prospectus is a part, with the understanding that our actual future results, levels of activity, performance and achievements may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements. You should also read carefully the factors described in the section of this prospectus captioned “Risk Factors” and elsewhere to better understand the risks and uncertainties inherent in our business and underlying and forward-looking statements. In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

Unless otherwise indicated, information contained in this prospectus concerning our industry, our business, and the markets for treatments of certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions is based on information from various third-party sources. In presenting this information, we have also made assumptions based on such data and other similar sources, and on our knowledge of, and our experience to date in our industry. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of factors, including those described in the “Risk Factors” section. These and other factors could cause results to differ materially from those expressed in the estimates made by third parties and by us.



## USE OF PROCEEDS

We estimate that the net proceeds from the sale of 15,625,000 shares of common stock in this public offering will be approximately \$115.0 million, based on the initial public offering price of \$8.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds from this public offering will be approximately \$132.4 million, based on the initial public offering price of \$8.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. Our net proceeds from the concurrent private placement will be approximately \$50.0 million.

We intend to use the net proceeds of this offering and the concurrent private placement, together with our existing cash, cash equivalents and short-term investments, as follows:

- approximately \$80.0 million to complete planned Phase 3 development for volanesorsen in both FCS and FPL, including regulatory expenses for global marketing authorizations for FCS, and to support the launch and initial commercialization of volanesorsen for FCS, if approved;
- approximately \$30.0 million to complete the planned Phase 2 program for AKCEA-APO(a)-L<sub>Rx</sub>;
- approximately \$16.0 million to complete the planned Phase 2 program for AKCEA-ANGPTL3-L<sub>Rx</sub>;
- approximately \$24.0 million to complete the planned Phase 2 program for AKCEA-APOCIII-L<sub>Rx</sub>; and
- the remainder for development personnel expenses, other development activities, working capital and other general corporate purposes.

We believe that the net proceeds from this offering, the concurrent private placement and our existing cash, cash equivalents and short-term investments, together with interest thereon, will be sufficient to fund our operations for at least the next 12 months, including those activities listed above.

Our expected use of the net proceeds from this offering and the concurrent private placement represents our current intentions based upon our present plans and business condition. We are also undertaking this offering in order to create a public market for our common stock and thereby facilitate access to the public equity markets, increase our visibility in the marketplace, obtain additional capital, and increase our liquidity. Further, we may use a portion of the net proceeds to acquire complementary businesses, products, or technologies, although we have no present commitments or agreements for any specific acquisitions.

The amount and timing of our actual expenditures will depend upon numerous factors, including the results of our development efforts, the results of our ongoing nonclinical and clinical studies or nonclinical and clinical studies we may commence in the future, feedback from regulatory agencies, the timing of approval of any of our drugs and the results of any commercialization efforts. We may find it necessary or advisable to use the net proceeds for other purposes, our management will have broad discretion over the use of the net proceeds from this offering and the concurrent private placement, and investors will be relying on our judgement regarding the application of the aggregate net proceeds.

Until any such net proceeds are used, we intend to invest the net proceeds in short-term, investment-grade, interest-bearing securities.

## **DIVIDEND POLICY**

We have never declared or paid any cash dividends on our common stock or any other securities. We anticipate that we will retain all available funds and any future earnings, if any, for use in the operation of our business and do not anticipate paying cash dividends in the foreseeable future. In addition, future debt instruments may materially restrict our ability to pay dividends on our common stock. Payment of future cash dividends, if any, will be at the discretion of our board of directors after taking into account various factors, including our financial condition, operating results, current and anticipated cash needs, the requirements of then-existing debt instruments and other factors our board of directors deems relevant.

## CAPITALIZATION

The following table sets forth our cash, cash equivalents and short-term investments and capitalization as of March 31, 2017:

- on an actual basis;
- on a pro forma basis to reflect (1) the conversion of all our outstanding Series A convertible preferred stock into an aggregate of 28,884,540 shares of our common stock, which will occur immediately prior to the closing of this offering, and (2) the filing of our amended and restated certificate of incorporation immediately prior to the closing of this offering; and
- on a pro forma as adjusted basis to reflect (1) the transactions described in the preceding clause, (2) payment of our \$15.0 million payable to lonis, which was paid in May 2017, (3) the sale of 15,625,000 shares of common stock in this offering at the initial public offering price of \$8.00 per share, after deducting the underwriting discounts and commissions and estimated unpaid offering expenses payable by us, (4) \$15.0 million of additional borrowing under our line of credit with lonis in May 2017, (5) the issuance of 13,438,339 lonis Conversion Shares, based on the initial public offering price of \$8.00 per share, in full satisfaction of our obligations to lonis pursuant to our line of credit and (6) the issuance of 6,250,000 Novartis Private Placement Shares, based on the initial public offering price of \$8.00 per share.

You should read this table in conjunction with the sections of this prospectus entitled “Selected Consolidated Financial Data,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” and our consolidated financial statements and related notes included elsewhere in this prospectus.

(in thousands, except share and per share data)	As of March 31, 2017		
	Actual	Pro Forma	Pro Forma as Adjusted
			(unaudited)
Cash, cash equivalents and short-term investments . . . . .	\$ 124,522	\$ 124,522	\$ 290,799
Payable to Ionis . . . . .	15,000	15,000	—
Line of credit with Ionis(1) . . . . .	91,541	91,541	—
Stockholders' (deficit) equity:			
Series A convertible preferred stock, \$0.001 par value per share; 28,884,540 shares authorized, issued and outstanding, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted . . . . .	100,000	—	—
Preferred stock, \$0.001 par value per share; no shares authorized, issued or outstanding, actual; 10,000,000 shares authorized, no shares issued or outstanding, pro forma and pro forma as adjusted . . . . .	—	—	—
Common stock, \$0.001 par value per share; 100,000,000 shares authorized, no shares issued and outstanding, actual; 100,000,000 shares authorized, 28,884,540 shares issued and outstanding, pro forma; 100,000,000 shares authorized, 64,197,879 shares issued and outstanding, pro forma as adjusted . . . . .	—	29	64
Additional paid-in capital . . . . .	60,116	160,087	432,559
Accumulated other comprehensive loss . . . . .	(43)	(43)	(43)
Accumulated deficit . . . . .	(235,015)	(235,015)	(235,981)
Total stockholders' (deficit) equity . . . . .	(74,942)	(74,942)	196,599
Total capitalization . . . . .	\$ (74,942)	\$ (74,942)	\$ 196,599

(1) As of March 31, 2017, we borrowed \$91.0 million under our line of credit with Ionis. In May 2017, we borrowed an additional \$15.0 million under our line of credit with Ionis. As of the date of this prospectus, we have borrowed \$106.0 million under our line of credit with Ionis. The outstanding principal and accrued interest under our line of credit will convert into 13,438,339 Ionis Conversion Shares, based on the initial public offering price of \$8.00 per share. The pro forma as adjusted information set forth above reflects this conversion.

The number of shares of our common stock shown as issued and outstanding on a pro forma as adjusted basis in the table above is based on 28,884,540 shares of common stock outstanding as of March 31, 2017, and excludes:

- 5,063,585 shares of common stock issuable upon the exercise of options outstanding as of March 31, 2017, at a weighted-average exercise price of \$6.48 per share;
- 3,436,415 shares of common stock reserved for future issuance under our 2015 equity incentive plan, as amended, of which 1,678,661 shares of common stock are issuable upon exercise of options granted subsequent to March 31, 2017; and
- 500,000 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, which will become effective upon the closing of this offering.

## DILUTION

If you invest in our common stock in this offering, your interest will be diluted to the extent of the difference between the initial public offering price per share and the pro forma as adjusted net tangible book value per share of our common stock immediately after this offering.

Our historical net tangible book value as of March 31, 2017 was \$(76.3) million, or \$(2.64) per share of preferred stock. Our historical net tangible book value per share represents our total tangible assets less our total liabilities divided by the number of shares of preferred stock outstanding as of March 31, 2017.

Our pro forma net tangible book value as of March 31, 2017 was \$(76.3) million, or \$(2.64) per share of common stock. Pro forma net tangible book value per share is determined by dividing our total tangible assets less total liabilities by the number of shares of our common stock outstanding as of March 31, 2017, after giving effect to the conversion of all of our outstanding Series A convertible preferred stock into shares of common stock in connection with the closing of this offering.

Our pro forma as adjusted net tangible book value represents our pro forma net tangible book value, plus (1) payment of our \$15.0 million payable to Ionis, which was paid in May 2017, (2) the effect of the sale of 15,625,000 shares of common stock in this offering at the initial public offering price of \$8.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, (3) \$15.0 million of additional borrowing under our line of credit with Ionis in May 2017, (4) the issuance of 13,438,339 Ionis Conversion Shares, based on the initial public offering price of \$8.00 per share, in full satisfaction of our obligations to Ionis pursuant to our line of credit and (5) the issuance of 6,250,000 Novartis Private Placement Shares, based on the initial public offering price of \$8.00 per share.

Our pro forma as adjusted net tangible book value as of March 31, 2017 was \$195.3 million, or \$3.04 per share of common stock. This amount represents an immediate increase in pro forma as adjusted net tangible book value of \$5.68 per share to Ionis, our sole existing stockholder, and an immediate dilution of \$4.96 per share to investors participating in this offering other than Ionis. We determine dilution per share to investors participating in this offering other than Ionis by subtracting pro forma as adjusted net tangible book value per share after this offering from the assumed initial public offering price per share paid by investors participating in this offering.

Initial public offering price per share . . . . .	\$ 8.00
Historical net tangible book value per share as of March 31, 2017 . . . . .	\$(2.64)
Increase per share attributable to the pro forma transactions described above . . . . .	—
Pro forma net tangible book value per share as of March 31, 2017 . . . . .	\$(2.64)
Increase in pro forma net tangible book value per share attributed to new investors purchasing shares from us in this offering and to Novartis in the concurrent private placement . . . . .	<u>\$ 5.68</u>
Pro forma as adjusted net tangible book value per share after giving effect to this offering and the concurrent private placement . . . . .	<u>\$ 3.04</u>
Dilution in pro forma as adjusted net tangible book value per share to new investors in this offering and to Novartis in the concurrent private placement . . . . .	<u><u>\$ 4.96</u></u>

If the underwriters exercise their option in full to purchase an additional 2,343,750 shares of our common stock in this offering, the pro forma as adjusted net tangible book value per share of our common stock after the offering would be \$3.20 per share, representing an immediate increase to Ionis of \$5.84 per share and immediate dilution of \$4.80 per share to investors participating in this offering other than Ionis.

The following table summarizes as of March 31, 2017, on the pro forma as adjusted basis described above, the number of shares of our common stock, the total consideration and the average price per share (1) paid to us by Ionis, including with respect to the issuance of the Ionis Conversion Shares and shares purchased by Ionis in this offering and (2) to be paid by (i) investors purchasing our common stock in this offering other than Ionis at the initial public offering price of \$8.00 per share, before deducting the underwriting discounts and commissions and estimated offering expenses payable by us and (ii) by Novartis in the concurrent private placement at the initial public offering price of \$8.00 per share.

	Shares Purchased		Total Consideration		Weighted-Average Price Per Share
	Number	Percent	Amount	Percent	
Ionis . . . . .	45,447,879	70.8%	\$231,000,000	60.6%	\$ 5.08
New investors (including Novartis) . . . . .	18,750,000	29.2	150,000,000	39.4	8.00
Total . . . . .	<u>64,197,879</u>	<u>100.0%</u>	<u>\$381,000,000</u>	<u>100.0%</u>	

Except as otherwise indicated, the above discussion and tables assume no exercise of the underwriters' option to purchase additional shares. If the underwriters exercise their option in full, Ionis would own 68.3% and our new investors would own 31.7% of the total number of shares of our common stock outstanding after the completion of this offering.

The foregoing table and calculations above are based on 28,884,540 shares of common stock outstanding as of March 31, 2017, and exclude:

- 5,063,585 shares of common stock issuable upon the exercise of options outstanding as of March 31, 2017, at a weighted-average exercise price of \$6.48 per share;
- 3,436,415 shares of common stock reserved for future issuance under our 2015 equity incentive plan, as amended, of which 1,678,661 shares of common stock are issuable upon exercise of options granted subsequent to March 31, 2017; and
- 500,000 shares of common stock reserved for future issuance under our 2017 employee stock purchase plan, which will become effective upon the closing of this offering.

To the extent that options are exercised, new options or other securities are issued under our equity incentive plans or we issue additional shares of common stock in the future, there will be further dilution to investors participating in this offering. In addition, we may choose to raise additional capital because of market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. If we raise additional capital through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.



## SELECTED CONSOLIDATED FINANCIAL DATA

The following tables set forth our historical financial data as of and for the periods indicated. The selected consolidated financial data for the years ended December 31, 2014, 2015 and 2016 and as of December 31, 2015 and 2016 have been derived from our audited consolidated financial statements included elsewhere in this prospectus. The selected consolidated financial data for three months ended March 31, 2016 and 2017 and as of March 31, 2017 have been derived from our unaudited financial statements included elsewhere in this prospectus. We have prepared the unaudited financial statements on the same basis as the audited financial statements, and the unaudited financial data include, in our opinion, all adjustments, consisting only of normal recurring adjustments, that we consider necessary for a fair presentation of our financial position and results of operations for these periods. Our historical operating results are not necessarily indicative of future operating results and results for the three months ended March 31, 2017 are not necessarily indicative of the results for the full year. We have derived the consolidated financial statements we present in this registration statement by carving out the expenses associated with our drugs from Ionis' consolidated financial statements in accordance with applicable accounting standards and Securities and Exchange Commission regulations.

The following data should be read together with our consolidated financial statements and the related notes thereto, as well as the section entitled “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” included elsewhere in this prospectus.

(in thousands, except share and per share amounts)	Years Ended December 31,			Three Months Ended March 31,	
	2014	2015	2016	2016	2017
<b>Consolidated statement of operations data:</b>					
Research and development revenue under collaborative agreements . . . . .	\$ —	\$ —	\$ —	\$ —	\$ 9,597
Research and development expenses . . . . .	\$ 29,028	\$ 50,885	\$ 68,459	\$ 11,796	\$ 64,794
General and administrative expenses . . . . .	\$ 995	\$ 10,553	\$ 15,053	\$ 4,253	\$ 4,676
Net loss . . . . .	\$ (30,023)	\$ (61,422)	\$ (83,217)	\$ (15,962)	\$ (60,353)
Net loss per share of preferred stock, basic and diluted(1) . . .	\$ (1.04)	\$ (2.13)	\$ (2.88)	\$ (0.55)	\$ (2.09)
Weighted-average shares of preferred stock outstanding, basic and diluted(1) . . . . .	28,884,540	28,884,540	28,884,540	28,884,540	28,884,540
Pro forma net loss per share, basic and diluted (unaudited)(1)(2) . . . . .			\$ (2.88)		\$ (2.09)
Pro forma weighted-average shares of common stock outstanding, basic and diluted (unaudited)(1)(2) . . . . .			28,884,540		28,884,540

- (1) See note 1, *Organization and significant accounting policies*, to our consolidated financial statements appearing elsewhere in this prospectus for further detail on the calculation of basic and diluted net loss per share.
- (2) Pro forma basic and diluted net loss per share represents net loss divided by the pro forma weighted-average shares of common stock outstanding. Pro forma weighted-average shares of common stock outstanding reflects the conversion of all outstanding shares of preferred stock into common stock as though the conversion had occurred on the first day of the relevant period.

(in thousands)	Year Ended December 31,		As of March 31,
	2015	2016	2017
<b>Consolidated balance sheet data:</b>			
Cash, cash equivalents and short-term investments . . . . .	\$ 64,310	\$ 7,857	\$ 124,522
Working capital(1) . . . . .	53,761	(19,344)	51,922
Total assets . . . . .	66,067	10,684	132,981
Payable to Ionis . . . . .	9,198	24,355	15,000
Line of credit with Ionis(2) . . . . .	—	—	91,541
Series A convertible preferred stock . . . . .	100,000	100,000	100,000
Accumulated deficit . . . . .	(91,445)	(174,662)	(235,015)
Stockholders' equity (deficit) . . . . .	55,267	(17,747)	(74,942)

- (1) We define working capital as current assets less current liabilities. See our consolidated financial statements included elsewhere in this prospectus for further details regarding our current assets and current liabilities.
- (2) As of March 31, 2017 we borrowed \$91.0 million under our line of credit with Ionis. In May 2017 we borrowed an additional \$15.0 million. As of the date of this prospectus, we have borrowed \$106.0 million under our line of credit with Ionis. The outstanding principal and accrued interest under our line of credit will convert into 13,438,339 Ionis Conversion Shares, based on the initial public offering price of \$8.00 per share. The pro forma as adjusted information set forth above reflects this conversion.

## MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

*You should read the following discussion in conjunction with the "Selected Consolidated Financial Data" and our consolidated financial statements and related notes thereto included elsewhere in this prospectus. In addition to historical information, this discussion contains forward-looking statements that involve risks, uncertainties and assumptions that could cause actual results to differ materially from management's expectations. We discuss factors that could cause such differences in the sections entitled "Special Note Regarding Forward-Looking Statements and Industry Data" and "Risk Factors." We are not undertaking any obligation to update any forward-looking statements or other statements we may make in the following discussion or elsewhere in this document even though these statements may be affected by events or circumstances occurring after the forward-looking statements or other statements were made.*

### Overview

We are a late-stage biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. Our goal is to become the premier company offering treatments for inadequately treated lipid disorders. We are advancing a mature pipeline of four novel drugs with the potential to treat multiple diseases. Our drugs, volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, are all based on antisense technology developed by Ionis Pharmaceuticals, Inc., or Ionis. Our most advanced drug, volanesorsen, has completed a Phase 3 clinical program for the treatment of familial chylomicronemia syndrome, or FCS, and is currently in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. FCS and FPL are both severe, rare, genetically defined lipid disorders characterized by extremely elevated levels of triglycerides. Both diseases have life-threatening consequences and the lives of patients with these diseases are impacted daily by the associated symptoms. In our clinical program, we have observed consistent and substantial (>70%) decreases in triglycerides and improvements in other manifestations of FCS, including pancreatitis attacks and abdominal pain. We believe the safety and efficacy data from the volanesorsen program demonstrate a favorable risk-benefit profile for patients with FCS. In the third quarter of 2017, we plan to file for marketing authorization for volanesorsen to treat patients with FCS.

We are assembling the infrastructure to commercialize our drugs globally with a focus on lipid specialists as the primary call point. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed lipid disorders will allow us to partner efficiently and effectively with the specialized medical community that supports these patients.

To maximize the commercial potential of two of the drugs in our pipeline, we initiated a strategic collaboration with Novartis Pharma AG, or Novartis, for the development and commercialization of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. After we complete Phase 2 development of each of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, if, on a drug by drug basis, Novartis exercises its option to license a drug, Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize such drug worldwide. We plan to co-commercialize any approved drugs resulting from this collaboration with Novartis in selected markets, under terms and conditions that

we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen.

Our strategic collaboration with Novartis has a potential aggregate transaction value of over \$1.0 billion, plus royalties, which we will generally share equally with Ionis. The calculation of potential aggregate transaction value assumes that Novartis licenses, successfully develops and achieves regulatory approval for both AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> in the United States, Europe and Japan, and that Novartis achieves pre-specified sales targets with respect to both drugs. We received \$75.0 million in an upfront option payment, of which we retained \$60.0 million and paid \$15.0 million as a sublicense fee under our license agreement with Ionis. If Novartis exercises its option for a drug, Novartis will pay us a license fee equal to \$150.0 million for each drug licensed by Novartis. In addition, for AKCEA-APO(a)-L<sub>Rx</sub> we are eligible to receive up to \$600.0 million in milestone payments, 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 \$285.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L<sub>Rx</sub> we are eligible to receive up to \$530.0 million in milestone payments, including \$25.0 million for the achievement of a development milestone, up to \$240.0 million for the achievement of regulatory milestones and up to \$265.0 million for the achievement of commercialization milestones. Further, we are eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of each drug. As a sublicense fee, we will pay to Ionis 50% of the license fees, milestone payments and royalties we receive from Novartis. See “Business—Our Strategic Collaboration with Novartis” and “Certain Relationships and Related Person Transactions” for additional information.

Through 2016, we did not generate revenue and we have incurred net losses in each period since inception. In January 2017, we initiated a strategic collaboration with Novartis and began recognizing revenue under this collaboration. Our revenue for the first quarter of 2017 was \$9.6 million. Our net losses were \$30.0 million, \$61.4 million and \$83.2 million for the years ended December 31, 2014, 2015 and 2016, respectively and \$16.0 million and \$60.4 million for the three months ended March 31, 2016 and 2017, respectively. Our net loss increased in the first quarter of 2017 compared to the same period in 2016 because we incurred \$48.4 million of sublicensing expenses related to our collaboration with Novartis, of which \$33.4 million was non-cash. As of March 31, 2017, we had an accumulated deficit of \$235.0 million. Our net losses have resulted from costs incurred in developing volanesorsen and the other drugs in our pipeline, preparing to commercialize volanesorsen and general and administrative activities associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future as we continue to develop volanesorsen and our other drugs, and seek regulatory approval for and prepare to commercialize volanesorsen. We expect to incur significant expenses to continue to build the infrastructure to support volanesorsen’s commercialization, including manufacturing, marketing, sales and distribution functions. Further, we expect to incur additional costs associated with operating as a public company and in building our internal resources to become less reliant on Ionis.

We have funded our operating activities through a \$100.0 million cash contribution that we received from Ionis in 2015, \$75.0 million from initiating our collaboration with Novartis that we received in the first quarter of 2017 and \$106.0 million in drawdowns under our line of credit with Ionis that we received in the first and second quarters of 2017. We entered into our line of credit agreement with Ionis in January 2017 and it allows us to borrow up to \$150.0 million. The outstanding principal and accrued interest under our line of credit will convert into shares of our common stock at the initial public offering price in connection with the closing of this offering. As of March 31, 2017, we had cash, cash equivalents and short-term investments of \$124.5 million.

We believe that the net proceeds from this offering and the concurrent private placement, together with our existing cash, cash equivalents and short-term investments, will be sufficient to fund our operations for at least the next 12 months. However, we will need to raise additional capital in the future to continue developing the drugs in our pipeline and to commercialize any approved drug, including volanesorsen. We may seek to obtain additional financing in the future through the issuance of our common stock, through other equity or debt financings or through collaborations or partnerships with other companies. We may not be able to raise additional capital on terms acceptable to us, or at all, and any failure to raise capital as and when needed could compromise our ability to execute on our business plan.

### ***Our Relationship with Ionis***

Prior to January 2015, the drugs we licensed from Ionis were part of Ionis' broad pipeline of antisense drugs. Ionis' employees performed all of the development, regulatory and manufacturing activities for these drugs either themselves or through third-party providers. As such, Ionis incurred all of the expenses associated with these activities and reported them in its consolidated financial statements. Ionis formed Akcea as a wholly owned subsidiary to complete development of and commercialize Ionis' drugs to treat lipid disorders. We began business operations in January 2015.

We have derived the consolidated financial statements we present in this registration statement by carving out the expenses associated with our drugs from Ionis' consolidated financial statements in accordance with applicable accounting standards and Securities and Exchange Commission, or SEC, regulations. We have a development, commercialization and license agreement, which we refer to as the license agreement, and a services agreement with Ionis that we entered into in January 2015. We have prepared our consolidated financial statements for 2014 and 2015 as if these agreements with Ionis were in place for the entirety of both annual periods.

We exclusively licensed our pipeline of four novel drugs from Ionis effective in January 2015. Prior to then, Ionis had been advancing these drugs in development and incurring the expenses for those activities. Under our license agreement with Ionis, Ionis continued and is continuing to conduct development, regulatory and manufacturing activities for our drugs and charge us for this work. In this way, we benefit from Ionis' more than 25 years of experience developing and manufacturing antisense drugs. As we build our development, regulatory and manufacturing capabilities and capacity, we expect to assume increasing responsibility for these functions and Ionis' responsibilities will decrease. We expect that our collaborative approach will allow us to build these capabilities and capacity while still working closely with Ionis to help ensure a smooth transition as our drugs advance. Moreover, because Ionis is currently conducting the majority of the development activities for our drugs, we are focused on building the commercial organization and conducting the pre-commercialization activities necessary to support the launch of volanesorsen, if approved, for marketing.

We pay Ionis for the research and development expenses it incurs on our behalf, which include both external and internal expenses in accordance with our license agreement with Ionis. External research and development expenses include costs for contract research organizations, or CROs, costs to conduct nonclinical and clinical studies on our drugs, costs to acquire and evaluate clinical study data such as investigator grants, patient screening fees and laboratory work, and fees paid to consultants. Internal development expenses include costs for the work that Ionis' development employees perform for us. Ionis charges us a full-time equivalent rate that covers personnel-related expenses, including salaries and benefits, plus an allocation of facility-related expenses, including rent, utilities, insurance and property taxes, for those research and development employees who work either directly or indirectly on the development of our drugs. In accordance with the license agreement, we began paying Ionis for external research and development expenses on January 1,



2015 and began paying Ionis for internal research and development expenses on January 1, 2016. All Ionis-provided research and development expenses shown in our consolidated financial statements for 2014 and all internal research and development expenses for 2015 were treated as a capital contribution from Ionis. We also pay Ionis for the active pharmaceutical ingredient, or API, and drug product we use in our nonclinical and clinical studies for all of our drugs. Ionis manufactures the API for us and charges us a price per gram consistent with the price Ionis charges its pharmaceutical partners, which includes the cost for direct materials, direct labor and overhead required to manufacture the API. If we need the API filled in vials or pre-filled syringes for our clinical studies, Ionis will contract with a third party to perform this work and Ionis will charge us for the resulting cost. We began paying Ionis for API that commenced manufacturing during 2015 in accordance with the license agreement. The cost of Ionis-manufactured API that began the manufacturing process prior to 2015 was treated as a capital contribution from Ionis.

Under the services agreement, Ionis also provides us certain services, including, without limitation, general and administrative support services and development support services. We pay Ionis for our share of the internal and external expenses for each of these functions based on our relative use of each function, plus an allocation of facility-related expenses. We began paying Ionis for these services on January 1, 2015 in accordance with the services agreement. All Ionis-provided general and administrative expenses shown in our consolidated financial statements for 2014 were treated as a capital contribution from Ionis. As our business grows and we assume increasing responsibility from Ionis, we will assume direct responsibility for procuring and financing the services we currently receive from Ionis and Ionis' responsibility to provide us with these services will decrease.

We do not pay a mark-up or profit on the external or internal expenses Ionis bills to us or on the cost of the drugs Ionis manufactures for us. Moreover, Ionis only charges us for the portion of its resources that we use. For example, we do not have to pay for a full time person if we only need the person's skills for 50% of the time. In this way, we can increase our headcount as our requirements grow and as we assume increasing responsibility for our drugs from Ionis, rather than building capabilities and capacity in advance of full utilization. We believe that our expenses reasonably reflect the expenses we would have incurred if we had the capabilities and capacity in place to perform this work ourselves. Further, we do not believe that our expenses will increase significantly as we assume development, regulatory, manufacturing and administrative responsibilities from Ionis because we will only assume these functions when we believe we can do so in a cost-efficient manner. See note 3, *Development, Commercialization and License Agreement and Services Agreement with Ionis*, to our consolidated financial statements for more information on our agreements with Ionis.

In addition, Ionis has helped fund our operations through a line of credit agreement for up to \$150.0 million that we entered into in January 2017. As of the date of this prospectus, we had borrowed an aggregate of \$106.0 million pursuant to the line of credit, which together with accrued interest will automatically convert upon completion of this offering into an aggregate of 13,438,339 Ionis Conversion Shares, based on the initial public offering price of \$8.00 per share.

### **Basis of Presentation**

We have derived the consolidated financial statements presented in this registration statement by carving out the expenses associated with our drugs from Ionis' consolidated financial statements in accordance with applicable accounting standards and SEC regulations. These results reflect amounts specifically attributable to our business, including the costs Ionis incurred for the drugs we exclusively licensed from Ionis under our license agreement with Ionis. We also have a services agreement with Ionis that provides us with certain general and administrative and development

support services that became effective in January 2015. However, consistent with accounting regulations, we have assumed that the services agreement was in place in 2014 and we have reflected the related expenses in our results. We have calculated our income tax amounts using a separate return methodology and we have presented these amounts as if we were a separate taxpayer from Ionis in each jurisdiction for each period we present. We have not determined the amount of tax attributes, including net operating losses and tax credit carryovers, that we would retain if we were to deconsolidate for tax purposes from Ionis. An analysis will be performed at a future date, if necessary.

We consider our expense methodology and results to be reasonable for all periods we present. However, our allocations may not be indicative of the actual expenses we would have incurred had we operated as an independent, publicly traded company for the periods we present.

We discuss our agreements with Ionis in note 3, *Development, Commercialization and License Agreement and Services Agreement with Ionis*, to our consolidated financial statements.

### **Revenue**

Through 2016, we did not generate any revenue. In January 2017, we initiated a strategic collaboration with Novartis and began recognizing revenue under this collaboration. During the first quarter of 2017, we recognized \$9.6 million in research and development revenue from our collaboration with Novartis.

### **Operating Expenses**

Our operating expenses consist of research and development expenses and general and administrative expenses, which are described below.

#### *Research and Development Expenses*

Since our inception, we have focused on developing our lead drug, volanesorsen, and the other drugs in our pipeline. Our research and development expenses primarily consist of:

- salaries and related expenses for research and development personnel, including expenses related to stock-based compensation granted to personnel in development functions;
- fees paid to clinical study sites and vendors, including CROs, in connection with our clinical studies, costs of acquiring and evaluating clinical study data such as investigator grants, patient screening fees, laboratory work and statistical compilation and analysis, and fees paid to clinical consultants;
- expenses to acquire clinical study materials, including fees paid to Ionis;
- other consulting fees paid to third parties;
- expenses related to compliance with drug development regulatory requirements;
- travel, facilities, depreciation and amortization, insurance and other expenses; and
- sublicense expenses related to partnered drugs that we licensed from Ionis.

As described above, Ionis charges us for many of the expenses listed above because it is performing many of the development activities for our drugs on our behalf. As we assume increasing responsibility for developing and manufacturing our drugs, we will also increase the amount of expenses that we directly incur. As Ionis' responsibilities decrease, the expenses Ionis charges us will also decrease. We do not expect our overall research and development expenses to change significantly as we transition work from Ionis to us. However, we expect our overall development expenses to increase as we advance our pipeline. This increase will be driven by external costs associated with larger clinical studies as the pipeline moves into the later stages of development,

costs of manufacturing drug product to be used in clinical studies and for validation and regulatory purposes, regulatory costs associated with seeking approval for our drugs and costs associated with expanding our internal development organization to support our pipeline as it advances into the later stages of development.

We expense our research and development costs as we incur them. We do not track research and development expenses by project, with the exception of costs related to volanesorsen. We typically use our employees, consultants and infrastructure resources across all of our projects. Thus, some of our research and development expenses are not attributable to an individual project, but are included in other research and development projects in our results of operations.

Our expenses related to clinical studies are based on estimates of patient enrollment and related expenses at clinical investigator sites as well as estimates for the services received and efforts expended pursuant to contracts with CROs that we may use to conduct and manage our clinical studies on our behalf. We generally accrue expenses related to clinical studies based on contracted amounts applied to the level of patient enrollment and activity. If we modify timelines or contracts based upon changes in the clinical study protocol or scope of work to be performed, we modify our estimates of accrued expenses accordingly on a prospective basis.

Development activities are central to our business model. We cannot determine with certainty the timing of initiation, the duration or the costs to complete current or future clinical studies of our drugs, including volanesorsen. Clinical development timelines, the probability of success and development costs can differ materially from expectations. The cost of clinical studies may vary significantly over the life of a project as a result of differences arising during clinical development, including, among others:

- per patient study costs;
- the number of studies required for approval;
- the number of sites included in the studies;
- the length of time required to enroll suitable patients;
- the number of doses that patients receive;
- the number of patients that participate in the studies;
- the drop-out or discontinuation rates of patients;
- the duration of patient follow-up;
- potential additional safety monitoring or other studies requested by regulatory agencies;
- the number and complexity of analyses and tests performed during the study;
- the phase of development of the drug; and
- the efficacy and safety profile of the drug.

In addition, we expect to incur substantial expenses beyond our present and planned nonclinical and clinical studies to file for marketing authorization for volanesorsen and our other drugs in development, assuming the data are supportive.

We cannot forecast which drugs may be subject to future collaborations, when we will complete such arrangements, if at all, and to what degree such arrangements would affect our development plans and capital requirements.

#### *General and Administrative Expenses*

Our general and administrative expenses consist of salaries and personnel-related costs, including stock-based compensation, for our employees in executive, sales and marketing, and administrative functions. Significant external general and administrative expenses also include costs

associated with the pre-commercialization activities we are performing to prepare to launch volanesorsen, if approved, for marketing. Our general and administrative expenses also include professional fees for accounting, auditing and consulting services, legal services, investor relations, travel and facilities. As described above, Ionis charges us for many of the expenses associated with these functions, including, among others, accounting, human resources, legal and investor relations. We expect to assume responsibility from Ionis for these general and administrative functions as our business grows and we build our internal development and commercialization capabilities. As Ionis' efforts on our behalf decrease, so will the expenses Ionis charges us for those efforts. We expect the increase in expenses we will incur for performing the work ourselves will be largely offset by the decrease in expenses Ionis charges us. We do not expect our overall general and administrative expenses to change significantly as we transition work from Ionis to us.

We anticipate our general and administrative expenses to increase in the future to support our continued development and potential commercialization of volanesorsen and the continued development of the other drugs in our pipeline. In addition, we expect to incur increased expenses associated with expanding our sales and marketing team and commercialization infrastructure to support the launch of volanesorsen. Increases over and above the level of work Ionis is currently performing on our behalf will result in an increase in general and administrative expenses and could include costs related to hiring additional personnel, increased office space, implementing new IT systems and other costs associated with expanding our general and administrative functions. Our general and administrative expenses will also increase due to the costs of operating as a public company. These public company expenses will likely include increased costs related to outside consultants, attorneys, accountants and investor relations personnel, among other expenses.

## **Results of Operations**

### ***Comparison of the Three Months Ended March 31, 2016 and March 31, 2017***

#### *Revenue*

During the first quarter of 2017, we recognized \$9.6 million in research and development revenue from our collaboration with Novartis, which we initiated in January 2017.

#### *Operating Expenses*

Operating expenses were \$16.0 million for the three months ended March 31, 2016 and increased to \$69.5 million for the same period in 2017 as a result of the following:

- We incurred \$48.4 million of sublicensing expenses related to our collaboration with Novartis of which \$33.4 million was non-cash.
- We continued to build our organization and advance the pre-commercialization activities necessary to launch volanesorsen, if approved for marketing.

### Research and Development Expenses

The following table sets forth our research and development expenses for the periods presented:

<u>(in thousands)</u>	<b>Three Months Ended March 31,</b>	
	<b>2016</b>	<b>2017</b>
External volanesorsen expenses . . . . .	\$ 5,337	\$ 5,603
Other external research and development project expenses . . . . .	2,632	4,910
Sublicensing expenses . . . . .	—	48,394
Research and development personnel and overhead expenses . . . . .	2,992	4,287
Total research and development expenses, excluding non-cash stock-based compensation expense . . . . .	10,961	63,194
Non-cash stock-based compensation expense . . . . .	835	1,600
Total research and development expenses . . . . .	<u>\$11,796</u>	<u>\$64,794</u>

Research and development expenses were \$11.8 million for the three months ended March 31, 2016 and increased to \$64.8 million for the same period in 2017. The increase in expenses was primarily due to sublicensing expenses, the majority of which were non-cash, related to our collaboration with Novartis, and the progression of our other drugs in development, including AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-ANGPTL3-L<sub>Rx</sub>.

### General and Administrative Expenses

The following table sets forth our general and administrative expenses for the periods presented:

<u>(in thousands)</u>	<b>Three Months Ended March 31,</b>	
	<b>2016</b>	<b>2017</b>
General and administrative support expenses . . . . .	\$1,205	\$1,578
Pre-commercialization expenses for volanesorsen . . . . .	694	1,518
Total general and administrative expenses, excluding non-cash stock-based compensation expense . . . . .	1,899	3,096
Non-cash stock-based compensation expense . . . . .	2,354	1,580
Total general and administrative expenses . . . . .	<u>\$4,253</u>	<u>\$4,676</u>

General and administrative expenses were \$4.3 million for the three months ended March 31, 2016 and increased slightly to \$4.7 million for the same period in 2017. Our general and administrative expenses increased primarily because we were continuing to build the organization and advance pre-commercialization activities necessary to launch volanesorsen, if approved for marketing, offset in part by reduced non-cash stock-based compensation expense.

### Comparison of the Years Ended December 31, 2015 and December 31, 2016

#### Revenue

Through 2016, we did not generate any revenue.

### Operating Expenses

Operating expenses were \$61.4 million for 2015 and increased to \$83.5 million for 2016 as a result of the following:

- We were conducting more and later-stage clinical studies in 2016 than we were in 2015, including the continuation of our Phase 3 studies for volanesorsen in patients with FCS and FPL.
- Our operating expenses also increased in 2016 as we continued to build our organization and advance the pre-commercialization activities necessary to launch volanesorsen, if approved for marketing.

### Research and Development Expenses

The following table sets forth our research and development expenses for the periods presented:

(in thousands)	Years Ended December 31,	
	2015	2016
External volanesorsen expenses . . . . .	\$23,137	\$38,403
Other external research and development project expenses . . . . .	19,199	11,567
Research and development personnel and overhead expenses . . . . .	7,722	13,913
Total research and development expenses, excluding non-cash stock-based compensation expense . . . . .	50,058	63,883
Non-cash stock-based compensation expense . . . . .	827	4,576
Total research and development expenses . . . . .	<u>\$50,885</u>	<u>\$68,459</u>

Research and development expenses were \$50.9 million for 2015 and increased to \$68.5 million for 2016. The increase in expenses was primarily due to our Phase 3 studies for volanesorsen, which continued to advance, and the progression of our other drugs, including AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-ANGPTL3-L<sub>Rx</sub>.

### General and Administrative Expenses

The following table sets forth our general and administrative expenses for the periods presented:

(in thousands)	Years Ended December 31,	
	2015	2016
General and administrative support expenses . . . . .	\$ 3,424	\$ 5,591
Pre-commercialization expenses for volanesorsen . . . . .	1,460	3,889
Total general and administrative expenses, excluding non-cash stock-based compensation expense . . . . .	4,884	9,480
Non-cash stock-based compensation expense . . . . .	5,669	5,573
Total general and administrative expenses . . . . .	<u>\$10,553</u>	<u>\$15,053</u>

General and administrative expenses were \$10.6 million for 2015 and increased to \$15.1 million for 2016. Our general and administrative expenses increased primarily because we were continuing to build the organization and advance pre-commercialization activities necessary to launch volanesorsen, if approved for marketing.



## Comparison of the Years Ended December 31, 2014 and December 31, 2015

### Revenue

We did not generate any revenue in 2014 or 2015.

### Operating Expenses

Operating expenses were \$30.0 million for 2014 and increased to \$61.4 million for 2015 as a result of the following:

- We were conducting more and later-stage clinical studies in 2015 than we were in 2014, including our Phase 3 program for volanesorsen. In 2015, we incurred a full year of expenses associated with the Phase 3 study of volanesorsen in patients with FCS, which we began in August 2014. We also incurred expenses for the initiation of the Phase 3 study of volanesorsen in patients with FPL, which we began in November 2015. In addition, we incurred expenses for an additional Phase 3 clinical study in patients with high triglycerides.
- Our operating expenses increased in 2015 as we began building our organization and advanced the pre-commercialization activities necessary to launch volanesorsen, if approved for marketing.
- We granted stock options to our employees for the first time during 2015 and therefore for 2014 we did not have any stock-based compensation expense.

### Research and Development Expenses

The following table sets forth our research and development expenses for the periods presented:

(in thousands)	Years Ended December 31,	
	2014	2015
External volanesorsen expenses . . . . .	\$11,455	\$23,137
Other external research and development project expenses . . . . .	11,014	19,199
Research and development personnel and overhead expenses . . . . .	6,559	7,722
Total research and development expenses, excluding non-cash stock-based compensation expense . . . . .	29,028	50,058
Non-cash stock-based compensation expense . . . . .	—	827
Total research and development expenses . . . . .	<u>\$29,028</u>	<u>\$50,885</u>

Research and development expenses were \$29.0 million for 2014, compared to \$50.9 million for 2015. The increase in expenses was primarily due to our Phase 3 studies for volanesorsen, which continued to advance, and the progression of our other drugs, including AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-ANGPTL3-L<sub>Rx</sub>. We granted stock options to our employees for the first time during 2015 and therefore for 2014 we did not have any non-cash stock-based compensation expense.

### General and Administrative Expenses

The following table sets forth our general and administrative expenses for the periods presented:

(in thousands)	Years Ended December 31,	
	2014	2015
General and administrative support expenses . . . . .	\$995	\$ 3,424
Pre-commercialization expenses . . . . .	—	1,460
Total general and administrative expenses, excluding non-cash stock-based compensation expense . . . . .	995	4,884
Non-cash stock-based compensation expense . . . . .	—	5,669
Total general and administrative expenses . . . . .	<u>\$995</u>	<u>\$10,553</u>

General and administrative expenses were \$1.0 million for 2014 and increased to \$10.6 million for 2015. Our general and administrative expenses increased as we continued to build the organization and advance the pre-commercialization activities necessary to launch volanesorsen, if approved for marketing. We granted stock options to our employees for the first time during 2015 and therefore for 2014 we did not have any non-cash stock-based compensation expense.

### Liquidity and Capital Resources

At March 31, 2017 we had cash, cash equivalents and short-term investments of \$124.5 million and stockholders' deficit of \$74.9 million.

We have funded our operating activities through a \$100.0 million cash contribution that we received from Ionis in 2015, \$75.0 million from initiating our collaboration with Novartis that we received in the first quarter of 2017 and \$106.0 million in drawdowns under our line of credit with Ionis that we received in the first and second quarters of 2017. Our line of credit agreement with Ionis allows us to borrow up to \$150.0 million. The outstanding principal and accrued interest under our line of credit will convert into shares of our common stock at the initial public offering price in connection with the closing of this offering, and we will no longer have access to the line of credit following the completion of this offering.

At December 31, 2016, we had working capital of \$(19.3) million, compared to working capital of \$51.9 million at March 31, 2017. Working capital increased in 2017 primarily due to the increase in our cash and short-term investments and a decrease in our payable to Ionis under our development, commercialization and license agreement and services agreement. As of March 31, 2017, our outstanding payable to Ionis was \$15.0 million. In January 2017, we initiated a strategic collaboration with Novartis and we received \$75.0 million in an upfront option payment, of which we retained \$60.0 million and paid Ionis \$15.0 million as a sublicense fee under our license agreement with Ionis, in May 2017. During the first quarter of 2017, we recognized \$9.6 million in research and development revenue from our collaboration with Novartis, which we initiated in January 2017.

We do not currently have any approved drugs and, therefore, we do not expect to generate significant revenue from drug sales unless and until we or our partners obtain regulatory approval for and commercialize volanesorsen or one of our other drugs in development. We anticipate that we will continue to incur losses for the foreseeable future, and we expect the losses to increase as we continue to develop, seek regulatory approval for, and begin to commercialize our drugs. We are subject to all of the risks incident in developing and commercializing new drugs, and we may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that

may adversely affect our business. Upon the completion of this offering, we expect to incur additional costs associated with operating as a public company.

### ***Future Funding Requirements***

We will need to raise additional capital in the future to continue developing the drugs in our pipeline and to commercialize any approved drug, including volanesorsen. We believe that the net proceeds from this offering and the concurrent private placement, together with our existing cash, cash equivalents and short-term investments, will be sufficient to fund our operations for at least the next 12 months. Until such time, if ever, as we can generate substantial product revenue, we may finance our cash needs through revenue received under our strategic collaboration with Novartis and any one or a combination of stock offerings, debt financings, collaborations, licensing arrangements and additional funding from Ionis. In any event, we do not expect to generate revenue from product sales prior to the use of the net proceeds from this offering and the concurrent private placement. We do not have any committed external source of funds and we will no longer have access to our line of credit with Ionis following completion of this offering. Additional capital may not be available on reasonable terms, if at all. To the extent that we raise additional capital through the sale of stock or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include increased fixed payment obligations and covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, declaring dividends, selling or licensing intellectual property rights and other operating restrictions that could adversely affect our ability to conduct our business. If we raise additional funds through collaborations or licensing arrangements with third parties, we may have to relinquish valuable rights to our drugs or grant licenses on terms that may not be favorable to us. If we cannot raise additional funds through stock offerings or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and commercialize our drugs even if we would otherwise prefer to develop and commercialize the drugs ourselves.

Our forecast of the period of time through which our financial resources will be adequate to support our operations involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. The amount and timing of future funding requirements, both near- and long-term, will depend on many factors, including, but not limited to:

- the design, initiation, progress, size, timing, costs and results of our clinical and nonclinical studies;
- the outcome, timing and cost of regulatory approvals by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than, or evaluate clinical endpoints other than, those that we currently expect;
- the number and characteristics of drugs that we may pursue;
- our need to expand our development activities, including our need and ability to hire additional employees;
- the effect of competing technological and market developments;
- the cost of establishing sales, marketing, manufacturing and distribution capabilities for our drugs;
- our strategic collaborators' success in developing and commercializing our drugs;
- our need to add infrastructure, implement internal systems and hire additional employees to operate as a public company; and

- the revenue, if any, generated from commercial sales of our drugs for which we receive marketing authorization, which may be affected by market conditions, including obtaining coverage and adequate reimbursement of our drugs from third-party payors, including government programs and managed care organizations, and competition within the therapeutic class to which our drugs are assigned.

If we cannot expand our operations or otherwise capitalize on our business opportunities because we lack sufficient capital, our business, financial condition and results of operations could be materially adversely affected.

### Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2016, which consist of our operating lease for our office facility. The table provides a breakdown of when our office facility lease obligations become due:

<u>Contractual obligations</u>	Payments due by period (in thousands)		
	Total	Less than 1 year	1 - 2 years
Office facility operating lease payments . . . . .	\$646	\$407	\$239

As of December 31, 2016, we did not have any contractual obligations that extended beyond two years.

The following table shows our contractual obligations as of March 31, 2017:

<u>Contractual obligations</u>	Payments due by period (in thousands)			
	Total	Less than 1 year	1 - 2 years	3 - 5 years
Sublicense fee payable to Ionis . . . . .	\$15,000	\$15,000	\$ —	\$ —
Office facility operating lease payments . . . . .	\$ 1,289	\$ 633	\$635	\$21

The tables above do not reflect the line of credit agreement for up to \$150.0 million we entered into with Ionis in January 2017. As of the date of this prospectus, we have drawn \$106.0 million. The outstanding principal and accrued interest under our line of credit will convert into shares of our common stock at the initial public offering price in connection with the closing of this offering.

Excluding the \$15.0 million sublicense fee payable to Ionis shown in the table above, which we paid in May 2017, we have not included potential milestone payments, sublicense fees and royalties that we may be required to pay Ionis for the license of intellectual property. We have not included these potential obligations in the table above because they are contingent upon the occurrence of future events, and we do not know the timing and likelihood of such potential obligations with certainty.

The table above does not include certain general and administrative and development support services for which we will pay Ionis under our services agreement or obligations under agreements that we can cancel without a significant penalty.

We describe our agreements with Ionis in more detail in note 3, *Development, Commercialization and License Agreement and Services Agreement with Ionis*, to our consolidated financial statements.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2016 and March 31, 2017 for the purchase of services and materials as part of our normal course of business.

## **Other Information**

### ***Recently Issued Accounting Pronouncements***

We describe the recently issued accounting pronouncements that apply to us in note 1 to our consolidated financial statements, *Organization and Significant Accounting Policies*.

### ***Off-balance Sheet Arrangements***

We did not have any off-balance sheet arrangements during the period presented, as defined in the rules and regulations of the SEC.

### ***Quantitative and Qualitative Disclosures about Market Risk***

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We place our cash equivalents and short-term investments with reputable financial institutions. We primarily invest our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or Fitch, respectively. We have established guidelines relative to diversification and maturities that are designed to maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

Our results of operations are subject to foreign currency exchange rate fluctuations as we have a foreign subsidiary, Akcea Therapeutics UK Ltd., or Akcea UK., with a functional currency other than the U.S. dollar. We created Akcea UK to support our initial pre-commercialization activities in Europe, and to serve as a potential entity for future United Kingdom and/or European operations. We translate Akcea UK's functional currency, the British pound sterling, or British pound, to our reporting currency the U.S. dollar. As a result, our financial position, results of operations and cash flows can be affected by market fluctuations in the British pound to U.S. dollar exchange rate which are difficult to predict. However, because Akcea UK currently has limited operations, the effect on fluctuations of the British pound to U.S. dollar exchange rate on our consolidated results is immaterial to our consolidated financial statements. Our business strategy incorporates potentially significant international expansion, particularly in anticipation of approval of volanesorsen, therefore we expect that the impact of foreign currency exchange rate fluctuations may become more substantial in the future.

### **Critical Accounting Policies**

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States, or GAAP. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. In the

following paragraphs, we describe our most significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results. As described below, there are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

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

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities;
- Determining the stock-based compensation expense and valuation assumptions;
- Determining the fair value of our common stock; and
- Determining the appropriate cost estimates for unbilled preclinical and clinical development activities.

Descriptions of these critical accounting policies follow.

### ***Revenue Recognition***

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

Research and development revenue under collaborative agreements

#### *Arrangements with multiple deliverables*

Our strategic collaboration, option and license agreement, or collaboration agreement, with Novartis, which we entered into in January 2017, contains multiple elements, or deliverables, including options to obtain licenses to drugs, research and development services, and manufacturing services. Therefore, we accounted for the collaboration under the multiple deliverables guidance.

#### *Multiple agreements*

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

We entered into the collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. Under the collaboration agreement, we received a \$75.0 million upfront payment. For each drug, we are responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and delivering active pharmaceutical ingredient, or API. Under the collaboration agreement, Novartis has an exclusive option to develop and



commercialize AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. If Novartis exercises an option for one of these drugs, it will pay us a license fee and will assume all further global development, regulatory and commercialization activities for the licensed drug. We are also eligible to receive a development milestone payment, milestone payments if Novartis achieves pre-specified regulatory milestones, commercial milestone payments and tiered royalties on net sales from each drug under the collaboration.

Under the SPA, Novartis purchased 1.6 million shares of Ionis' common stock for \$100.0 million in the first quarter of 2017 and paid a premium over the weighted average trading price at the time of purchase. Additionally, Novartis agreed to purchase up to \$50.0 million of our common stock in a separate private placement concurrent with the completion of this offering at a price per share equal to the initial public offering price, subject to a number of conditions. If we do not complete this offering or a similar offering by the 15 month anniversary of the SPA, or if we complete an offering that does not meet the specified criteria for Novartis to invest, then Novartis is required to purchase \$50.0 million of Ionis' common stock at a premium over the weighted average trading price of Ionis' common stock at the time of purchase.

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

#### *Identifying deliverables and units of accounting*

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

We identified the following four separate units of accounting under the collaboration, each with stand-alone value:

- Development activities for AKCEA-APO(a)-L<sub>Rx</sub>;
- Development activities for AKCEA-APOCIII-L<sub>Rx</sub>;
- API for AKCEA-APO(a)-L<sub>Rx</sub>; and
- API for AKCEA-APOCIII-L<sub>Rx</sub>.

The development activities and the supply of API each have stand-alone value because Novartis or another third party could provide these items without our assistance.

#### *Measurement and allocation of arrangement consideration*

Our Novartis collaboration provides for various types of payments to us including upfront payments, milestone payments, licensing fees, royalties on product sales and payments for the purchase of common stock. We first evaluated the total consideration under both the collaboration agreement and SPA and determined how much of the total consideration was attributable to elements that we are delivering under the collaboration.

We determined that our portion of the allocable arrangement consideration for the Novartis collaboration was \$108.4 million, comprised of the following:

- \$75.0 million from the upfront payment received;
- \$28.4 million for the premium paid by Novartis, which represents the excess of the fair value Ionis received from Novartis' purchase of Ionis' stock at a premium in the first quarter of 2017; and
- \$5.0 million for the potential premium Novartis will pay if Novartis purchases Ionis' stock in the future at a premium.

We will recognize the \$75.0 million upfront payment plus the premium paid by Novartis from its purchase of Ionis' stock and the potential premium if Novartis purchases Ionis' stock in the future as revenue because we are the party providing the services and API under the collaboration agreement.

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

We allocated the consideration based on the relative BESP of each unit of accounting. We estimated the selling price of the development services over the expected period during which we will perform these services. The significant inputs we used to determine the selling price of the development services included:

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

For purposes of determining BESP of the services we will perform and the API we will deliver under our Novartis collaboration, accounting guidance required us to include a markup for a reasonable profit margin.

Based on the units of accounting under the Novartis collaboration, we allocated the \$108.4 million of allocable consideration as follows:

- \$64.0 million for development services for AKCEA-APO(a)-L<sub>Rx</sub>;
- \$40.1 million for development services for AKCEA-APOCIII-L<sub>Rx</sub>;
- \$1.5 million for the delivery of AKCEA-APO(a)-L<sub>Rx</sub> API; and
- \$2.8 million for the delivery of AKCEA-APOCIII-L<sub>Rx</sub> API.

#### *Timing of revenue recognition*

We recognize revenue as we deliver each item under our Novartis collaboration as we provide services and the related revenue is realizable and earned. We also recognizes revenue over time. Our Novartis collaboration agreement includes a development project plan outlining the activities the

agreement requires each party to perform during the collaboration. We estimated our period of performance when the agreement was entered into because the agreement did not clearly define such information. We then recognize revenue from development services ratably over such period. We made estimates of our time to complete our obligations under our Novartis collaboration agreement, and in certain instances the timing of satisfying these obligations may change as the development plans for our drugs progress. If our estimates and judgments change over the course of the Novartis collaboration agreement, it may affect the timing and amount of revenue that we will recognize in future periods. Any changes in estimates are recognized on a prospective basis.

The following are the periods over which we are recognizing revenue for each of our units of accounting under the Novartis collaboration:

- We are recognizing the amount attributed to the development services for AKCEA-APO(a)-L<sub>Rx</sub> over the period of time we are performing the services, currently estimated to be through August 2018;
- We are recognizing the amount attributed to the development services for AKCEA-APOCIII-L<sub>Rx</sub> over the period of time we are performing the services, currently estimated to be through May 2019;
- We will recognize the amount attributed to the AKCEA-APO(a)-L<sub>Rx</sub> API supply when we deliver API to Novartis; and
- We will recognize the amount attributed to the AKCEA-APOCIII-L<sub>Rx</sub> API supply when we deliver API to Novartis.

#### *Milestone payments*

Our Novartis collaboration contains contractual milestone payments that relate to the achievement of pre-specified development, regulatory and commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraphs.

The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

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

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

If a drug achieves marketing authorization, it moves into the commercialization stage, during which we or our partners will market and sell the drug to patients. Although our partner may

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

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

Development milestones in our Novartis collaboration agreement or potential future collaborations may include the following types of events:

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

Regulatory milestones in our Novartis collaboration agreement or potential future collaborations may include the following types of events:

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

Commercialization milestones in our Novartis agreement or potential future collaborations may include the following types of events:

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

We will assess whether a substantive milestone exists at the inception of the collaboration agreement. When a substantive milestone is achieved, we will recognize revenue related to the milestone payment immediately. In evaluating if a milestone is substantive we will consider whether:

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

If any of these conditions are not met, we will not consider the milestone to be substantive and we will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. We have determined that all milestones under our Novartis collaboration are substantive milestones.

#### *Option to license*

When we have a multiple element arrangement that includes an option to obtain a license, we will evaluate if the option is a deliverable at the inception of the arrangement. We do not consider the option to be a deliverable if we conclude that it is substantive and not priced at a significant and incremental discount. We will consider an option substantive if, at the inception of the arrangement, we are at risk as to whether the collaboration partner will choose to exercise its option to obtain the license. In those circumstances, we do not include the associated license fee in the allocable consideration at the inception of the agreement. Rather, we account for the license fee when our partner exercises its option. Under the Novartis collaboration, we concluded that the option to license is a substantive option. Therefore, we did not include any amounts in the initial allocable consideration at the inception of the collaboration. We will recognize any future exercise of an option to license a drug under the Novartis agreement in full in the period in which the option is exercised.

#### **Valuation of Investments**

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term investments as “available-for-sale” and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold. We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investments in equity securities in publicly held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or

professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

### ***Stock-Based Compensation Expense and Valuation Assumptions***

We measure stock-based compensation expense for equity-classified stock option awards based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

Prior to December 2015, Ionis granted our employees options to purchase shares of Ionis' common stock, or Ionis options. In December 2015, we granted our employees holding Ionis options additional options to purchase shares of our common stock, or Akcea options. Subject to service based vesting requirements, the Ionis options only become exercisable if (1) our company is not acquired or if we do not complete a qualified financing transaction, such as an initial public offering, by June 30, 2017 and (2) the employee forfeits his or her Akcea equity. Upon the consummation of any such transaction, our employees would forfeit their rights to the Ionis options that they hold such that under no circumstances would an employee be able to exercise both Ionis options and Akcea options.

We determined the stock-based compensation expense for the Ionis options at the date of grant and recognized compensation expense over the vesting period of the Ionis options. In December 2015, we accounted for the issuance of the Akcea options as a modification to the original grant of the Ionis options because the grant of the Ionis options and Akcea options essentially represented a single stock award as the exercisability provisions of the Ionis options and Akcea options grants were interrelated and mutually exclusive. The total compensation expense measured on the modification date was the sum of the grant date fair value of the Ionis options plus any incremental compensation expense resulting from the grant of the Akcea options.

In 2016, we began concurrently granting Ionis options and Akcea options to our employees. Because the exercisability provisions of the awards are interrelated and mutually exclusive as described above, the fair values of the Ionis options and the Akcea options were determined on the date of grant and the option with the greater fair value is recognized over the vesting period of the awards.

Following the completion of this offering, all outstanding Ionis options granted to our employees will cease to be exercisable and our employees will only hold Akcea options.

We recognize compensation expense for option awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach, also known as the graded-vesting method, an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

We and Ionis value our stock option awards using the Black-Scholes option pricing model. The determination of the grant date fair value of options using an option pricing model is affected principally by the estimated common stock fair value and requires management to make a number of other assumptions, including: the risk-free interest rate, expected dividend yield, expected volatility, expected term, rate of forfeiture and fair value of common stock.



Ionis considered the following factors in valuing options for its common stock granted to our employees:

- *Risk-free interest rate.* Ionis bases the risk-free interest rate assumption on the yields of U.S. Treasury securities with maturities that correspond to the term of the award.
- *Expected dividend yield.* Ionis bases the dividend yield assumption on its history and expectation of dividend payouts. Ionis has not paid dividends in the past and it does not expect to do so in the foreseeable future.
- *Expected volatility.* Ionis uses an average of the historical stock price volatility of Ionis' stock. Ionis computes its historical stock volatility based on the expected term of its awards.
- *Expected term.* The expected term of stock options Ionis has granted represents the period of time that it expects them to be outstanding. Ionis estimates the expected term of options it has granted based on actual and projected exercise patterns.
- *Rate of forfeiture.* Ionis estimates forfeitures at the time of grant and revises its estimates, if necessary, in subsequent periods if actual forfeitures differ from those estimates. It estimates forfeitures based on historical experience. Ionis' historical forfeiture estimates have not been materially different from its actual forfeitures.
- *Fair value of common stock.* Ionis uses the market closing price for its common stock on the date of grant as reported on Nasdaq to determine the fair value of Ionis' common stock on the date of grant.

We considered the following factors in valuing options for our common stock:

- *Risk-free interest rate.* We determine the risk-free interest rate assumption based on the yields of U.S. Treasury securities with maturities that correspond to the term of the award.
- *Expected dividend yield.* We assume a dividend yield of zero as we have not paid dividends in the past and do not expect we will pay dividends on our common stock for the foreseeable future.
- *Expected volatility.* We do not have sufficient history to estimate the volatility of our common stock. We calculate expected volatility based on reported data from selected publicly traded peer companies for which historical information is available. We plan to continue to use a peer group to calculate our volatility until the historical volatility of our common stock is sufficient to measure expected volatility for future option grants.
- *Expected term.* Our expected term estimates represent the period of time that we expect the options to be outstanding. As we do not have historical information, we use the simplified method for estimating the expected term. Under the simplified method, we calculate the expected term as the average time-to-vesting and the contractual life of the options. As we gain additional historical information, we will transition to calculating our expected term based on our exercise patterns.
- *Rate of forfeiture.* We estimate forfeitures based on Ionis' historical rates of forfeiture as we do not have similar historical information for ourselves. We and Ionis are engaged in similar businesses and we believe this is a good estimate of expected forfeitures. As we gain additional historical information, we will transition to using our historical forfeiture rate.
- *Fair value of common stock.* As our common stock has not historically been publicly traded, we estimated the fair value of our common stock. See “—Fair Value of Common Stock” below.

### ***Fair Value of Common Stock***

We granted all options to purchase shares of our common stock with an exercise price per share no less than the fair value per share of our common stock underlying those options on the date of grant. Historically, for all periods prior to this offering, the fair values of the shares of common stock underlying our stock options were estimated on each grant date by our board of directors. Given the absence of a public trading market of our common stock, our board of directors exercised reasonable judgment and considered a number of objective and subjective factors to determine the best estimate of the fair value of our common stock. To determine the fair value of our common stock, our board of directors considered, among other things, contemporaneous valuations of our common stock prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants 2013 Practice Aid, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*, or the Practice Aid. Our board of directors also considered various objective and subjective factors in estimating the fair value of our common stock on the date of grant, including:

- the prices, rights, preferences and privileges of our preferred stock relative to our common stock;
- our business, financial condition and results of operations, including related industry trends affecting our operations;
- the likelihood of achieving a liquidity event, such as an initial public offering or sale of our company, given prevailing market conditions;
- the lack of marketability of our common stock;
- the market performance of comparable publicly traded companies; and
- U.S. and global economic and capital market conditions and outlook.

### ***Enterprise Valuation Methodologies***

Our third party valuation firm prepares our valuations in accordance with the guidelines in the Practice Aid, which prescribes several valuation approaches for setting the value of an enterprise, such as the cost, income and market approaches, and various methodologies for allocating the value of an enterprise to its common stock. The cost approach establishes the value of an enterprise based on the cost of reproducing or replacing the property less depreciation and functional or economic obsolescence, if present. The income approach establishes the value of an enterprise based on the present value of future cash flows that are reasonably reflective of a company's future operations, discounting to the present value with an appropriate risk adjusted discount rate or capitalization rate. The market approach is based on the assumption that the value of an asset is equal to the value of a substitute asset with the same characteristics. Our third party valuation firm uses the income and market valuation approaches to determine our stock price. When applying the income approach, our third party valuation firm uses a discounted cash flow analysis based on our projections. When applying the market approach, our third party valuation firm uses the guideline publicly traded companies method choosing pharmaceutical companies whose business descriptions, including products and/or stage of development, are similar to ours. Our third party valuation firm calculates our enterprise value under each of the income and market approaches and then uses an equal weighting of these two approaches to arrive at our enterprise value.

### ***Methods Used to Allocate Our Enterprise Value to Classes of Securities***

In accordance with the Practice Aid, our third party valuation firm considers the various methods for allocating the enterprise value across our classes and series of capital stock to determine the fair

value of our common stock at each valuation date. The methods the third party valuation firm considers consist of the following:

#### *Current Value Method*

Under the current value method, once the fair value of the enterprise is established, the value is allocated to the various series of preferred and common stock based on their respective seniority, liquidation preference or conversion values, whichever is greatest. This method was considered, but not used in any of the valuations discussed below.

#### *Option Pricing Method*

The option pricing method, or OPM, treats common stock and preferred stock as call options on the total equity value of a company, with exercise prices based on the liquidation preference of the preferred stock. Under this method, the common stock has value only if the funds available for distribution to the stockholders exceed the value of the liquidation preference at the time of a liquidity event such as a merger, sale, or initial public offering, assuming the enterprise has funds available to make a liquidation preference meaningful and collectible by the stockholders. The common stock is modeled as a call option on the underlying equity value at a predetermined exercise price. In the model, the exercise price is based on a comparison with the total equity value, rather than, as in the case of a regular call option, a comparison with a per share stock price. The OPM uses the Black-Scholes option-pricing model to price the call option.

The valuation of our common stock as of January 1, 2015 used the OPM. We applied a discount to the valuation due to the lack of marketability of our stock. We calculated the discount for lack of marketability using the Finnerty model and applied it as applicable to each allocation.

#### *Probability-Weighted Expected Return Method*

The probability-weighted expected return method, or PWERM, considers various potential liquidity outcomes, including in our case an initial public offering, the sale of our company, dissolution and staying private, and assigns probabilities to each outcome to arrive at a weighted equity value.

We performed an updated valuation analysis of our common stock as of January 1, 2017 using a hybrid of the OPM and the PWERM, consistent with how such hybrid method is described in the Practice Aid. We calculated the discount for lack of marketability using the Finnerty model and applied it as applicable to each allocation.

After completion of this offering, we expect to use the market closing price for our common stock as reported on Nasdaq to determine the fair value of our common stock. See note 4, *Stockholders' Equity (Deficit)*, to our consolidated financial statements for additional information regarding our stock-based compensation plans and valuation assumptions.

#### ***Estimated Liability for Research and Development Costs***

We record accrued liabilities related to expenses for which vendors or service providers have not yet billed us. These liabilities are for products or services that we have received and primarily relate to ongoing nonclinical studies and clinical studies. These costs primarily include third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We have drugs in concurrent nonclinical studies and clinical studies at several sites throughout the world. To ensure that we have adequately provided for ongoing nonclinical and clinical research and development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment

of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

### **JOBS Act and Emerging Growth Company Status**

Under Section 107(b) of the Jumpstart our Business Startups Act of 2012, or the JOBS Act, an emerging growth company, or EGC, can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We are in the process of evaluating the benefits of relying on other exemptions and reduced reporting requirements under the JOBS Act. Subject to certain conditions, as an EGC, we intend to rely on certain of these exemptions, including exemptions from the requirement to provide an auditor's attestation report on our system of internal control over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002. We will remain an EGC until the earlier to occur of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of this offering, (b) in which we have total annual gross revenue of at least \$1.07 billion or (c) in which we are deemed to be a "large accelerated filer" under the rules of the SEC, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the prior June 30th and (2) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

## BUSINESS

We are a late stage biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. Our goal is to become the premier company offering treatments for inadequately treated lipid disorders. We are advancing a mature pipeline of four novel drugs with the potential to treat multiple diseases. Our drugs, volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, are all based on antisense technology developed by Ionis Pharmaceuticals, Inc., or Ionis. Our most advanced drug, volanesorsen, has completed a Phase 3 clinical program for the treatment of familial chylomicronemia syndrome, or FCS, and is currently in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. FCS and FPL are both severe, rare, genetically defined lipid disorders characterized by extremely elevated levels of triglycerides. Both diseases have life-threatening consequences and the lives of patients with these diseases are impacted daily by the associated symptoms. In our clinical program, we have observed consistent and substantial (>70%) decreases in triglycerides and improvements in other manifestations of FCS, including pancreatitis attacks and abdominal pain. We believe the safety and efficacy data from the volanesorsen program demonstrate a favorable risk-benefit profile for patients with FCS. In the third quarter of 2017, we plan to file for marketing authorization for volanesorsen to treat patients with FCS. We plan to report data from the Phase 3 study in patients with FPL in 2019. If the data are positive, in 2019 we plan to file for marketing authorization for volanesorsen to treat patients with FPL.

We are assembling the infrastructure to commercialize our drugs globally with a focus on lipid specialists as the primary call point. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed lipid disorders will allow us to partner efficiently and effectively with the specialized medical community that supports these patients. In the future, this global infrastructure may support commercialization of additional drugs within and outside the cardiometabolic arena.

To maximize the commercial potential of two of the drugs in our pipeline, we initiated a strategic collaboration with Novartis Pharma AG, or Novartis, for the development and commercialization of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. As part of our collaboration, we received \$75.0 million in an upfront option payment, of which we retained \$60.0 million and paid \$15.0 million to Ionis as a sublicense fee. After we complete Phase 2 development of each of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, if, on a drug by drug basis, Novartis exercises its option to license a drug and pays us the \$150.0 million license fee to do so, Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize such drug worldwide. We plan to co-commercialize any licensed drug commercialized by Novartis in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen. Overall, we are eligible to receive significant license fees, milestone payments and royalties on sales of each drug Novartis licenses if and when it meets the development, regulatory and sales milestones specified in our agreement. We will share any license fees, milestone payments and royalties equally with Ionis.

Cardiometabolic disease, which includes cardiovascular diseases and metabolic diseases, is the number one cause of death globally. According to the American Heart Association, or AHA,

cardiovascular disease, or CVD, alone accounts for 17.3 million deaths per year globally, a number that the AHA expects to grow to more than 23.6 million by 2030. Further, between 2010 and 2030, total direct medical costs of CVD in the United States alone are projected to triple from \$272.5 billion to \$818.1 billion, according to the AHA. In addition, the number of individuals with metabolic diseases, including diabetes, is rising dramatically. According to a 2010 study published in *Population Health Metrics*, the number of people in the United States with diabetes is projected to grow from approximately 20 million in 2010 to between 46 million and 87 million by 2050. Cardiometabolic risk factors include metabolic syndrome, dyslipidemia, hypertension, obesity and insulin resistance. Lipid risk factors driven by abnormalities in lipid molecules or the processing of lipid molecules contribute to cardiometabolic diseases, with elevated low density lipoprotein cholesterol, or LDL-C, being the most widely recognized. Despite the availability of powerful drugs to lower LDL-C, many people remain at significant risk due to other lipid disorders that are not adequately addressed with current therapies. We believe this treatment gap represents a significant commercial opportunity both in rare and in broader patient populations.

Each of the four drugs in our pipeline targets the specific ribonucleic acid, or RNA, that encodes for a unique protein associated with lipid dysfunction, robustly and selectively inhibiting the production of such protein. These drugs were designed and developed at Ionis, and use Ionis' proprietary antisense technology, which is a potent and specific way of reducing disease-causing proteins. Specifically, our drugs utilize Ionis' generation 2.0+ antisense technology, which is designed for increased potency and enhanced safety characteristics relative to Ionis' generation 2.0 technology. Additionally, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> utilize Ionis' advanced Ligand Conjugated Antisense, or LICA, technology. We believe the enhancements offered by Ionis' LICA technology can provide greater patient convenience by allowing for significantly lower doses and less frequent administration. Our current pipeline includes drugs with the potential to treat patients with a wide range of lipid disorders associated with cardiometabolic disease that other technologies, such as small molecules and antibodies, have not been able to adequately address. Our development approach and commercialization strategy include:

- transforming the lives of patients with serious diseases that are currently inadequately addressed;
- addressing the root cause of each disease;
- maximizing near-term and long-term commercial opportunities; and
- optimizing the efficiency of our sales, marketing and patient support infrastructure by focusing on rare and specialty diseases.

Our clinical pipeline contains novel drugs with the potential to treat inadequately addressed lipid disorders beyond elevated LDL-C that are contributing to the dramatic increase in the incidence of cardiometabolic disease, such as elevated triglycerides, oxidized phospholipids and other lipoproteins such as lipoprotein(a), or Lp(a).

- **Volanesorsen.** We are developing volanesorsen to treat patients with FCS and FPL, orphan diseases characterized by extremely elevated triglyceride levels and a high risk of life-threatening pancreatitis. Patients with FCS and FPL live with daily and chronic manifestations of their disease that negatively affect their lives, including severe, recurrent abdominal pain, cognitive impairment and fatigue. Volanesorsen acts to reduce triglyceride levels by inhibiting the production of apolipoprotein C-III, or ApoC-III, a protein that is a key regulator of triglyceride clearance. We demonstrated in Phase 2 studies that volanesorsen robustly reduced ApoC-III and triglycerides in patients, including in FCS patients, and also had a beneficial impact on insulin sensitivity. We published our findings from the Phase 2 studies with volanesorsen in two publications in the *New England Journal of Medicine*. We



recently completed the Phase 3 program for volanesorsen to treat patients with FCS and are planning to file for regulatory approval in this indication in the third quarter of 2017. The Phase 3 program consisted of two studies, the APPROACH study and the COMPASS study. The APPROACH study, a one year randomized, placebo-controlled study in 66 patients with FCS (average incoming triglycerides of 2,209 mg/dL), achieved its primary endpoint of reduction in triglycerides at three months, with a 77% mean reduction in triglycerides, which translated into a 1,712 mg/dL mean absolute triglyceride reduction in volanesorsen-treated patients. We observed 50% of treated patients achieved triglyceride levels below 500 mg/dL, a commonly accepted threshold for pancreatitis risk. In addition, in the APPROACH study, treatment with volanesorsen was associated with a statistically significant reduced rate of pancreatitis attacks in the group of patients who had the highest incidence of pre-study pancreatitis, and reduced abdominal pain in patients reporting pain before treatment in the study. The triglyceride lowering effects we observed were maintained throughout the 12 month study period. The COMPASS study, a six month randomized placebo-controlled study in 113 patients with very high triglycerides (>500 mg/dL), also achieved its primary endpoint of reduction in triglycerides at three months, with a 71% mean reduction in triglycerides. In the COMPASS study, treatment with volanesorsen was associated with a statistically significant reduction in pancreatitis attacks. The data from the COMPASS and APPROACH studies is consistent with and supports the robust triglyceride lowering we observed in the Phase 2 program for volanesorsen. Overall in our volanesorsen program, data are available for 43 FCS patients treated with volanesorsen, including 33 in the APPROACH study, seven in the COMPASS study and three in Phase 2 studies. In these patients, treatment with volanesorsen was associated with robust reduction of triglyceride levels. The most common adverse event in patients in the studies was injection site reactions, which were mostly mild. In addition, declines in platelet counts were observed in many patients. These platelet declines were not clinically significant in most patients and were generally well managed with monitoring and dose adjustment. Five patients discontinued participation in the APPROACH study due to platelet count declines and four patients discontinued due to other non-serious adverse events, including one case each of sweating and chills, severe fatigue, rash and injection site reaction. In the volanesorsen program as a whole, which includes approximately 280 individuals who received volanesorsen, there were five treatment-related or potentially treatment related serious adverse events, or SAEs. Two of the SAEs were described by the investigators as serum sickness-like reaction and serum sickness, respectively, and both patients fully recovered. The other three SAEs were serious platelet events (grade 4 thrombocytopenia), which resolved without complication after cessation of dosing. We believe our current regimen of platelet monitoring is designed to adequately identify any such potential event to provide patient safety. There have been no deaths and no treatment-related cardiovascular events in any volanesorsen clinical study. The ongoing study of volanesorsen in patients with FPL, called BROADEN, is currently enrolling and we plan to report data from this study in 2019. If the data are positive, in 2019 we plan to file for marketing authorization for volanesorsen to treat patients with FPL. If approved, we plan to globally commercialize volanesorsen ourselves for both FCS and FPL.

The remainder of our pipeline incorporates Ionis' LICA technology that enhances delivery and potency of the drugs.

- **AKCEA-APO(a)-L<sub>Rx</sub>**. We are developing AKCEA-APO(a)-L<sub>Rx</sub> for patients who are at significant risk of CVD because of their elevated levels of Lp(a). AKCEA-APO(a)-L<sub>Rx</sub> inhibits the production of the apolipoprotein(a), or Apo(a), protein, thereby reducing Lp(a). Apo(a) is a form of low density lipoprotein, or LDL, that is very atherogenic (promoting the formation

of plaques in the arteries) and very thrombogenic (promoting the formation of blood clots). We have started a Phase 2b dose-ranging study of AKCEA-APO(a)-L<sub>Rx</sub> in patients with hyperlipoproteinemia(a), a condition in which individuals have levels of Lp(a) greater than 60 mg/dL, and established CVD. We have initiated a strategic collaboration with Novartis for this drug. In this collaboration, we intend to complete the above-referenced Phase 2b study. Following completion of this study, Novartis has an option to license the drug. If Novartis exercises its option to license AKCEA-APO(a)-L<sub>Rx</sub>, Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize AKCEA-APO(a)-L<sub>Rx</sub> worldwide.

- **AKCEA-ANGPTL3-L<sub>Rx</sub>**. We are developing AKCEA-ANGPTL3-L<sub>Rx</sub> to treat multiple lipid disorders. In preclinical studies, an analog of AKCEA-ANGPTL3-L<sub>Rx</sub> inhibited the production of the angiopoietin-like 3, or ANGPTL3, protein in the liver, inhibiting liver fat accumulation and lowering blood levels of triglycerides, LDL-C and very low density lipoprotein cholesterol, or VLDL-C. We are conducting a Phase 1/2 program for AKCEA-ANGPTL3-L<sub>Rx</sub> in people with elevated triglycerides. We reported results for the initial cohort from this study at the AHA meeting in November 2016. In the second half of 2017, we plan to begin a study of AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with hyperlipidemia with metabolic complications including insulin resistance and fatty liver, in which we plan to include patients with nonalcoholic fatty liver disease, or NAFLD, or nonalcoholic steatohepatitis, or NASH. Further, in the second half of 2017, we also plan to study AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with rare hyperlipidemias, including patients with FCS. If we find that AKCEA-ANGPTL3-L<sub>Rx</sub> can effectively lower triglyceride levels in patients with rare hyperlipidemias, including patients with FCS, through a different mechanism of action from volanesorsen, it may represent an opportunity to expand our FCS franchise.
- **AKCEA-APOCIII-L<sub>Rx</sub>**. We are developing AKCEA-APOCIII-L<sub>Rx</sub> to inhibit the production of ApoC-III, the same protein inhibited by volanesorsen, for the broad population of patients who have cardiometabolic disease due to their elevated triglyceride levels. We believe that the enhancements offered by Ionis' LICA technology can provide greater patient convenience by allowing for significantly lower doses and less frequent administration, compared to volanesorsen. We are conducting a Phase 1/2 study of AKCEA-APOCIII-L<sub>Rx</sub> in people with elevated triglycerides and plan to report results from this study in the second half of 2017. We have initiated a strategic collaboration with Novartis for this drug. In this collaboration, we intend to complete the Phase 2 program required to define the appropriate dose and regimen to support a planned cardiovascular outcome study. We plan to initiate a Phase 2b dose-ranging study of AKCEA-APOCIII-L<sub>Rx</sub> in patients with hypertriglyceridemia and established CVD in the second half of 2017 and plan to report data from this study in 2019. At the completion of Phase 2 development, Novartis has an option to license the drug. If Novartis exercises its option to license AKCEA-APOCIII-L<sub>Rx</sub>, Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize AKCEA-APOCIII-L<sub>Rx</sub> worldwide.

## Commercial Approach

We plan to commercialize volanesorsen ourselves globally, with a specialized and comprehensive patient-centric approach. Our orphan-focused commercial model will include a small highly focused salesforce in each country that we are targeting, complemented by medical affairs and patient and healthcare provider services. We plan to provide high touch patient and healthcare provider support through reimbursement assistance, partnerships with specialty pharmacies, injection training, routine platelet monitoring and dietary counseling, which we believe will enable strong integration with treating physicians and facilitate patient uptake and compliance. Reimbursement assistance may include activities such as a reimbursement hotline, patient assistance, co-pay assistance through foundations and insurance verification. We plan to include dedicated case

managers as part of our support team who will work directly with patients, caregivers and healthcare providers to help patients start and stay on therapy. Our global commercial organization is initially focused on our nearest term opportunities with volanesorsen to treat patients with FCS and FPL. Our initial plan is to focus on lipid specialists, specialized endocrinologists and pancreatologists as our primary call points. At the outset, we plan to focus our commercial efforts in the United States, Canada and Europe, and intend to expand over time to other relevant geographies. We believe the relatively small number of specialized physicians treating FCS and FPL patients will allow us to address this market with a nimble, scalable organization. We are currently identifying patients and having them referred to specialists for treatment, which we believe will facilitate successful commercialization. Building awareness of these orphan diseases among not only lipid specialists, but also referring physicians, is a key element of our pre-commercial and commercial plans. We are focused on disease education and market access, with the goal of ensuring that identified patients can most effectively obtain our drugs once commercialized. We are also creating the specialized support required to potentially address other rare disease patient populations.

We plan to commercialize by ourselves any approved drugs with a rare disease or specialty focus. We may enter into additional strategic relationships to commercialize certain of our drugs, particularly in indications with large patient populations, as evidenced by our collaboration with Novartis. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. We also plan to co-commercialize any such drug in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen.

### ***Integrated Development and Commercial Opportunities***

Our drugs are designed to target a variety of lipid disorders, present in both orphan and broad patient populations, which available therapies do not adequately address. We are initially focused on developing volanesorsen and AKCEA-ANGPTL3-L<sub>Rx</sub> for orphan indications that will not require large cardiovascular outcome studies. The smaller, orphan size populations allow a potentially rapid path to commercialization and we believe will allow us to address the commercial market with a nimble, scalable organization. At the same time, we initiated a strategic collaboration with Novartis for AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, allowing development of these drugs in larger populations with the potential to expand the commercial opportunity.

While preparing to commercialize volanesorsen, we are building relationships with specialist physicians. These specialists influence and drive treatment practice across lipid disorders. Accordingly, we believe that we will be able to leverage these relationships in commercializing all of the drugs in our pipeline.

### **Experienced Team**

Our senior management team has extensive experience in successfully developing and commercializing drugs for orphan, endocrine and cardiometabolic diseases through their involvement with major pharmaceutical and biotechnology companies. Our team members have led commercial development activities in orphan diseases, including identifying patients, obtaining orphan pricing and reimbursement and establishing patient support programs to facilitate long-term adherence to drug therapy.

- Paula Soteropoulos, our Chief Executive Officer, has extensive global executive management experience leading commercialization, business and manufacturing operations,

preclinical and clinical development, global strategic alliances and business development in multiple therapeutic areas at companies including Genzyme Corporation and Moderna Therapeutics.

- Dr. Louis St. L. O'Dea, our Chief Medical Officer, is a board-certified physician specializing in endocrinology and metabolism and has successfully led global drug development resulting in thirteen clinical new drug applications, or NDAs, including four for orphan drugs, at several companies including Serono and Radius Health.
- Jeffrey M. Goldberg, our Chief Operating Officer, has led teams through drug development, from discovery to commercialization, as well as business development, manufacturing and supply chain development, global launches and market access at companies including Genzyme, Sanofi S.A. and Proteostasis Therapeutics.

### **Our Relationship with Ionis**

We founded our operations in 2015 as a wholly owned subsidiary of Ionis to develop and commercialize Ionis' drugs to treat lipid disorders. Ionis has funded our expenses to date. We are becoming an independent company building a focus and excellence in development and commercialization. We expect Ionis to remain our principal stockholder for the foreseeable future. Through our relationship with Ionis, we benefit in the following ways:

- We have access to Ionis' innovative generation 2.0+ antisense and LICA technologies for use in our drugs. These technologies allow for precise specificity, favorable dosing properties and no anticipated drug-to-drug interactions.
- We obtained exclusive rights to globally commercialize a robust, mature pipeline of drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development. Our licensed rights also include access to Ionis' intellectual property and expertise to develop, manufacture and commercialize these drugs.
- We have a joint development program that provides us access to Ionis' development and regulatory organization, which has significant expertise in developing drugs to treat patients with lipid disorders. Ionis also provides resources to support our nonclinical and clinical studies.
- We contract with Ionis for support in areas such as legal, finance and human resources, which allows us to be more capital efficient than a typical company of our size and stage of development. This support allows us to focus our efforts and resources on developing and preparing to commercialize our drugs.
- We are not required to make any upfront or pre-commercialization payments to Ionis for drugs we are developing under our development, commercialization and license agreement, as would be typical in a drug license. Our agreement allows us to more efficiently invest our capital in developing and preparing to commercialize our drugs, as we are only required to make milestone and royalty payments post-commercialization or if we grant a sublicense to Ionis' technology.
- As a result of our relationship with Ionis, we may have the opportunity to evaluate additional antisense drugs that may complement our efforts in becoming the premier lipid disease company. For example, Ionis has granted us a right of first negotiation with respect to Ionis development candidates that are designed to treat a rare cardiometabolic disease or a rare inherited metabolic disease.

While we and Ionis intend our relationship to enhance our capabilities, certain terms of our relationship may limit our ability to achieve this expected benefit, including:

- Some of our directors and officers may have a conflict of interest because of their positions with Ionis.

- A Joint Steering Committee, or JSC, sets the development and regulatory strategy for our drugs by mutual agreement. If the JSC cannot come to a mutual agreement, it could delay our ability to develop and commercialize our drugs in development.
- We will need to mutually agree with Ionis on the terms of any additional sublicense to a third party for our drugs in development. If we cannot mutually agree, it could delay or prevent our ability to develop and commercialize our drugs.
- Our agreements prevent Ionis from developing and commercializing drugs targeting ApoC-III, Apo(a) or ANGPTL3 RNA. However, our agreements do not prevent Ionis from developing and commercializing other drugs to pursue the same indications we are pursuing with our drugs.

## Our Strategy

Our goal is to become the premier company offering treatments for previously inadequately treated lipid disorders. The critical components of our business strategy to achieve this goal include the following:

- **Successfully complete development, obtain regulatory approval and commercialize volanesorsen in two orphan indications.** We are focused on rapidly and efficiently developing and commercializing volanesorsen for the treatment of patients with FCS and FPL. There are limited therapeutic options available for these patients, who suffer from serious health issues including heightened risk of premature death. Volanesorsen has completed a Phase 3 clinical program for the treatment of FCS and is currently being investigated in the Phase 3 BROADEN clinical study for the treatment of FPL. We announced data from the APPROACH study in FCS patients in March 2017, and the COMPASS study in patients with high triglycerides in December 2016. We are planning to file for regulatory approval in this indication in the third quarter of 2017 and are preparing for commercialization. Enrollment in the BROADEN study is ongoing and we plan to report data in 2019. If the data are positive, in 2019 we plan to file for marketing authorization for volanesorsen to treat patients with FPL.
- **Pursue indications that drive the greatest near and long term value.** We seek to maximize near-term and long-term commercial opportunities through development paths in both orphan and broader patient populations. We are developing our first drug for the treatment of orphan lipid disorders, which may provide a more rapid path to marketing authorization, nearer-term commercial value and more immediate clinical benefit for the patients with the greatest need and their physicians.
- **Advance multiple novel clinical-stage drugs to commercialization and further grow our pipeline.** Our pipeline of antisense drugs currently contains four clinical-stage novel therapies that we plan to develop and commercialize by ourselves or in conjunction with a partner, such as Novartis, for multiple indications driven by lipid disorders. To sustain our goal of being the premier lipid disorder company, we also plan to actively replenish our pipeline as our current drugs advance through development. For example, we will have the opportunity to potentially license antisense drugs that Ionis advances to treat rare cardiometabolic and rare inherited metabolic diseases under our right of first negotiation that Ionis granted us.
- **Build a leading, fully integrated, independent development and commercialization organization with a specialized and focused global team centered around a high touch patient and physician experience.** As our drug pipeline and commercialization efforts mature, we plan to strategically expand our internal development and regulatory capabilities. Further, we plan to establish our own global commercial organization, which will begin with a small, highly focused commercial organization for volanesorsen. This organization will work closely with the same specialists who are participating in developing



our drugs, including lipid specialists, specialized endocrinologists and pancreatologists. We plan to efficiently manage this organization to access additional markets as our commercial opportunities for both volanesorsen and our other drugs expand into additional patient populations. We plan to provide high touch patient and healthcare provider support through dedicated case management providing reimbursement assistance, as well as by establishing partnerships with specialty pharmacies, injection training, routine platelet monitoring and dietary counseling, which we believe will enable strong integration with treating physicians and facilitate patient uptake and compliance.

- **Create value through strategic collaborations, such as our strategic collaboration with Novartis, to drive drugs to their fullest potential.** We believe that each of the drugs in our pipeline can be developed for multiple lipid disorders, some of which have very large patient populations. In these patient populations, large, costly, late-stage clinical development programs, as well as large sales forces, are required to maximize a drug's commercial potential. As a result, in some cases, partnering with a large organization with global scale may be the optimal approach for maximizing the potential of drugs in these indications. As an example, we have initiated a strategic collaboration with Novartis for AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, to provide us with an opportunity to move rapidly to Phase 3 cardiovascular outcome studies with both drugs, which should enhance the commercial potential of each drug. We also plan to co-commercialize these two drugs in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders.

## **Background**

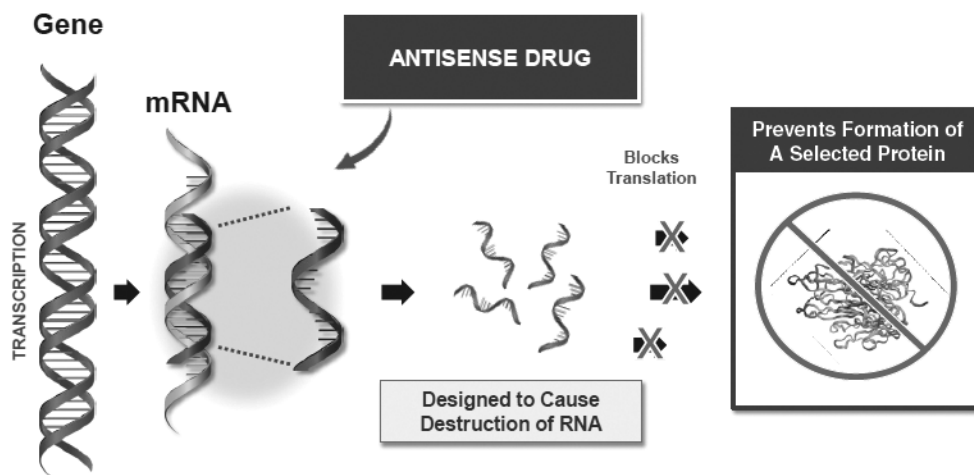
### ***Antisense Technology***

Ionis discovered each of the drugs in our pipeline using its innovative antisense technology platform. Antisense technology is based on the use of synthetic nucleic acid sequences to interrupt the production of a specified protein by targeting the specific corresponding messenger RNA, or mRNA, that encodes that protein. In this way, antisense drugs can be used to reduce the level of proteins that cause, or contribute to, the progression of various diseases. Because there are virtually no undruggable mRNA targets, we believe antisense technology may have broader potential than other small molecule- and antibody-based technologies that target proteins. Furthermore, antisense technology has the potential to target a growing number of disease-related genes more directly and efficiently than other protein-directed modalities. We believe this technology represents an important advance in treating diseases.

The production of a protein starts with a process called transcription, where the instructions for making a protein are transcribed from a gene, or DNA, into mRNA. The cell's protein production process is called translation, and antisense drugs interrupt this process by causing the destruction of



the targeted mRNA and therefore preventing the production of a protein of interest. The graphic below further illustrates the impact of antisense drugs on the production of proteins:



Ionis has made significant improvements in its antisense drug technology in recent years. These include improving the discovery screening processes, which resulted in second-generation drugs, or generation 2.0+ drugs, with better properties. In clinical studies, Ionis observed an approximate two fold increase in potency with generation 2.0+ drugs over Ionis' generation 2.0 drugs. In addition, Ionis observed lower incidences of injection-site reactions and flu-like symptoms compared to Ionis' generation 2.0 drugs.

The unique properties of our antisense drugs provide several potential advantages over traditional drug modalities. These advantages include:

- **Precise specificity.** Our antisense drugs are designed using Ionis' generation 2.0+ screening processes to target single mRNAs, which minimizes or eliminates the possibility of our drugs binding to unintended genetic targets that can cause unwanted side effects.
- **Favorable dosing properties.** We believe our drugs have predictable safety, pharmacokinetic and pharmacodynamic properties based on Ionis' experience with dosing over 6,000 people with antisense drugs to date. Further, our drugs have a relatively long half-life of two to four weeks, which enables volanesorsen to be dosed once weekly and other drugs in our pipeline, which incorporate Ionis' LICA technology, to potentially be dosed once monthly or less frequently. Upon dosing, our drugs distribute well throughout the body, eliminating the need for special formulations or delivery vehicles.
- **No anticipated drug-to-drug interactions.** Because they are nucleic acid-based, we believe our drugs can be used in combination with virtually any existing treatment modality without the risk of drug-to-drug interactions or susceptibility to traditional enzyme degradation or metabolism pathways.

### **LICA Technology**

Ionis' LICA technology conjugates specific chemical structures or molecules to antisense drugs to increase the efficiency of drug uptake in a particular tissue. Three of the drugs in our pipeline contain Ionis' most advanced liver-targeting LICA. Ionis has demonstrated that this technology can further enhance the potency of its drugs. Ionis has designed N-acetyl galactosamine, or GalNAc, LICA that interact specifically with receptors present on the surface of important liver cells to achieve this advanced potency. We observed AKCEA-APO(a)-L<sub>Rx</sub>, the most advanced of our Ionis-designed

LICA drugs, to be more than 30 fold more potent than its unconjugated drug counterpart in a Phase 1 study in patients with elevated levels of Lp(a). We saw a similar increase in potency with AKCEA-ANGPTL3-L<sub>Rx</sub>. We believe that the enhancements offered by Ionis' LICA technology can allow for at least an order of magnitude lower doses and less frequent administration. Therefore, we expect fewer side effects and improved patient convenience when using LICA drugs as compared to their non-LICA forms.

### **Lipid Biology**

Lipids are a group of organic compounds that, together with carbohydrates and proteins, constitute the primary structural material of living cells. Lipids include fatty acids and cholesterol, as well as triglycerides, which are lipids that contain three fatty acid molecules and are a major source of energy. Triglycerides are made in the liver or in the intestine after a person eats foods containing fat.

Because lipids are relatively insoluble in water, they must be transported from one site in the body to another in the form of lipoproteins. Lipoproteins package the lipids in a soluble form and also contain special proteins, known as apolipoproteins, that help regulate the metabolism of the lipids and direct their sub-cellular delivery. Commonly recognized lipoproteins are LDL, which transports cholesterol made in the liver to other tissues and is associated with elevated CVD risk, and high density lipoprotein, or HDL, which transports cholesterol from the body back to the liver. Another important lipoprotein is an aggressive form of LDL known as Lp(a). Lp(a) not only carries the risks of LDL, but also has attached a protein, known as Apo(a), which carries highly-inflammatory oxidized phospholipids. When levels of these lipoproteins are high, they can accumulate in the walls of blood vessels, leading to cholesterol accumulation and inflammation. This cholesterol deposition and inflammation can profoundly damage the arteries and, if continued, cause CVD, which includes heart attacks, strokes and disease of the peripheral arteries in the legs. Lp(a) both accumulates in the artery with higher affinity and has a longer residence time than LDL, causing more thrombogenesis and atherosclerosis.

Triglycerides are also transported by lipoproteins known as triglyceride rich lipoproteins, such as chylomicrons and VLDL. High levels of these lipoproteins can cause metabolic complications such as pancreatitis, insulin resistance and diabetes. When triglyceride levels are too high, remnants, which are cholesterol-containing breakdown products of the triglyceride rich lipoproteins, can also enter the artery and, in a similar manner as LDL, lead to atherosclerosis. Further, the release of excess fatty acids can promote insulin resistance and diabetes.

### **Statistical Significance**

In the description of our clinical trials below, n represents the number of patients in a particular group and p or p-values represent the probability that random chance caused the result (e.g., a p-value = 0.001 means that there is a 0.1% probability that the difference between the placebo group and the treatment group is purely due to random chance). A p-value  $\leq 0.05$  is a commonly used criterion for statistical significance, and may be supportive of a finding of efficacy by regulatory authorities. However, regulatory authorities, including the FDA and EMA, do not rely on strict statistical significance thresholds as criteria for market approval and maintain the flexibility to evaluate the overall risks and benefits of a treatment.

### **Clinical Pipeline**

Cardiometabolic disease, which includes cardiovascular diseases and metabolic diseases such as diabetes, is the number one cause of death globally. According to the AHA, CVD alone accounts for 17.3 million deaths per year globally, a number that the AHA expects to grow to more than 23.6 million by 2030. Further, the number of individuals with metabolic diseases, including diabetes, is also rising dramatically. According to a 2010 study published in *Population Health Metrics*, the number of people in the United States with diabetes is projected to grow from approximately 20 million in 2010 to between 46 million and 87 million by 2050. Cardiometabolic risk factors include metabolic syndrome, dyslipidemia, hypertension, obesity and insulin resistance.

Lipid risk factors driven by abnormalities in lipid molecules contribute to cardiometabolic diseases, with elevated LDL-C being the most widely recognized. Despite the availability of powerful drugs to lower LDL-C, many people remain at significant risk due to other lipid disorders that are not adequately addressed with current therapies. This treatment gap represents a significant commercial opportunity both in orphan and in broader diseases, with new therapies needed.

The following figure illustrates our pipeline:

Drug <sup>(1)</sup>	Preclinical	Phase 1	Phase 2	Phase 3	Preparing Filings	Planned Next Milestone
<b>Volanesorsen</b>	Familial Chylomicronemia Syndrome (FCS)					Filings Q3:17
	Familial Partial Lipodystrophy (FPL)					Phase 3 Data 2019
<b>AKCEA-APO(a)-L<sub>Rx</sub></b> <sup>(2)</sup>	Hyperlipoproteinemia(a) with CV Risk					Phase 2b Data Mid 18
<b>AKCEA-ANGPTL3-L<sub>Rx</sub></b>	Rare Hyperlipidemias					Phase 2 start H2:17
	NAFLD/Metabolic complications					Phase 2 start H2:17
<b>AKCEA-APOCIII-L<sub>Rx</sub></b> <sup>(2)</sup>	Hypertriglyceridemia with CV risk					Phase 1/2 Data H2:17

(1) We have used alternate names for our drugs:

- Volanesorsen also has been known as IONIS-APOCIII<sub>Rx</sub>, ISIS-APOCIII<sub>Rx</sub> and ISIS 304801.
- AKCEA-APO(a)-L<sub>Rx</sub> also has been known as IONIS-APO(a)-L<sub>Rx</sub>, ISIS-APO(a)-L<sub>Rx</sub> and ISIS 681257.
- AKCEA-ANGPTL3-L<sub>Rx</sub> also has been known as IONIS-ANGPTL3-L<sub>Rx</sub>, ISIS-ANGPTL3-L<sub>Rx</sub> and ISIS 703802.
- AKCEA-APOCIII-L<sub>Rx</sub> also has been known as IONIS-APOCIII-L<sub>Rx</sub>, ISIS-APOCIII-L<sub>Rx</sub> and ISIS 678354.

(2) We have initiated a strategic collaboration with Novartis for AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>.

Note: The arrows designate the current phase of development for each drug and indication, and do not represent the extent of completion of the activities we are currently conducting within the phase.

Note: The “L” designation indicates drugs that use Ionis’ LICA technology.

## **Volanesorsen**

### *Overview*

We are developing volanesorsen to treat patients with FCS and FPL, orphan diseases characterized by extremely elevated triglyceride levels and a high risk of life-threatening pancreatitis. Patients with FCS and FPL live with daily and chronic manifestations of their disease that negatively affect their lives, including severe, recurrent abdominal pain and cognitive impairment. Volanesorsen acts to reduce triglyceride levels by inhibiting the production of apolipoprotein C-III, or ApoC-III, a protein that is a key regulator of triglyceride clearance. People who have low levels of ApoC-III or reduced ApoC-III function have lower levels of triglycerides and a lower incidence of CVD.

We believe volanesorsen has the potential to significantly improve the lives of patients with FCS and FPL. We demonstrated in Phase 2 studies that volanesorsen robustly reduced ApoC-III and triglycerides in patients, including in FCS patients, and also had a beneficial impact on insulin sensitivity. Further, in a Phase 2 study, the triglyceride levels in all patients with FCS treated with volanesorsen were reduced to levels below 500 mg/dL, which is a commonly accepted level associated with reduced risk of pancreatitis. We published our findings from the Phase 2 studies with volanesorsen in two publications in the New England Journal of Medicine.

We recently completed the Phase 3 program for volanesorsen to treat patients with FCS and are planning to file for regulatory approval in multiple jurisdictions for this indication in the third quarter of 2017. The Phase 3 program consisted of two studies, the APPROACH study and the COMPASS study. The APPROACH study, a one year randomized, placebo-controlled study in 66 patients with FCS (average incoming triglycerides of 2,209 mg/dL), achieved its primary endpoint of reduction in triglycerides at three months, with a 77% mean reduction in triglycerides ( $p < 0.0001$ ), which translated into a 1,712 mg/dL mean absolute triglyceride reduction in volanesorsen-treated patients ( $p < 0.0001$ ). In the study, we observed that more than 75% of treated patients achieved triglyceride levels below 750 mg/dL, the level at which chylomicron formation begins to become significant, and 50% of treated patients achieved triglyceride levels below 500 mg/dL, a commonly accepted threshold for pancreatitis risk. Each of these results was statistically significant compared to placebo-treated patients, none of whom achieved triglyceride levels below 500 mg/dL. In addition, in the APPROACH study, treatment with volanesorsen was associated with a statistically significant reduced rate of pancreatitis attacks in the group of patients who had a documented history of recurrent pancreatitis attacks in the 5 years prior to the study ( $p = 0.02$ ). Patients treated with volanesorsen who had reported abdominal pain before treatment in the study, also experienced reduced and less frequent pain than their placebo-treated counterparts, a difference that was more evident as the study progressed. The triglyceride lowering effects we observed were maintained throughout the 12 month study period. The COMPASS study, a six month randomized placebo-controlled study in 113 patients with very high triglycerides ( $> 500$  mg/dL), also achieved its primary endpoint of reduction in triglycerides at three months, with a 71% mean reduction in triglycerides. In the COMPASS study, treatment with volanesorsen was associated with a statistically significant reduction in pancreatitis attacks ( $p = 0.036$ ). The data from the COMPASS and APPROACH studies is consistent with and supports the robust triglyceride lowering we observed in the Phase 2 program for volanesorsen. Overall in our volanesorsen program, data are available for 43 patients with FCS treated with volanesorsen, including 33 in the APPROACH study, seven in the COMPASS study and three in Phase 2 studies. In these patients, treatment with volanesorsen was associated with robust reduction of triglyceride levels.

The most common adverse event in the studies was injection site reactions, which were mostly mild. In addition, declines in platelet counts were observed in many patients. These platelet declines were not clinically significant in most patients and were generally well managed with monitoring and dose adjustment. Five patients discontinued participation in the APPROACH study due to platelet count declines and four patients discontinued due to other non-serious adverse events, including one case each of sweating and chills, severe fatigue, rash and injection site reaction. In the volanesorsen program as a whole (approximately 280 individuals who received volanesorsen), there were five treatment-related or potentially treatment-related SAEs. Two of the SAEs were described by the investigators as serum sickness-like reaction and serum sickness, respectively. Both patients fully recovered. The other three SAEs were serious platelet events (grade 4 thrombocytopenia): two in APPROACH and one in the APPROACH open label extension study (where a deviation from the protocol occurred in a patient who was on placebo during APPROACH). These events resolved without incident following cessation of dosing. We believe our current regimen of platelet monitoring is designed to adequately identify any such potential event and to provide patient safety. There have

been no deaths and no treatment-related cardiovascular events in any volanesorsen clinical study. We have now simplified our platelet monitoring program such that monitoring is expected to occur once weekly in all patients on volanesorsen. We believe our greater involvement with physicians and patients, which will be a core focus of the education and support provided by our patient-centric commercial approach, should allow us to better maintain patients on volanesorsen therapy.

Based on what we believe is a favorable risk-benefit profile supported by data from both APPROACH and COMPASS, we are actively preparing our regulatory filings in multiple jurisdictions for volanesorsen in FCS. If approved, we plan to globally commercialize volanesorsen ourselves for both FCS and FPL. The FPL study, called BROADEN, is currently enrolling and we plan to report data from this study in 2019. If the data are positive, in 2019 we plan to file for marketing authorization for volanesorsen to treat patients with FPL. The FDA and EMA have granted orphan drug designation to volanesorsen for the treatment of patients with FCS. The EMA has granted orphan drug designation to volanesorsen for the treatment of patients with FPL and we are in the process of applying for orphan drug status for FPL in the United States.

### *Disease Background*

#### Familial chylomicronemia syndrome

FCS is an inherited orphan disorder and includes type 1 hyperlipoproteinemia, Fredrickson type 1 hyperlipidemia and lipoprotein lipase, or LPL, deficiency. Patients with FCS lack the ability to produce enzymes to clear triglycerides, normally due to one or more loss of function mutations in genes related to triglyceride metabolism, which often results in triglyceride levels higher than 2,000 mg/dL—more than 10 times the normal level. As a result, patients with FCS may suffer from many health issues including severe, recurrent abdominal pain, fatigue and a high risk of life-threatening pancreatitis. In addition, they also suffer from daily conditions that can negatively impact their quality of life including neuropsychiatric symptoms such as memory loss, dementia, mild depression, and cognitive impairment (described as brain fog and forgetfulness), as well as gastrointestinal symptoms including nausea and vomiting. There are no approved therapeutic options for patients with FCS. Standard triglyceride lowering agents, including niacin, fish oils and fibrates, are generally not effective in this patient population. Patients are required to adhere to a very strict, low fat diet, which is extremely burdensome, difficult to maintain, and many patients still experience symptoms, even if they are compliant with the diet. At the 2016 meeting of the European Atherosclerosis Society, Dr. Daniel Gaudet presented natural history data showing that patients with FCS experience substantial fluctuations in platelet counts, sometimes reaching levels as low as 42,000 platelets/ml. We believe these abnormal fluctuations in platelets may be related to the patient's extremely high triglyceride levels. We observed similar fluctuations in patients on placebo in the APPROACH study. By inhibiting the production of ApoC-III, volanesorsen is able to increase triglyceride clearance in FCS patients, reducing their triglyceride levels.

#### Familial Partial Lipodystrophy

People with FPL lack subcutaneous adipose tissue and have abnormal subcutaneous fat distribution. Because FPL patients are unable to store fat properly, they may have triglyceride levels higher than 1,000 mg/dL—more than five times the normal level. Additionally, because FPL patients cannot store excess triglycerides, their triglyceride levels may be extremely elevated after meals. These triglycerides deposit in organs other than normal fat tissue, known as ectopic fat. Ectopic fat accumulation may affect many organs, but primarily leads to health issues in the liver, pancreas and skeletal muscles. As a result, patients with FPL experience an increased incidence of potentially life-threatening pancreatitis, diabetes and extreme insulin resistance, as well as the accumulation of harmful fat in the liver, known as hepatic steatosis. Without enough fat tissue, an FPL patient's metabolic system, which regulates energy use, also falls out of balance. We believe that the robust



triglyceride reduction and the improvements in glucose control and insulin sensitivity we observed in our Phase 2 program support development of volanesorsen for patients with FPL.

### Burden of Disease

Due to the high levels of triglycerides in their blood, patients with FCS and FPL may suffer from many chronic health issues including severe, recurrent abdominal pain, fatigue, high risk of life-threatening pancreatitis and abnormal enlargement of the liver or spleen. When triglyceride levels are very high (greater than 750 mg/dL), they form chylomicrons, which are large particles that can block pancreatic ducts causing an inflammatory cascade that ultimately results in pancreatitis, which is when the organ begins to digest itself. The presence of excess chylomicrons results in blood that is milky-white in appearance due to the excess of these fat particles. Patients with FCS may also experience organ failure and pancreatic necrosis. Some of these debilitating conditions may also result in lengthy hospitalization stays, including time in the intensive care unit. In addition, they also suffer from daily conditions that can negatively impact their quality of life, including neuropsychiatric symptoms such as memory loss, dementia, mild depression, and cognitive impairment (described as brain fog and forgetfulness), as well as gastrointestinal symptoms, including nausea and vomiting. In addition, patients with FCS or FPL have to adhere to a very low fat diet, which is extremely burdensome. Generally, patients try to consume no more than the equivalent of approximately one tablespoon of olive oil per day. As a result of these factors, patients with FCS and FPL are often unable to work, adding to the burden of the disease.

In order to quantify the burden of FCS on patients and the healthcare system, we, in conjunction with patients and clinicians, developed and conducted a global FCS patient survey called IN-FOCUS. We have recruited approximately 170 patients, from multiple countries, to take this survey, and have performed an interim analysis on the first 60 respondents in the United States. In this analysis, we found that pain, fatigue and chronic pancreatitis impact employment and productivity. Other key findings were:

- Age: The majority of respondents were between 20 and 40 years of age, with an average age of 36.
- Diagnosis: Respondents saw an average of five physicians (range: 1-30) before receiving a diagnosis of FCS.
- Symptoms: All of the symptoms described below occurred daily to several times per week and were moderate to very severe in magnitude.
  - Physical symptoms: generalized abdominal pain, bloating, indigestion and lack of appetite as well as generalized weakness and fatigue.
  - Emotional symptoms: anxiety about their overall health due to FCS, constant uncertainty about having an attack of pain or acute pancreatitis at any time, embarrassment about always thinking about and planning for food and anxiety about eating food prepared by someone else.
    - 22% of patients reported feeling depressed, as compared to a 6.7% rate of depression diagnosis in the general adult U.S. population.
    - 33% of patients reported constant anxiety, fear or worry about having an attack of pain or acute pancreatitis at any time.
  - Cognitive symptoms: difficulty concentrating, “brain fog” (i.e. lack of thought clarity), impaired judgment, forgetfulness and recent memory loss.
- Acute Pancreatitis: Lifetime number of pancreatitis attacks ranged from 1-31+, with a mean of 12. Additionally, over their lifetimes, 40% of those hospitalized for acute pancreatitis were readmitted within 30 days of their discharge.
- Diet: The average fat intake of respondents was 20-21g/day. 87% of the respondents noted that managing their diet was extremely challenging.

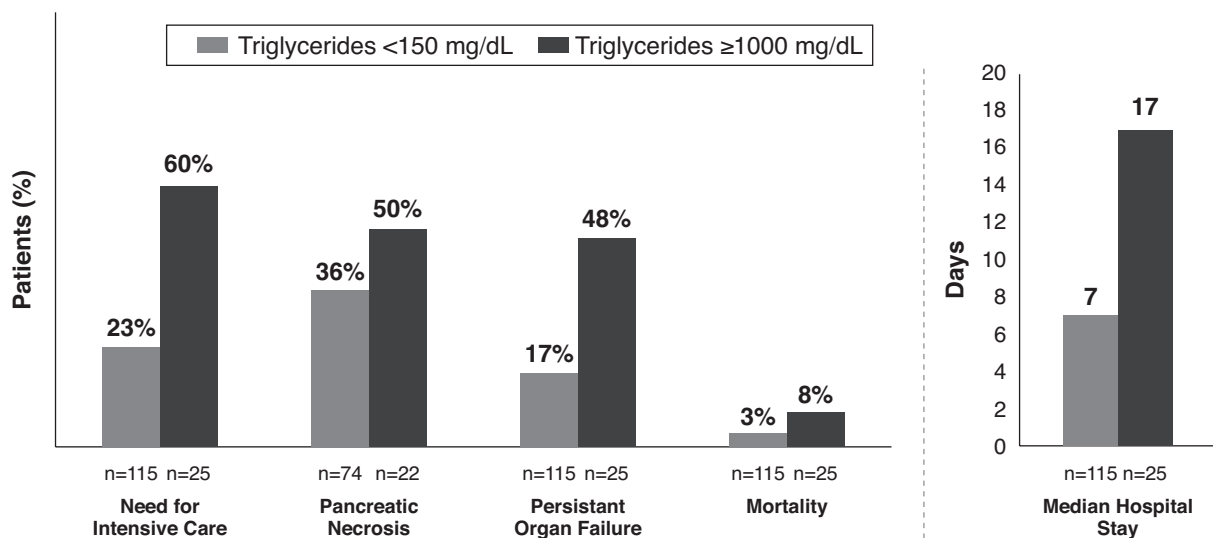


- Employment: Only 22% of patients reported full time employment and 20% were unemployed.
- Absences: Time off from work due to FCS ranged from 0-61+ days with a mean of 30 days in the past 12 months, compared with the U.S. Bureau of Labor Statistics reported average absence of four to five days per calendar year.

Davidson et. al. The burden of familial chylomicronemia syndrome: interim results from the IN-FOCUS study. *Expert Rev Cardiovasc Ther.* May; 15(5): 415-423.

While all the complications of FCS cause patients to have a lower quality of life, pancreatitis is the most serious consequence of the disease. The mortality rate of acute pancreatitis ranges between six and eight percent. Some FCS patients have multiple episodes of acute pancreatitis in a year. Further, pancreatitis attacks generally become more frequent from the teenage years through patients' 30s and 40s. Patients are often admitted to the intensive care unit for further monitoring and hospitalization can last for multiple days. In severe cases, patients can have bleeding into the pancreas, serious tissue damage, infection and cyst formation, as well as damage to other vital organs such as the heart, lungs and kidneys. Further, even a single episode of acute pancreatitis can permanently damage the pancreas, potentially leading to pancreatic deficiency, which can cause digestive issues, oily stool and insulin dependent diabetes. The persistent and often severe abdominal pain that FCS patients may experience may also be indicative of episodes of undiagnosed pancreatitis. There is no specific drug treatment for acute pancreatitis and typically physicians manage pancreatitis with intravenous fluids and pain medications in the hospital.

Acute pancreatitis caused by high triglycerides can result in more days in the hospital, with a risk of irreversible organ damage and premature death. For example, a 2015 study published by Nawaz et. al. in *The American Journal of Gastroenterology*, demonstrated that acute pancreatitis caused by high triglycerides (triglycerides > 1000 mg/dL) can have serious manifestations, and can be substantially worse than pancreatitis from other causes (triglycerides < 150 mg/dL), leading to longer median hospital stays, increased need for intensive care, a higher rate of pancreatic necrosis, more frequent persistent (i.e. >48 hr.) organ failure, and higher rates of mortality, as illustrated in the figure below:



Adapted from Nawaz et. al. 2015

## Volanesorsen Clinical Development

### Phase 2 studies

We conducted a randomized, double-blind, placebo-controlled, dose-ranging, Phase 2 study to evaluate volanesorsen in both untreated patients with fasting triglyceride levels between 350 mg/dL and 2,000 mg/dL (volanesorsen monotherapy cohort) and in patients receiving stable fibrate therapy who had fasting triglyceride levels between 225 mg/dL and 2,000 mg/dL (volanesorsen—fibrate cohort). We randomly assigned eligible patients to receive either volanesorsen, at doses ranging from 100 to 300 mg, or placebo, once weekly for 13 weeks. The primary endpoint was percent change in ApoC-III level from baseline. We designed the secondary endpoints to evaluate the effects of volanesorsen on additional lipid parameters, including triglyceride, LDL and HDL levels. We also investigated pharmacokinetic and pharmacodynamic effects of volanesorsen in these patients. We published the results of this study, which was the first to support the role of ApoC-III as a key regulator of triglyceride metabolism in a wide variety of patients with hypertriglyceridemia, in the *New England Journal of Medicine* in 2015.

A total of 57 patients were treated in the volanesorsen monotherapy cohort (41 received volanesorsen and 16 received placebo), and 28 patients were treated in the volanesorsen—fibrate cohort (20 received volanesorsen and 8 received placebo). The mean baseline triglyceride levels in the two cohorts were 581 mg/dL and 376 mg/dL, respectively. Treatment with volanesorsen resulted in dose-dependent, highly consistent and prolonged decreases in plasma ApoC-III and in triglyceride levels when clinicians administered the drug as a single agent and as an add-on to fibrates.

The tables below illustrate the triglyceride changes in aggregate across the study cohorts:

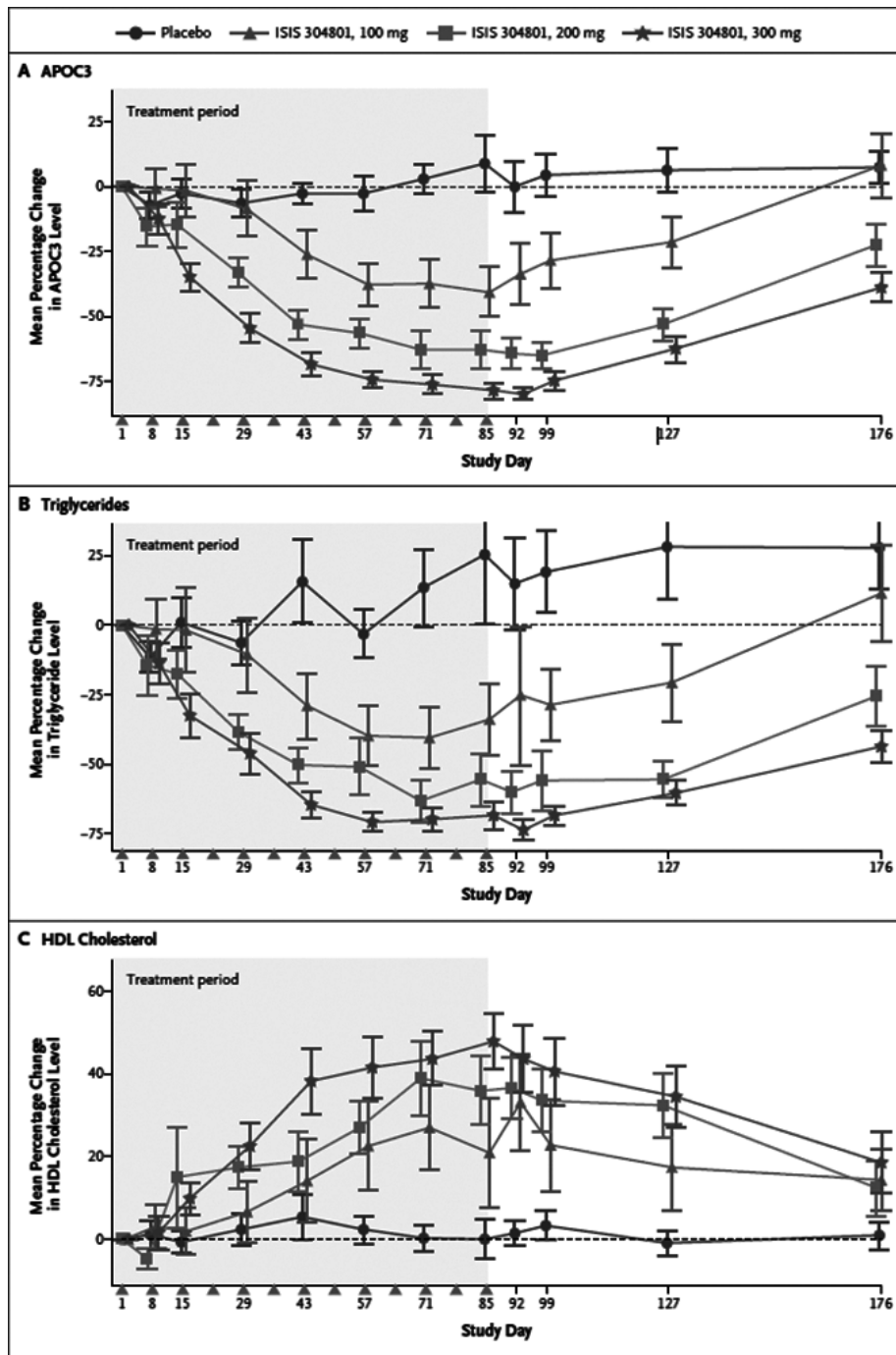
Monotherapy Cohort				
Dose (mg) / Patients(1)	Mean Baseline Triglyceride Level (mg/dL)	Average of Day 85 and 92 Triglyceride Level (mg/dL)	Mean Change (%)	p-value
100 (n=11)	591	312	-31.3	p = 0.015
200 (n=13)	642	235	-57.7	p = 0.001
300 (n=11)	559	139	-70.9	p < 0.001
Placebo (n=16)	523	547	20.1	

Volanesorsen-Fibrate Cohort				
Dose (mg) / Patients(1)	Mean Baseline Triglyceride Level (mg/dL)	Average of Day 85 and 92 Triglyceride Level (mg/dL)	Mean Change (%)	p-value
200 (n=8)	282	141	-51.0	p = 0.008
300 (n=10)	394	134	-63.9	p = 0.002
Placebo (n=8)	457	372	-7.7	

(1) The number of patients in the tables above represent those who completed the study. Additional patients received at least one dose of volanesorsen, but discontinued treatment prior to completing the study.

The graphics below illustrate certain changes as seen in the study published in the New England Journal of Medicine in 2015:

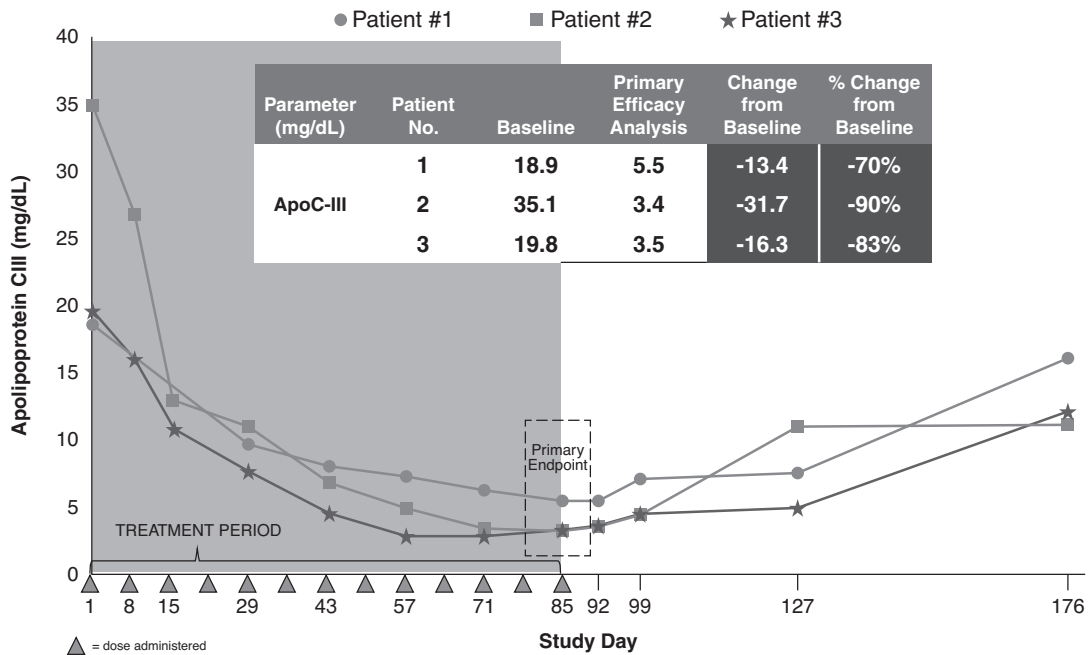


\* The graphics above show the mean percent changes from baseline over time in levels of ApoC-III, triglycerides and HDL cholesterol in the cohort that received ISIS 304801 (which we refer to as volanesorsen) monotherapy or placebo. Triangles indicate dosing days. I bars indicate standard errors. N Engl J Med 2015; 373:438-447.

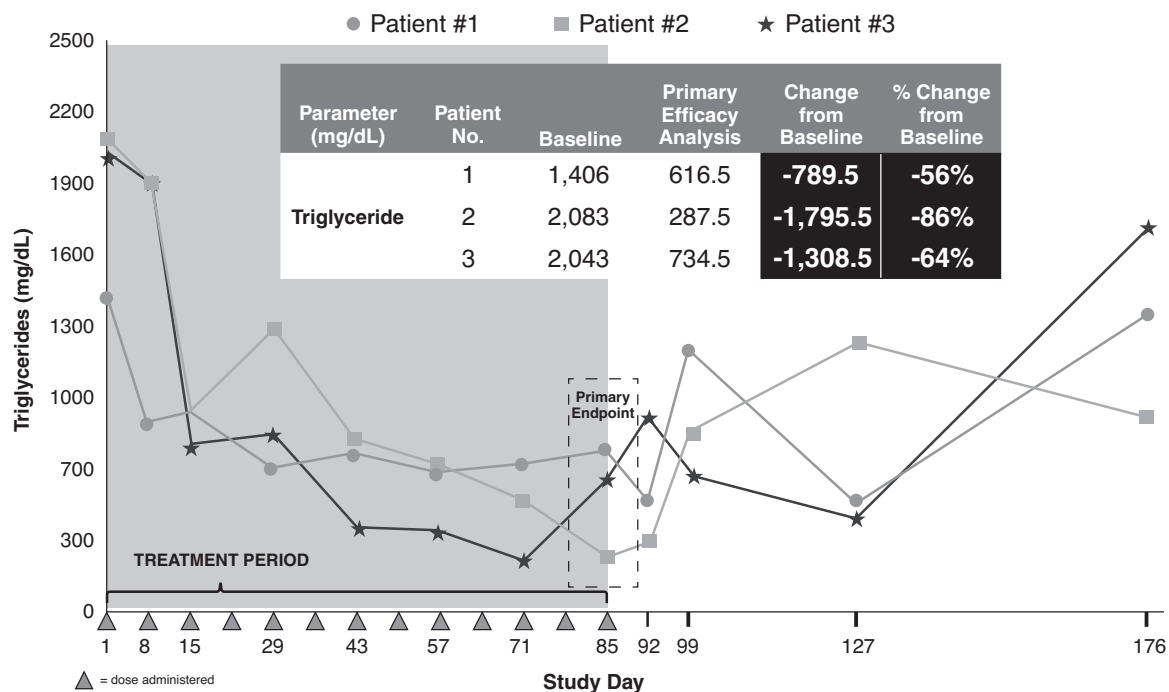
As part of our Phase 2 study, we included an open label cohort using a 300 mg dose of volanesorsen in three FCS patients. At baseline, ApoC-III levels were elevated to two to three times normal levels in all three patients. The patients' ApoC-III levels fell dramatically during the first two weeks of treatment with volanesorsen with reductions in ApoC-III from baseline ranging from approximately 70% to 90%. Baseline triglyceride levels in the three patients varied, but were all above 1,000 mg/dL, and fell rapidly during the first two weeks of treatment in parallel with decreases in ApoC-III, with triglyceride levels in all patients dropping below 500 mg/dL during the study. Triglyceride levels at day 85, the time of the primary analysis, were 56% to 86% lower than at baseline, with absolute reductions of 790 mg/dL to 1,796 mg/dL. The triglyceride levels of patients two and three, who had baseline triglyceride levels greater than 2,000 mg/dL, dropped to as low as 251 mg/dL and 234 mg/dL, respectively, during the treatment period. After cessation of dosing on day 85, triglycerides slowly began to return to pre-treatment levels.

The figures below further illustrate these results:

### Fasting ApoC-III levels in FCS patients treated with 300mg of volanesorsen



## Fasting triglyceride levels in FCS patients treated with 300mg of volanesorsen



We published the results of the FCS patient cohort in the *New England Journal of Medicine* in 2014 because they revealed for the first time that ApoC-III raised triglycerides by two different pathways, one dependent on LPL and one independent of LPL. It was previously thought that ApoC-III raised triglycerides primarily by inhibiting LPL, which breaks down triglycerides in the blood. Patients with FCS lack LPL activity and yet inhibiting ApoC-III with volanesorsen nevertheless dramatically lowered triglyceride levels.

Additionally, in a separate Phase 2 clinical study, patients with high triglycerides and type 2 diabetes treated with volanesorsen achieved significant reductions in ApoC-III and triglyceride levels and exhibited improvements in measures of glucose control and insulin sensitivity. We observed a 57% improvement in insulin sensitivity in patients treated with volanesorsen compared to patients receiving placebo, as measured by a hyperinsulinemic euglycemic clamp, which assesses how well the body uses insulin to remove sugar, in the form of glucose, from the blood and maintain normal blood sugar levels.

No safety concerns were identified in our Phase 2 study that included the monotherapy group, the volanesorsen-fibrate group and the FCS patient group. Injection site reactions occurred with 13% of injections of volanesorsen in the monotherapy group, 15% of injections in the volanesorsen—fibrate group and 46% of injections in the FCS group. These reactions were typically mild redness or pain, did not get worse or lead to other issues and resolved spontaneously. Six of 64 patients (9%) treated with volanesorsen in the Phase 2 program discontinued treatment because of adverse events; there was no apparent relationship between discontinuation and dose. Other safety assessments, including vital signs, electrocardiographic findings and urinalysis results, were clinically unremarkable. In addition, there was no clinical or laboratory evidence of drug-to-drug interactions in patients receiving concomitant medications, including statins, fibrates and glucose-lowering agents.

A similar safety profile was seen in the study involving patients with high triglycerides and type 2 diabetes. No patients treated in this study with volanesorsen discontinued treatment with the study drug because of adverse events.

Phase 3 program and regulatory approach

Volanesorsen has completed a Phase 3 clinical program for the treatment of FCS and is currently in Phase 3 clinical development for the treatment of FPL. The Phase 3 FCS program includes the APPROACH and COMPASS studies. The Phase 3 FPL program includes these same two studies, as well as the BROADEN study.

**APPROACH Study**

APPROACH is a randomized, double-blind, placebo-controlled study of 300 mg of volanesorsen administered by a subcutaneous injection in patients with FCS. Patients in the study were treated once a week for a period of one year. The primary endpoint in this study was percent change, relative to baseline, in fasting triglycerides at three months. In addition, we designed the secondary endpoints to allow us to further evaluate changes in triglycerides, changes in frequency and severity of abdominal pain and pancreatitis, and levels of hepatosplenomegaly, which is abnormal swelling of the spleen and liver. The patients were randomized 1:1, receiving either volanesorsen or placebo. After one year of dosing, patients were eligible to roll over into an open label extension study, in which all patients receive volanesorsen. APPROACH closed enrollment in December 2015 with a total of 66 patients. We dosed the last patient with his/her last dose in the study in January 2017. We reported top-line data from this study in March 2017.

The average incoming triglyceride level of patients in the study was 2,209 mg/dL. Patients treated with volanesorsen experienced clinically meaningful benefits in triglyceride levels, consistent with the Phase 2 experience described above as well as additional disease benefits, as summarized below. For the primary endpoint of the study, volanesorsen-treated patients (n=33) achieved a statistically significant (p<0.0001) mean reduction in triglycerides of 77% from baseline after three months of treatment, compared to a mean increase of 18% in placebo-treated patients (n=33). This represented a mean absolute reduction of 1,712 mg/dL in treated patients.

- The treatment effect was maintained over the 52-week treatment period.
- 50% of the treated patients achieved triglyceride levels less than 500 mg/dL after three months of treatment, a commonly accepted threshold for pancreatitis risk. By comparison, none of the placebo-treated patients achieved this level at the analysis time points (p<0.003). Additionally, 76.7% of the treated patients, as compared to 9.7% of the placebo-treated patients (p=0.0001), achieved triglyceride levels less than 750 mg/dL after three months of treatment, a level above which chylomicron formation begins.
- A statistically significant reduction in abdominal pain was observed in volanesorsen-treated patients compared to placebo-treated patients (p=0.02) who reported abdominal pain before treatment in the study.
- Volanesorsen-treated patients who had a documented history of recurrent pancreatitis attacks in the five years prior to the study experienced no attacks during the 52-week treatment period (p=0.02) as compared to the placebo. Further details are shown in the figure below:

	Placebo		Volanesorsen	
	Patients	Events	Patients	Events
Patients with Multiple Adjudicated Events in Past 5 Years . . . . .	4	17	7	24
Events During Study . . . . .	3	4	0	0
p-value . . . . .	p = 0.02			



The most common adverse event in the volanesorsen-treated group of patients was injection site reactions, which were mostly mild. In addition, declines in platelet counts were observed in many patients. These platelet declines were not clinically significant in most patients and were generally well managed with monitoring and dose adjustment, although five patients discontinued treatment with volanesorsen due to declines in platelet count. Five patients discontinued participation in the APPROACH study due to platelet count declines and four patients discontinued due to other non-serious adverse events, including one case each of sweating and chills, severe fatigue, rash and injection site reaction. In the volanesorsen Phase 3 program, serious platelet events (grade 4 thrombocytopenia) occurred in a total of three volanesorsen-treated patients: two in APPROACH and one in the APPROACH open label extension study (where a deviation from the protocol occurred in a patient who was on placebo during APPROACH). These events resolved without incident following cessation of dosing. In the study, there were no treatment-related liver adverse events, including no increases in liver fat. There were no treatment-related renal adverse events. There were no deaths and no treatment-related cardiovascular events in the study. We have now simplified our platelet monitoring program such that monitoring is expected to occur once weekly in all patients on volanesorsen. We believe our greater involvement with physicians and patients, which will be a core focus of the education and support provided by our patient-centric commercial approach, should allow us to better maintain patients on volanesorsen therapy.

### **COMPASS Study**

COMPASS is a randomized, double-blind, placebo-controlled Phase 3 study of 300 mg of volanesorsen administered by subcutaneous injection in patients with elevated triglyceride levels (greater than 500 mg/dL). Patients in the study were dosed once a week for a period of six months. The primary endpoint is percent change, relative to baseline, in fasting triglycerides at week 13. We designed the secondary endpoints to allow us to further evaluate changes in triglycerides, incidence of pancreatitis and parameters associated with insulin resistance and diabetes. The patients were randomized 2:1, receiving either volanesorsen or placebo. We completed enrollment in this study in May 2016 with 113 patients dosed. We dosed the last patient with his/her last dose in the study in November 2016.

In December 2016, we announced that the COMPASS study met its primary endpoint. The average incoming triglyceride level of patients in the study was 1,261 mg/dL. Patients treated with volanesorsen experienced clinically meaningful benefits in triglyceride levels, consistent with the Phase 2 experience described above, and as summarized below:

- For the primary endpoint of the study, volanesorsen-treated patients (n=75) achieved a statistically significant ( $p<0.0001$ ) mean reduction in triglycerides of 71% from baseline after 13 weeks of treatment, compared with a mean reduction of 0.9% in placebo-treated patients (n=38). This represented a mean absolute reduction of 869 mg/dL in treated patients. The treatment effect observed was maintained through the end of the 26 week treatment period.
- In a subset of seven patients with FCS, whose average incoming triglyceride level was 2,280 mg/dL, volanesorsen-treated patients (n=5) achieved a mean reduction in triglycerides of 73% from baseline after 13 weeks of treatment, compared with a mean increase of 70% in placebo-treated patients (n=2). This represented a mean absolute reduction of 1,511 mg/dL in treated patients. The treatment effect observed was maintained through the end of the 26 week treatment period. None of the reductions in triglyceride levels in the FCS group were statistically significant.
- In addition, 82% of patients treated with volanesorsen, including three of the volanesorsen-treated FCS patients, achieved triglyceride levels less than 500 mg/dL, a commonly

accepted threshold for pancreatitis risk, after 13 weeks of treatment, compared to 14% of placebo-treated patients ( $p < 0.0001$ ).

- Further, we observed a statistically significant reduction in pancreatitis events with volanesorsen treatment compared to placebo ( $p = 0.036$ ), with 5 pancreatitis events in the placebo-treated cohort and no pancreatitis events in the volanesorsen-treated cohort during the treatment period.

The most common adverse event in the volanesorsen-treated group of patients was injection site reactions, which were mostly mild. In this study, 13% of treated patients discontinued treatment due to injection site reactions and 7% of treated patients discontinued treatment for other adverse events. None of the FCS patients in the study discontinued. There were no deaths or cardiovascular events in the study. In addition, there were no serious platelet events in the study. There was one potentially related serious adverse event in the drug-treated arm. This was a report of serum sickness that occurred two weeks after the last study dose and resolved.

### **BROADEN Study**

BROADEN is a randomized, double-blind, placebo-controlled study of 300 mg of volanesorsen administered by a subcutaneous injection in patients with FPL. Patients in the study will be dosed once weekly for a period of one year. The primary endpoint is the percent change, relative to baseline, in fasting triglycerides at week 13. We designed the secondary endpoints to allow us to further evaluate changes in triglycerides, rates of pancreatitis, parameters associated with insulin resistance and diabetes, and changes in liver fat. The patients are randomized 1:1, receiving either volanesorsen or placebo. After one year of dosing, patients are eligible to roll over into an open label extension period in which all patients will receive volanesorsen. We treated the first patient in late 2015 and plan to complete enrollment by the end of 2017 with approximately 60 patients. We plan to report results from the BROADEN study in 2019. If the data are positive, in 2019 we plan to file for marketing authorization for volanesorsen to treat patients with FPL.

### **Volanesorsen Clinical Data Summary**

In both APPROACH and COMPASS, we saw reductions in rates of pancreatitis, one of the most important and impactful symptoms of FCS, in patients treated with volanesorsen. The table below describes the number of pancreatitis attacks in each study, and also shows the combined rate of pancreatitis across both studies. While the reduction in the total number of pancreatitis attacks in APPROACH was not statistically significant due to the small sample size, both COMPASS ( $p = 0.036$ ) and the combined data ( $p = 0.019$ ) showed statistically significant reductions in pancreatitis attacks.

<u>Incidence of Pancreatitis</u>	<u>Placebo</u>	<u>Volanesorsen</u>	
APPROACH (n) . . . . .	33	33	
# of pancreatitis events . . . . .	4	1	
COMPASS (n) . . . . .	38	75	
# of pancreatitis events . . . . .	5	0	( $p = 0.036$ )
COMPASS + APPROACH (n) . . . . .	71	108	
# of pancreatitis events . . . . .	9	1	( $p = 0.019$ )

Across the entire volanesorsen clinical program, we administered volanesorsen to approximately 280 individuals. This includes 43 patients with FCS for whom data are available, some of whom have been treated for over two years. Based on what we believe is a favorable risk-benefit profile, supported by data from both APPROACH and COMPASS, we plan to file for marketing authorization in the United States, Canada and Europe for volanesorsen to treat patients with FCS in the third quarter of 2017. We plan to file marketing applications to treat patients with FCS in regions outside

of the United States, Canada and Europe as soon as practical starting in 2018. Once we complete the BROADEN study, if positive, we plan to file to expand our drug label to include FPL patients.

#### *Volanesorsen Commercial Opportunity*

If we are successful in obtaining regulatory approval to commercialize volanesorsen to treat patients with FCS and FPL on our anticipated timeline, we believe volanesorsen could be the only drug on the market in the United States specifically approved for these indications. We also believe volanesorsen could be the only specifically approved drug for these indications on the market in Europe. We believe that volanesorsen could, over time, be used in a significant proportion of FCS and FPL patients, given that there are no currently approved, effective treatments for FCS or FPL.

We estimate there are 3,000 to 5,000 FCS patients and an additional 3,000 to 5,000 FPL patients globally. As with many orphan diseases, however, patients with FCS and FPL are underdiagnosed and, as a result, we believe the population sizes may be underestimated. We believe that our efforts to raise awareness of these diseases and improve diagnosis with simplified clinical diagnosis criteria, plus the availability of a drug, could significantly improve identification of patients and result in larger identified patient populations. We are building a database of identified patients by working with physicians and patient organizations and through improved diagnosis and referrals. We add patients to our database through communication with physicians, patient organizations, and other tools, such as electronic medical record database searches. We plan to use our database to help us engage with physicians who may have patients who could potentially benefit from our drugs. In order to protect patient confidentiality, we do not include patient-specific information in the database.

Due to the specialized nature of managing FCS and FPL, there are a limited number of treating physicians.

- In the United States, there are approximately:
  - 45 lipid treatment hubs; and
  - 200 to 300 lipid specialists, with an additional 300 to 400 endocrinologists specializing in lipids.
- In Europe, there are approximately:
  - 75 specialized lipid treatment hubs; and
  - 400 to 600 physician specialists who treat lipid disorders.

#### **AKCEA-APO(a)-L<sub>Rx</sub>**

##### *Overview*

We are developing AKCEA-APO(a)-L<sub>Rx</sub> for patients who are at significant risk of CVD because of their elevated levels of Lp(a). AKCEA-APO(a)-L<sub>Rx</sub> inhibits the production of the Apo(a) protein, thereby reducing Lp(a). Apo(a) is a very atherogenic and thrombogenic form of LDL. Elevated Lp(a) is recognized as an independent, genetic cause of coronary artery disease, heart attack, stroke and peripheral arterial disease. Inhibiting the production of Apo(a) in the liver reduces the level of Lp(a) in blood, potentially slowing down or reversing cardiovascular disease in patients with hyperlipoproteinemia(a), a condition in which individuals have levels of Lp(a) greater than 60 mg/dL. Lp(a) is difficult to inhibit using other technologies, such as small molecules and antibodies; there are multiple genetically-determined forms of the Apo(a) molecule and creating a small molecule or antibody that can interact with multiple targets is difficult. We believe antisense technology is particularly well suited to address hyperlipoproteinemia(a) because it specifically targets the RNA that codes for all forms of the Apo(a) molecule. As a result, it can stop the production of all of the forms of the protein. Furthermore, we believe addressing elevated Lp(a) is the next important horizon in

lipid-focused treatment and, through our collaboration with Novartis, we plan to develop AKCEA-APO(a)-L<sub>Rx</sub> to treat patients with established cardiovascular disease in whom hyperlipoproteinemia(a) likely plays a causal role.

We have completed a Phase 1/2 study with AKCEA-APO(a)-L<sub>Rx</sub> in patients with hyperlipoproteinemia(a) and we reported the results at the AHA meeting in November 2015. In this clinical study, we observed significant and sustained reductions in Lp(a) of up to 97% with a mean reduction of 79% after only a single, small volume dose of AKCEA-APO(a)-L<sub>Rx</sub>. With multiple doses of AKCEA-APO(a)-L<sub>Rx</sub>, we observed even greater reductions of Lp(a) of up to 99% with a mean reduction of 92%. Based on these results, we have started a Phase 2b dose-ranging study of AKCEA-APO(a)-L<sub>Rx</sub> in patients with hyperlipoproteinemia(a) and established CVD. We have initiated a strategic collaboration with Novartis for this drug. See “—Our Strategic Collaboration with Novartis” for additional information.

#### *Disease Background*

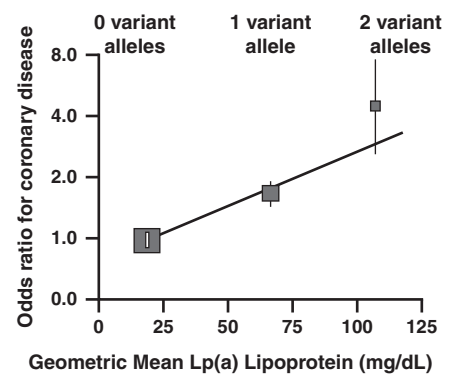
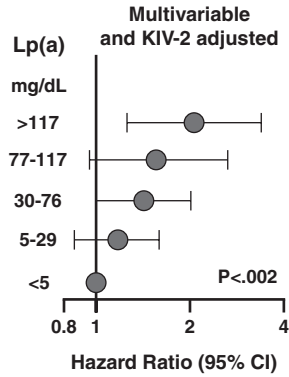
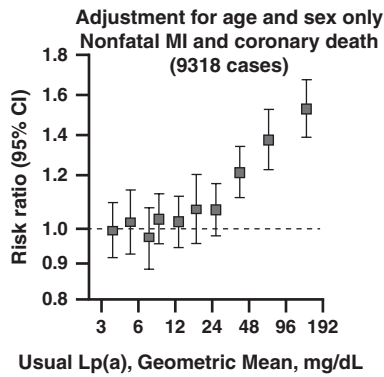
Despite the management of LDL-C with statins and other therapies, the incidence of CVD continues to rise dramatically. Lipid disorders are a cause of this continuing rise. Hyperlipoproteinemia(a), which is present in approximately 20% of the general population, causes CVD.

Currently, there is no effective drug therapy to specifically and robustly lower elevated levels of Lp(a). Lp(a) levels are determined at birth and, therefore, lifestyle modification, including diet and exercise, do not impact Lp(a) levels. Statins do not have significant effects on Lp(a) levels. Further, a new class of drugs that lower LDL-C and modestly lower Lp(a) levels, known as PCSK9 inhibitors, inactivate a protein in the plasma that regulates the number of LDL receptors on the liver cell surface, thereby capturing and removing additional LDL particles from the blood. While PCSK9 inhibitors reduce Lp(a) by approximately 25%, we believe this level of reduction is unlikely to materially reduce the risk of cardiovascular events related to hyperlipoproteinemia(a). The only currently known effective way to significantly reduce plasma Lp(a) is to physically remove the particles from blood through a process called apheresis. In this process, the patient's blood is filtered through a machine where the LDL-C and Lp(a) particles are removed and the blood is returned to the patient's body. Since 2010, apheresis has been an approved therapy in Germany to treat patients with hyperlipoproteinemia(a), but it is expensive, time consuming and only performed by a small number of centers worldwide. Lp(a) apheresis has been shown to lower the rate of cardiovascular events, providing support that lowering Lp(a) can provide therapeutic benefit.

A number of expert groups, including the National Institutes for Health, European Society of Cardiology and the National Lipid Association, and publications have stated that Lp(a) is an independent cause of cardiovascular risk. The authors of three such publications evaluated data from over 180,000 participants and used statistical and genetic approaches to evaluate the correlation between Lp(a) levels and cardiovascular risk. The specific techniques the authors used were epidemiological/meta-analyses, Mendelian randomization and genome wide associations. In each technique used, the authors demonstrated a clear relationship between elevated levels of Lp(a) and increased cardiovascular risk.

The graphics below further illustrate these correlations:

**Epi/Meta-analyses      Mendelian Randomization      Genome-wide Association**



Erqou et al JAMA 2009;302:412-23

Kamstrup et al JAMA 2009;301:2331-9

Clarke et al NEJM 2009;361:2518-28

**AKCEA-APO(a)-L<sub>Rx</sub> Clinical Development**

**Phase 1/2a studies**

We conducted a Phase 1/2a single and multiple ascending dose study with AKCEA-APO(a)-L<sub>Rx</sub> in 58 people with elevated levels of Lp(a). Individuals treated with AKCEA-APO(a)-L<sub>Rx</sub> achieved significant dose-dependent reductions in Lp(a), with the largest reductions at day 30. The results of this study were published in the Lancet in 2016. In the single dose portion of the study, we investigated five dose levels of AKCEA-APO(a)-L<sub>Rx</sub> ranging from 10 mg to 120 mg, compared to placebo.

The results from this portion of the study are illustrated in the tables below:

Single Dose; Randomized 3:1						
Dose	10mg	20mg	40mg	80mg	120mg	placebo
<b>Number of people</b> . . . . .	3	3	3	6	6	7
<b>Mean change from baseline at day 30 (%)</b> . . . . .	-26%	-33%	-44%	-79%	-85%	3%

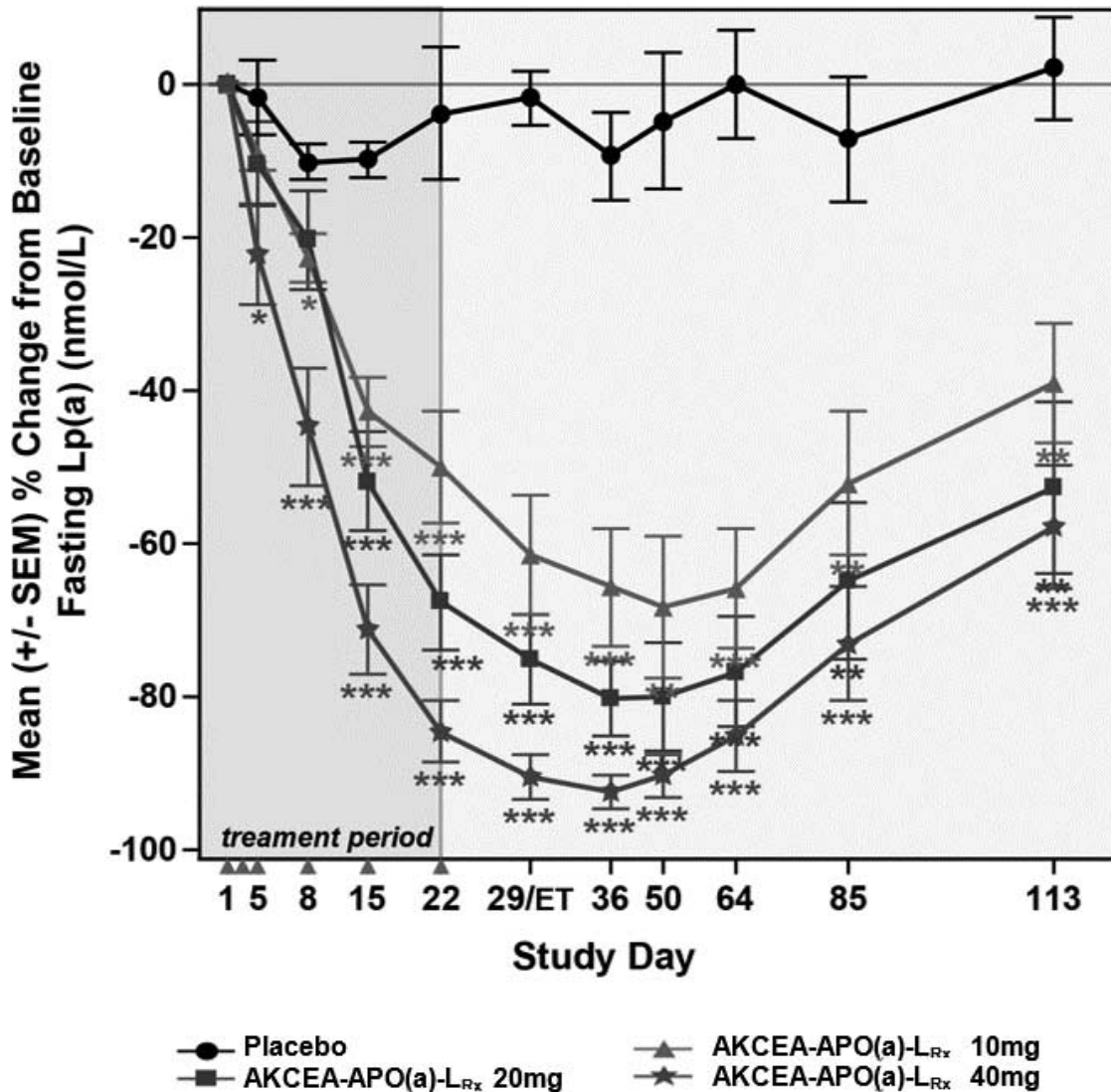
In the multiple ascending dose portion of the study, we investigated three dose levels of AKCEA-APO(a)-L<sub>Rx</sub>, compared to placebo. At each dose level, people received three doses on alternate days during the first week and then a single dose once a week for the next three weeks.

The results from this portion of the study are illustrated in the tables below:

Multiple Ascending Dose; Randomized 4:1				
Dose	10mg	20mg	40mg	placebo
<b>Number of people</b> . . . . .	8	8	8	6
<b>Mean change from baseline at day 30 (%)</b> . . . . .	-66%	-80%	-92%	-9%



The graphic below shows the mean percent change in Lp(a) in the multiple ascending dose groups:



\* The asterisks represent p-values as follows: \* $p < 0.05$ ; \*\* $p \leq 0.01$ ; \*\*\* $p \leq 0.001$ . Arrows indicate dosing at days 1, 3, 5, 8, 15, and 22. P values are for the primary efficacy endpoint at day 36 as determined by the Exact Wilcoxon Rank Sum comparing AKCEA-APO(a)-L<sub>Rx</sub> versus placebo.

AKCEA-APO(a)-L<sub>Rx</sub> was generally safe and well tolerated in the study, which supported continued development. Out of 165 injections, there were no injection site reactions or flu-like symptoms reported. Additionally, in the multiple-dose cohorts, there were no clinically-relevant changes in electrocardiograms or vital signs, or in safety laboratory parameters including liver and kidney markers, hematology (including platelet count), coagulation (including activated partial thromboplastin time), inflammation (high sensitivity C Reactive Protein), complement and urinalysis.



### Phase 2b study

We are conducting a Phase 2b study of AKCEA-APO(a)-L<sub>Rx</sub> in patients with hyperlipoproteinemia(a) and established CVD. The goal of the study is to determine the dose level and frequency for use in a future cardiovascular outcome study. The study is a randomized, double-blind, placebo-controlled, dose-ranging study of AKCEA-APO(a)-L<sub>Rx</sub> administered by a subcutaneous injection. Patients in the study will be dosed for a period of six months, and a portion of the patients will continue for up to one year. We are testing multiple different dosing levels and regimens. The primary endpoint is the percent change in plasma Lp(a) from baseline at six months. The secondary endpoints will be changes in LDL-C, responder analyses, and other key lipid parameters. Further, we will evaluate safety and pharmacokinetics of the different doses. We designed the study to enroll 270 patients, randomized 5:1, to receive AKCEA-APO(a)-L<sub>Rx</sub> or a matched quantity of placebo. We plan to report data from this study in the middle of 2018.

### *AKCEA-APO(a)-L<sub>Rx</sub> Commercial Opportunity*

Elevated levels of Lp(a) are associated with increased cardiovascular risk and lowering Lp(a) may reduce the risk. We estimate the eligible population to be 8.5 to 11 million people globally. We believe that positive results from a large cardiovascular outcome study will be required to support marketing authorization for the treatment of these patients. If Novartis exercises its option, it plans to conduct, at its expense, such a study pursuant to our strategic collaboration and, if approved, to commercialize AKCEA-APO(a)-L<sub>Rx</sub> for these patients.

### **AKCEA-ANGPTL3-L<sub>Rx</sub>**

#### *Overview*

We are developing AKCEA-ANGPTL3-L<sub>Rx</sub> to treat multiple lipid disorders. Studies have shown that elevated levels of the ANGPTL3 protein are associated with an increased risk of premature heart attacks, increased arterial wall thickness and multiple metabolic disorders, such as insulin resistance. In contrast, people with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels and thus lower risk of heart attacks and multiple metabolic disorders. In preclinical studies, an analog of AKCEA-ANGPTL3-L<sub>Rx</sub> inhibited the production of the ANGPTL3 protein in the liver, inhibiting liver fat accumulation and lowering blood levels of triglycerides, LDL-C and very low density lipoprotein cholesterol, or VLDL-C. In addition, our preclinical data and initial Phase 1 data suggest that inhibiting the production of ANGPTL3 could improve other lipid parameters, including triglyceride levels and total cholesterol.

We are conducting a Phase 1/2 program for AKCEA-ANGPTL3-L<sub>Rx</sub> in people with elevated triglycerides. We reported results for the initial cohort from this study at the AHA meeting in November 2016. We observed that the people with elevated triglycerides achieved dose-dependent, statistically significant mean reductions in ANGPTL3 of up to 83%. Treatment with AKCEA-ANGPTL3-L<sub>Rx</sub> was also associated with statistically significant mean reductions in triglycerides of up to 66%, in LDL-C of up to 35% and in total cholesterol of up to 36%. In this study, AKCEA-ANGPTL3-L<sub>Rx</sub> was reported to be well tolerated. The most common adverse events in the AKCEA-ANGPTL3-L<sub>Rx</sub> treated group of patients were mild headaches and dizziness that were approximately equal to the rate observed in the placebo group. In the second half of 2017, we plan to begin a study of AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with hyperlipidemia with metabolic complications including insulin resistance and fatty liver, in which we plan to include patients with NAFLD or NASH. We plan to report data from this study in 2019. Further, in the second half of 2017, we also plan to study AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with rare hyperlipidemias, including patients with FCS, and we plan to report data from this study in 2018. If we find that AKCEA-ANGPTL3-L<sub>Rx</sub> can effectively lower triglyceride levels in patients with rare hyperlipidemias, including patients with FCS, through a different mechanism of action from volanesorsen, it may represent an opportunity to expand our FCS

franchise. Additional potential indications for which we may consider developing AKCEA-ANGPTL3-L<sub>Rx</sub> include other rare hyperlipidemias and lipodystrophies.

### *Disease Background*

#### Fatty liver disease

While some fat in the liver is normal, a significant percentage of individuals have elevated levels of liver fat. Individuals with excessive fat accumulation in the liver also have elevated risk of developing insulin resistance and metabolic syndrome, type 2 diabetes and CVD. These risks are further elevated in patients with hyperlipidemia, especially those with elevated triglyceride levels. The most common form of fatty liver disease is NAFLD, which is associated with obesity-related disorders even in patients who drink little or no alcohol, and is characterized by the gradual accumulation of fat in the liver, or steatosis. One of the key causes of this condition is the Western diet, which is rich in processed foods with high fat and sugar content. In the early stages of NAFLD, patients typically experience steatosis that is slow-progressing. Over time, a subset of these patients progress to steatohepatitis, a more severe and progressive form of NAFLD characterized by chronic inflammation and liver-cell damage, called NASH. Over time, the chronic inflammation caused by NASH can lead to the formation of scar tissue in the liver, known as fibrosis. As scar tissue gradually replaces healthy liver tissue, blood flow is restricted, which can lead to the loss of normal liver function, cirrhosis, portal hypertension, liver cancer and ultimately liver failure. Currently, there are no approved treatments specifically for NAFLD or NASH. If the disease ultimately progresses beyond NASH, the only alternative is a liver transplant.

#### Rare Hyperlipidemias

Rare hyperlipidemias are genetic diseases characterized by high levels of lipids or lipoproteins in the blood. Function or levels of various lipid clearing enzymes, like LPL and hepatic lipase, are decreased in patients with rare hyperlipidemias. These patients may also have a reduced ability to clear other lipids, including LDL, leading to very high lipid levels. Examples of diseases in this category include FCS and familial hypercholesterolemia. Despite existing and emerging therapies, there remains an unmet need to reduce multiple lipid parameters in these patients, including LDL and triglycerides.

#### Lipodystrophies

Congenital and acquired forms of lipodystrophy are diseases characterized by abnormal or degenerative conditions of the body's adipose tissue. Patients with various forms of lipodystrophy may have difficulties in normal processing of lipids resulting in high LDL-C, triglycerides and fatty liver disease.

### *AKCEA-ANGPTL3-L<sub>Rx</sub> Clinical Development*

#### Preclinical and other related studies

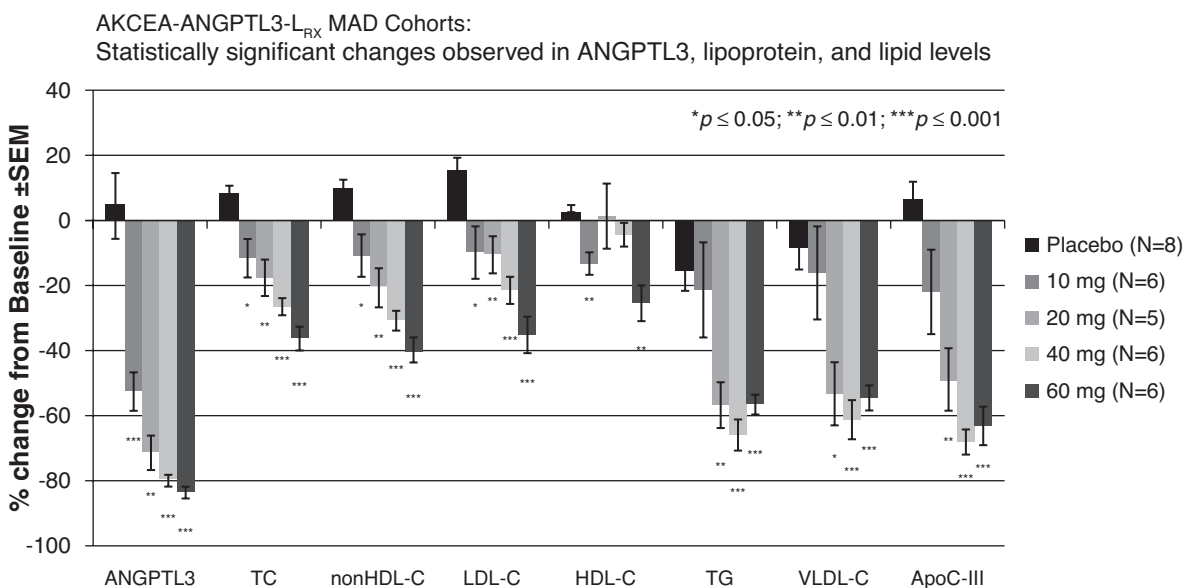
Our preclinical data suggest that reducing ANGPTL3 could improve lipid parameters, including LDL-C, triglycerides, and total cholesterol. In a mouse model of increased liver fat, we observed that treatment with an analog of AKCEA-ANGPTL3-L<sub>Rx</sub> reduced liver fat concentrations by more than 50%.

Further, in a Phase 1 study that Ionis conducted with a non-LICA version of AKCEA-ANGPTL3-L<sub>Rx</sub>, healthy volunteers experienced significant reductions of up to 93% in ANGPTL3, up to 63% in triglycerides and up to 46% in total cholesterol.

### Phase 1/2 program

We are conducting a placebo-controlled, dose escalation Phase 1/2 program to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of AKCEA-ANGPTL3-L<sub>Rx</sub> administered by a subcutaneous injection to people with elevated triglycerides. We are evaluating single doses of AKCEA-ANGPTL3-L<sub>Rx</sub> at 20mg, 40mg, 80mg and 120 mg and are randomizing people 3:1, active to placebo, where three participants will receive AKCEA-ANGPTL3-L<sub>Rx</sub> and one participant will receive placebo. The multiple dose cohorts used lower doses with eight participants in each cohort. We reported initial results for the initial group of people with elevated triglycerides from this study at the AHA meeting in November 2016.

People who received multiple doses of 10 mg, 20 mg, 40 mg, or 60 mg of AKCEA-ANGPTL3-L<sub>Rx</sub> achieved dose-dependent, statistically significant mean reductions at Day 37 in ANGPTL3 of up to 83% ( $p \leq 0.001$ ). These subjects also experienced statistically significant mean reductions in triglycerides of up to 66% ( $p \leq 0.001$ ), in LDL-C of up to 35% ( $p \leq 0.001$ ) and in total cholesterol of up to 36% ( $p \leq 0.001$ ). In this study, AKCEA-ANGPTL3-L<sub>Rx</sub> was reported to be well tolerated. The most common adverse events in the AKCEA-ANGPTL3-L<sub>Rx</sub> treated group of patients were mild headaches and dizziness that were approximately equal to the rate observed in the placebo group. There were no discontinuations due to adverse events and no clinically meaningful platelet declines. The graphic below further summarizes these results.



### Phase 2 studies

In the second half of 2017, we plan to begin a study of AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with hyperlipidemia with metabolic complications including insulin resistance and fatty liver, in which we plan to include patients with NAFLD or NASH. The goal of the study is to evaluate dose levels, frequencies and markers of liver fat. The study is expected to be a randomized, double-blind, placebo-controlled, dose-ranging study of AKCEA-ANGPTL3-L<sub>Rx</sub> administered by a subcutaneous injection. We expect to dose patients over a period of at least six months. We plan to test multiple doses, and expect to evaluate safety and efficacy to support dose selection in future trials. We have not determined the endpoints yet, but expect to include changes in key lipid parameters including triglycerides and LDL-C, as well as measures of liver fat and other metabolic parameters. We plan to enroll approximately 200 patients in this study. We plan to report data from this study in 2019.

We are also planning to study AKCEA-ANGPTL3-L<sub>Rx</sub> in patients with rare hyperlipidemias, including patients with FCS, in the second half of 2017. We expect the primary goal of the study to be to evaluate the ability of AKCEA-ANGPTL3-L<sub>Rx</sub> to lower triglyceride levels and/or other important lipid markers in patients with rare hyperlipidemias, including FCS. We plan to test multiple doses, and expect to evaluate safety and efficacy to support dose selection in future trials. We have not finalized the secondary endpoints yet, but expect to include markers of safety in FCS patients. We plan to report data from this study in 2018. If we demonstrate that we can successfully lower key lipid parameters in these patients, we plan to begin a Phase 3 study in rare hyperlipidemias in 2018.

#### *AKCEA-ANGPTL3-L<sub>Rx</sub> Commercial Opportunity*

NAFLD is the most common chronic liver disease worldwide and more than 75 million patients are affected in the United States alone. Approximately 30% of patients with NAFLD will eventually progress to NASH. In the United States, the most recent epidemiological studies show that approximately 3% to 5% of the general population has NASH. We believe there are a comparable number of patients in Europe and the rest of the world. While there are a number of treatments currently in development for the treatment of NAFLD and NASH, none are currently approved and we believe there will continue to be a significant unmet medical need in this population.

Rare hyperlipidemia contains multiple diseases, including FCS and familial hypercholesterolemia. We believe that these populations are all orphan sized.

There are several types of lipodystrophies, congenital generalized, acquired generalized, familial partial, acquired partial, mandibuloacral dysplasia associated, and HIV associated. We believe these populations are all orphan sized.

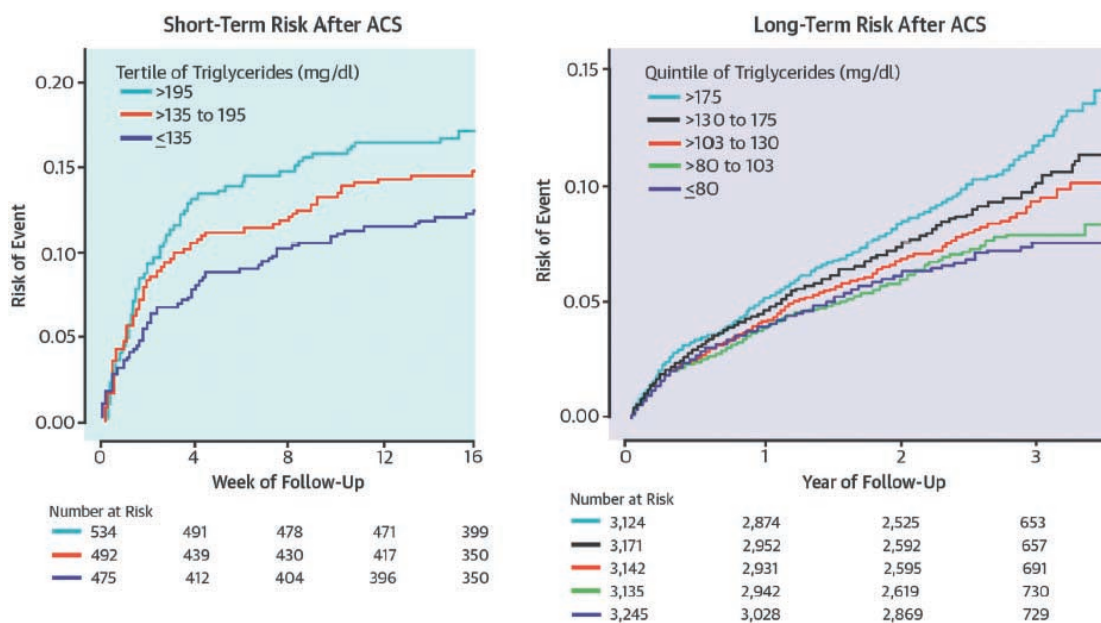
#### **AKCEA-APOCIII-L<sub>Rx</sub>**

##### *Overview*

We are developing AKCEA-APOCIII-L<sub>Rx</sub> to inhibit the production of ApoC-III, the same protein inhibited by volanesorsen, for the broad population of patients who have cardiometabolic disease due to their elevated triglyceride levels. ApoC-III impacts triglyceride levels and may also increase inflammatory processes. This combination of effects makes ApoC-III a promising target for patients with LDL-C already controlled on statin therapy, but for whom triglycerides remain poorly controlled. We believe that the enhancements offered by Ionis' LICA technology can provide greater patient convenience by allowing for significantly lower doses and less frequent administration, compared to volanesorsen. We are conducting a Phase 1/2 study of AKCEA-APOCIII-L<sub>Rx</sub> in people with elevated triglycerides and plan to report results from this study in the second half of 2017. We have initiated a strategic collaboration with Novartis for this drug. In this collaboration, we intend to complete the Phase 2 program required to define the appropriate dose and regimen to support a planned cardiovascular outcome study. We plan to initiate a Phase 2b dose-ranging study of AKCEA-APOCIII-L<sub>Rx</sub> in patients with hypertriglyceridemia and established CVD in the second half of 2017 and plan to report data from this study in 2019. At the completion of Phase 2 development, Novartis has an option to license the drug. If Novartis exercises its option to license AKCEA-APOCIII-L<sub>Rx</sub> and pays us the \$150.0 million license fee to do so, Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize AKCEA-APOCIII-L<sub>Rx</sub> worldwide. We plan to co-commercialize AKCEA-APOCIII-L<sub>Rx</sub> with Novartis in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver this potential therapy to patients at significant cardiovascular risk due to their elevated triglyceride levels.

### Disease Background

ApoC-III is an important emerging target linking hypertriglyceridemia with CVD. Several studies have found that ApoC-III levels are an independent risk factor for CVD. Further, its presence on lipoproteins may increase their atherogenicity. A study in the New England Journal of Medicine reported that out of a sample of over 100,000 people, individuals with an APOC3 gene loss of function mutation had a reduced risk of clinical coronary heart disease. Each decrease of 1 mg/dL in plasma levels of ApoC-III was associated with a 4% decrease in the risk of incident coronary heart disease. Triglycerides may also play a role in cardiovascular risk. As shown in the figure below, in two separate studies encompassing nearly 20,000 patients, as triglyceride levels increased, so did the risk of a cardiovascular event. In summary, ApoC-III impacts triglyceride levels and may also increase inflammatory processes, and this combination of effects makes ApoC-III a promising target for reducing the residual CVD risk in patients already on statin therapy, but for whom triglycerides are poorly controlled.



Schwartz, G.G. et al. J Am Coll Cardiol. 2015; 65(21):2267-75.

### AKCEA-APOCIII-L<sub>Rx</sub> Clinical Development

We have not completed any clinical studies with AKCEA-APOCIII-L<sub>Rx</sub> to date. We conducted a Phase 2 clinical study with volanesorsen in patients with high triglycerides and type 2 diabetes that showed patients treated with volanesorsen evidenced significantly reduced triglycerides, improved insulin sensitivity, and additionally reduced lipid parameters associated with cardiovascular disease, including ApoC-III.

We are conducting a Phase 1/2 study of AKCEA-APOCIII-L<sub>Rx</sub> in people with elevated triglycerides to evaluate the safety of various doses in humans. The first part of the study is a single ascending dose portion in which we will examine multiple different dose levels sequentially in approximately 40 people. We will administer each dose level, using a subcutaneous injection. Upon completion of the single ascending dose portion of the study, we plan to begin the multiple ascending dose portion of the study. In this part of the study, we plan to enroll approximately 34 people with elevated triglycerides. We are planning to examine multiple different dosing levels and regimens. We plan to administer each dose level to a cohort of people at multiple time points.



We have initiated a strategic collaboration with Novartis for this drug. See “—Our Strategic Collaboration with Novartis” for additional information.

#### *AKCEA-APOCIII-L<sub>Rx</sub> Commercial Opportunity*

ApoC-III levels and elevated triglycerides have been linked to increased cardiovascular risk and lowering ApoC-III and triglycerides may reduce the risk. We estimate the eligible population to be 8.5 to 14.5 million people globally. We believe that positive results from a large cardiovascular outcome study will be required to support marketing authorization for the treatment of these patients. If Novartis exercises its option, it plans to conduct, at its expense, such a study pursuant to our strategic collaboration to conduct this study and to commercialize AKCEA-APOCIII-L<sub>Rx</sub> for these patients.

### **Sales and Marketing**

Our goal is to become the premier company offering treatments for previously inadequately treated lipid disorders. We are assembling the global infrastructure to develop the drugs in our pipeline and to commercialize them with a focus on lipid specialists, specialized endocrinologists and pancreatologists as our primary call points. We are also creating the specialized support required to potentially address other rare disease patient populations. We plan to build a small, highly-focused salesforce to support the commercialization of volanesorsen, if approved, which would serve as the foundation of our sales, marketing and patient support efforts for all of the drugs in our pipeline, including our co-commercialization activities with Novartis for AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>, if and when approved under terms and conditions that we plan to negotiate with Novartis in the future.

### **Global Commercialization Infrastructure**

We plan to commercialize volanesorsen ourselves globally, with a specialized and comprehensive patient-centric approach. Our orphan-focused commercial model will include a small highly focused salesforce in each country that we are targeting, complemented by medical affairs and patient and healthcare provider services. We plan to provide high touch patient and healthcare provider support through reimbursement assistance, partnerships with specialty pharmacies, injection training, routine platelet monitoring and dietary counseling, which we believe will enable strong integration with treating physicians and facilitate patient uptake and compliance. Reimbursement assistance may include activities such as a reimbursement hotline, patient assistance, co-pay assistance through foundations and insurance verification. We plan to include dedicated case managers as part of our support team who will work directly with patients, caregivers and healthcare providers to help patients start and stay on therapy. Our global commercial organization is initially focused on our nearest term opportunities with volanesorsen to treat patients with FCS and FPL. Our initial plan is to focus on lipid specialists, specialized endocrinologists and pancreatologists as our primary call points. At the outset, we plan to focus our commercial efforts in the United States, Canada and Europe, and intend to expand over time to other relevant geographies. We believe the relatively small number of specialized physicians treating FCS and FPL patients will allow us to address this market with a nimble, scalable organization. We are currently identifying patients and having them referred to specialists for treatment, which we believe will facilitate successful commercialization. Building awareness of these orphan diseases among not only lipid specialists, but also referring physicians, is a key element of our pre-commercial and commercial plans. We are focused on disease education and market access, with the goal of ensuring that identified patients can most effectively obtain our drugs once commercialized. We are also creating the specialized support required to potentially address other rare disease patient populations.



Due to the specialized nature of managing FCS and FPL, there are a limited number of treating physicians.

- In the United States, there are approximately:
  - 45 lipid treatment hubs; and
  - 200 to 300 lipid specialists, with an additional 300 to 400 endocrinologists specializing in lipid disorders.
- In Europe, there are approximately:
  - 75 specialized lipid treatment hubs; and
  - 400 to 600 physician specialists who treat lipid disorders.

In North America and Europe, we are planning for an overall field force size of between 75 and 100 individuals for the initial launch of volanesorsen in FCS, which we expect to be sufficient to target substantially all of the potential volanesorsen prescribers. This field force would include sales representatives, medical liaisons, and personnel for reimbursement assistance and patient support.

In August 2016, we formed Akcea UK, our wholly-owned subsidiary located in the United Kingdom. Akcea UK is supporting our initial pre-commercialization activities in Europe, and will serve as a potential entity for future United Kingdom and/or European operations.

We expect to market our drugs to the same specialist call point as volanesorsen, enabling us to leverage this commercial organization as the core global infrastructure for all of our drugs. We plan to commercialize by ourselves any approved drugs with a rare disease or specialty focus. We may enter into strategic relationships to commercialize certain of our drugs, particularly in indications with large patient populations, as evidenced by our collaboration with Novartis. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub> to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. We also plan to co-commercialize any such drug in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize volanesorsen.

### ***Preparing for Successful Commercialization***

A key aspect of successfully commercializing therapies for orphan diseases is to identify eligible patients. Patient populations are frequently very small and sometimes heterogeneous. Our management team is experienced in maximizing patient identification for both clinical development and commercial purposes in orphan diseases. We also have significant experience in establishing the burden of disease in support of securing orphan pricing and reimbursement.

Our commercial organization is focused on the following priorities to prepare for the launch of volanesorsen:

- Improve diagnosis by working with a small number of specialist physician experts to advance the understanding of the signs and symptoms of FCS and FPL, and then communicate that simplified clinical diagnosis criteria to the broader physician and patient community.
- Build a database of patients by working with physicians and patient organizations and through improved diagnosis and referrals. We add patients to our database through communication with physicians, patient organizations, and other tools, such as electronic medical record database searches. We plan to use our database to help us engage with physicians who may have patients who could potentially benefit from our drugs. In order to protect patient confidentiality, we do not include patient-specific information in the database.

- Build an integrated high-touch patient support team to help patients start and stay on therapy. We plan to provide reimbursement assistance, injection training, platelet monitoring and dietary support, as well as establish partnerships with specialty pharmacies, to help patients remain on therapy over the long term. We plan to include dedicated case managers as part of our support team who will work directly with patients, caregivers and healthcare providers to help patients start and stay on therapy.
- Prepare for successful market access through payors and other reimbursement authorities by establishing and quantifying the burden of disease associated with living with FCS and FPL.

### **Our Relationship with Ionis**

We founded our operations in 2015 as a wholly owned subsidiary of Ionis to develop and commercialize Ionis' drugs to treat lipid disorders. Ionis has funded our expenses to date. We are becoming an independent company building a focus and excellence in development and commercialization. We expect Ionis to remain our principal stockholder for the foreseeable future. Ionis has been a publicly traded company for over 25 years and had over \$1.0 billion in assets and over 400 employees primarily focused on researching and developing antisense drugs as of March 31, 2017.

By partnering with Ionis, we require less infrastructure than a typical company of our size and stage of development, and can focus our efforts on developing and preparing to commercialize our drugs.

Through our relationship with Ionis, we benefit in the following ways:

- We have access to Ionis' innovative generation 2.0+ antisense and LICA technologies for use in our drugs. These technologies allow for precise specificity, favorable dosing properties and no anticipated drug-to-drug interactions.
- We obtained exclusive rights to globally commercialize a robust, mature pipeline of drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development. Our licensed rights also include access to Ionis' intellectual property and expertise to develop, manufacture and commercialize these drugs.
- We have a joint development program that provides us access to Ionis' development and regulatory organization, which has significant expertise in developing drugs to treat patients with lipid disorders. Ionis also provides resources to support our nonclinical and clinical studies.
- We contract with Ionis for support in areas such as legal, finance and human resources, which allows us to be more capital efficient than a typical company of our size and stage of development. This support allows us to focus our efforts and resources on developing and preparing to commercialize our drugs.
- We are not required to make any upfront or pre-commercialization payments to Ionis for drugs we are developing under our development, commercialization and license agreement, as would be typical in a drug license. Our agreement allows us to more efficiently invest our capital in developing and preparing to commercialize our drugs, as we are only required to make milestone and royalty payments post-commercialization or if we grant a sublicense to Ionis' technology.
- As a result of our relationship with Ionis, we may have the opportunity to evaluate additional antisense drugs that may complement our efforts in becoming the premier lipid disease company. For example, Ionis has granted us a right of first negotiation with respect to Ionis development candidates that are designed to treat a rare cardiometabolic disease or a rare inherited metabolic disease.

While we and Ionis intend our relationship to enhance our capabilities, certain terms of our relationship may limit our ability to achieve this expected benefit, including:

- Some of our directors and officers may have a conflict of interest because of their positions with Ionis.
- A Joint Steering Committee, or JSC, sets the development and regulatory strategy for our drugs by mutual agreement. If the JSC cannot come to a mutual agreement, it could delay our ability to develop and commercialize our drugs in development.
- We will need to mutually agree with Ionis on the terms of any additional sublicense to a third party for our drugs in development. If we cannot mutually agree, it could delay or prevent our ability to develop and commercialize our drugs.
- Our agreements prevent Ionis from developing and commercializing drugs targeting ApoC-III, Apo(a) or ANGPTL3 RNA. However, our agreements do not prevent Ionis from developing and commercializing other drugs to pursue the same indications we are pursuing with our drugs.

### ***Exclusive Rights to Development Pipeline and Intellectual Property; Right of First Negotiation***

Ionis is the leading company researching and developing antisense drugs. Under our agreements with Ionis, we have rights to Ionis' proprietary technologies for use with our drugs. Specifically, we obtained an exclusive license from Ionis to globally commercialize our development pipeline of drugs, including volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. Ionis also agreed that it would not work on its own or with other parties to develop or commercialize antisense drugs that target the same gene targets as the drugs we are developing and commercializing. Under our agreements with Ionis, we have a license to use Ionis' technology platform with our drugs. We also have access to future improvements Ionis may make to its antisense technology platform, such as improved manufacturing technologies.

In addition, Ionis has granted us a right of first negotiation with respect to Ionis development candidates that are designed to treat a rare cardiometabolic disease or a rare inherited metabolic disease.

### ***Access to Ionis' Development, Regulatory and Manufacturing Expertise***

#### *Development*

We receive access to Ionis' infrastructure and expertise in developing antisense drugs and, in particular, drugs to treat lipid disorders. We have a joint steering committee comprised of Akcea and Ionis representatives who set the development strategy for each of our drugs. In addition, a team of Akcea and Ionis employees run each clinical study for our drugs. This way we can stay focused on developing our drugs and preparing for commercialization rather than immediately building an extensive development organization. Over time as we strategically expand our internal development capabilities, we plan to assume more and more responsibility for each development program. Because of our relationship with a much larger company like Ionis, we can use Ionis' relationships and negotiating power with clinical research organizations and other vendors to obtain lower pricing and better resourcing from these vendors than we otherwise could achieve on our own as a relatively new and smaller company. These benefits help us manage our development costs.

#### *Regulatory*

We take a similar approach to regulatory affairs as we do for drug development. We have a joint regulatory committee comprised of Akcea and Ionis representatives that sets the regulatory strategy for each of our drugs. Because Ionis has filed over 30 investigational new drug applications, or INDs, for antisense drugs, and supported the approval of three new drug applications, or NDAs,

for antisense drugs, Ionis understands how to successfully work with the FDA and other regulatory agencies. We can also benefit from Ionis' more than 25 years of knowledge regarding antisense drugs to prepare important sections of an IND or NDA. These are important benefits we can immediately access as we continue to build our own regulatory organization and assume more regulatory responsibility for our drugs.

#### *Manufacturing*

As the leader in antisense technology, Ionis has discovered many of the breakthroughs that have made it possible to manufacture antisense drugs at commercial scale and at a commercially feasible price. Through our relationship with Ionis, we enjoy the benefit of Ionis' historical and continuing investment in antisense drug manufacturing. Specifically, Ionis has agreed to supply the active pharmaceutical ingredient, or API, and, through its outside vendors, the finished drug product for the clinical studies for each of the drugs in our pipeline through the end of 2017. Ionis also has agreed to supply the API and the finished drug product for at least the first two years of volanesorsen's commercial launch. Ionis has long-standing and strong relationships with third party vendors who can supply us with both API and finished drug product, and are currently supplying API and finished drug product to other of Ionis' partners. Ionis also has long-standing and strong relationships with the vendors who supply the key raw materials to Ionis to make our drugs and to the other major oligonucleotide contract manufacturers. We plan to use these relationships to establish our own long term raw material and drug supplies at competitive prices.

#### *Infrastructure*

When Ionis formed our company, a key premise was to initially utilize Ionis' existing infrastructure in areas like business development, finance, patents, legal, human resources, benefits and other general and administrative areas, so that we could remain critically focused on developing and preparing to commercialize our drugs and could more efficiently utilize our capital. By taking advantage of Ionis' existing infrastructure in these areas, we can spend very little of our management and financial resources building these functions ourselves. As we commercialize our drugs, we expect to be able to expand these systems with a relatively modest additional investment. We can use Ionis' extensive corporate partnering expertise and resources to help us if and when we choose to partner our drugs for the larger indications.

#### ***Payment Structure Under our Agreements with Ionis***

We have agreed to pay Ionis for the services it provides us. We intentionally designed our agreements with Ionis to allow us to invest our initial capital to develop and prepare to commercialize our drugs. We were not required to make an upfront cash payment to license Ionis' drugs and technology. In addition, other than paying Ionis the cost of the support services Ionis provides to us, we are not required to make significant payments to Ionis until we successfully commercialize or partner our drugs. For drug development Ionis conducts on our behalf, we will reimburse Ionis for its out-of-pocket expenses and for the cost of Ionis' employees who conduct the research and development activities for our drugs. For general and administrative services, we pay Ionis for our share of internal and external expenses for each of the functions they provide based on our relative use of each function, plus an allocation of facility-related expenses.

For the drugs we commercialize ourselves, we will pay Ionis royalties ranging from the mid-teens to the mid-twenties on sales related to those drugs. If we sell a drug for an orphan disease indication, defined in our agreement as less than 500,000 patients worldwide, or an indication that required a Phase 3 program of less than 1,000 patients and less than two years of treatment, we pay a higher royalty rate to Ionis than we do if we sell a drug for a disease having more than 500,000 patients worldwide or an indication that required a Phase 3 program of 1,000 or

more patients and two or more years of treatment. Other than with respect to the drugs licensed to Novartis under the strategic collaboration, option and license agreement, if our annual sales reach \$500.0 million, \$1.0 billion and \$2.0 billion, we will pay Lonis sales milestones in the amount of \$50.0 million for each sales milestone reached by each drug, spread in equal installments over the 12 quarters following the milestone event.

For drugs we sublicense to a commercial partner, we will share 50% of any revenue from the commercial partner with Lonis, excluding money received from our partner specifically designated to fund future development costs and money we are obligated to spend to co-commercialize a drug. Regarding our Novartis collaboration, we paid Lonis \$15.0 million of the \$75.0 million upfront option payment we received from Novartis. We will pay Lonis 50% of any additional payments we receive from Novartis, excluding money received specifically designated to fund future development costs and money we are obligated to spend to co-commercialize a drug.

### ***Line of Credit Agreement***

In addition, Lonis has helped fund our operations through a line of credit agreement of up to \$150.0 million. As of the date of this prospectus, we had borrowed an aggregate of \$106.0 million pursuant to the line of credit, which together with accrued interest will automatically convert upon completion of this offering into an aggregate of 13,438,339 Lonis Conversion Shares, based on the initial public offering price of \$8.00 per share.

We have four main agreements that govern our relationship with Lonis, a development, commercialization and license agreement, a services agreement, a line of credit agreement and an investor rights agreement. We describe each of these agreements in greater detail under the section entitled "Certain Relationships and Related Person Transactions."

### ***Our Strategic Collaboration with Novartis***

In January 2017, we initiated a strategic collaboration with Novartis for the development and commercialization of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. Under the strategic collaboration, option and license agreement, Novartis has an exclusive option to develop and commercialize these drugs. We are responsible for completing a Phase 2 program and conducting an end-of-Phase 2 meeting with the FDA for each drug and delivering active pharmaceutical ingredient, or API. Following the successful completion of each Phase 2 program, and prior to initiation of the Phase 3 study, Novartis will be able to exercise its option to license and commercialize each drug. Novartis will have 60 days following the end of the applicable end-of-Phase 2 meeting to exercise its option for each of these drugs. If Novartis exercises its option for a drug, Novartis will be responsible, at its expense, to use commercially reasonable efforts to develop and commercialize that drug. We received \$75.0 million in an upfront option payment, of which we retained \$60.0 million and paid Lonis \$15.0 million as a sublicense fee under our license agreement with Lonis. During the first quarter of 2017, we recognized \$9.6 million of revenue related to our Novartis collaboration. In conjunction with this collaboration, Novartis purchased \$100.0 million of Lonis' common stock at a premium.

If Novartis exercises its option for a drug, Novartis will pay us a license fee equal to \$150.0 million for each drug licensed by Novartis. In addition, for AKCEA-APO(a)-L<sub>Rx</sub>, we are eligible to receive up to \$600.0 million in milestone payments, 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 \$285.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L<sub>Rx</sub>, we are eligible to receive up to \$530.0 million in milestone payments, including \$25.0 million for the achievement of a development milestone, up to \$240.0 million for the

achievement of regulatory milestones and up to \$265.0 million for the achievement of commercialization milestones. We are eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. In addition, we and Novartis may negotiate in good faith a potential adjustment to the Novartis royalty as a result of changes in active pharmaceutical ingredient costs. We will pay 50% of these license fees, milestone payments and royalties to Ionis as a sublicense fee.

For each product Novartis commercializes under this agreement, we will have the right to co-commercialize the product with Novartis in selected markets, through the specialized sales force we are building to commercialize volanesorsen, on terms and conditions that we plan to negotiate with Novartis in the future.

If Novartis does not exercise its option, or stops developing or commercializing after exercising its option with respect to a particular drug, we will have all rights to develop or commercialize the drug (including the right to sublicense these rights to a third party) at our sole expense. If Novartis stops developing or commercializing a drug after exercising its option, and we subsequently commercialize the drug 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 drug.

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

- Novartis may terminate the agreement as a whole or with respect to any drug at any time by providing written notice to us;
- Either we or Novartis may terminate the agreement with respect to any drug by providing written notice to the other party in good faith that we or Novartis has determined that the continued development or commercialization of the drug presents safety concerns that pose an unacceptable risk or threat of harm in humans or would violate any applicable law, ethical principles, or principles of scientific integrity;
- Either we or Novartis may terminate the agreement for a drug by providing written notice to the other party upon the other party's uncured failure to perform a material obligation related to the drug under the agreement, or the entire agreement if the other party becomes insolvent; and
- We may terminate the agreement if Novartis disputes or assists a third party to dispute the validity of any of our patents.

Novartis has agreed to purchase \$50.0 million of our common stock in a separate private placement concurrent with the completion of this offering at a price per share equal to the initial public offering price. Novartis has agreed that it will not sell any of these shares until the earlier of January 5, 2020 or six months after we stop developing a drug under the agreement, and if Novartis wishes to sell such shares after this initial period, then Novartis may only sell a limited number of shares each day.

Immediately following the completion of this offering, Novartis will own approximately 9.7% of the total number of shares of our common stock outstanding after the completion of this offering.



Based on the initial public offering price of \$8.00 per share, we will issue 6,250,000 Novartis Private Placement Shares.

## Competition

The commercialization of new drugs is competitive, and we may face worldwide competition from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, nutraceutical companies and ultimately generic companies. Our competitors may develop or market therapies that are more effective, safer, more convenient to use, or less costly than any that we are commercializing, or may obtain regulatory or reimbursement approval for their therapies more rapidly than we may obtain approval for ours. Many of our competitors have substantially greater financial, technical and human resources than we have. Additionally, mergers and acquisitions in the pharmaceutical industry may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields.

With respect to volanesorsen to treat patients with FCS, we believed Glybera, which is a gene therapy made by uniQure N.V., could compete with volanesorsen. However, in April 2017 uniQure announced it would not renew Glybera's marketing authorization in Europe, and has previously announced it is not pursuing approval in the United States. To our knowledge, there are currently no direct competitors in clinical development.

Metreleptin is the only approved drug we believe could be a competitor to volanesorsen for FPL patients. Metreleptin is currently approved for use in generalized lipodystrophy, or GL, patients. The FDA denied initial approval in FPL patients, not all of whom are leptin deficient, the mechanism by which metreleptin works. In December 2016, Novelion Therapeutics, Inc. submitted a marketing authorization application to the EMA seeking approval for Metreleptin as replacement therapy to treat complications of leptin deficiency in a small subset of FPL patients and in patients with GL. An investigator-sponsored study is currently ongoing with the support of Novelion to evaluate Metreleptin in FPL patients who also have NASH. Metreleptin does not affect ApoC-III levels. ApoC-III levels have been shown to be elevated in FPL patients, and directly correlate to triglyceride levels. To our knowledge, there are currently no other direct competitors lowering ApoC-III in clinical development.

In addition, many patients with FCS and FPL use diet, niacin, fish oils and/or fibrates to reduce their elevated triglycerides. Niacin, fish oils and fibrates are generally not effective in patients with FCS. The ultra-low fat diet that patients with FCS and FPL are required to maintain is extremely burdensome to patients and their families. Based on our volanesorsen clinical experience, including in individuals with FCS, we believe that volanesorsen will work equally well as a single agent or in combination with other triglyceride-lowering drugs or approaches.

With respect to AKCEA-APO(a)-L<sub>Rx</sub>, we are not aware of any other drugs currently in clinical development specifically for the treatment of hyperlipoproteinemia(a) and associated cardiovascular disease. In September 2016, Arrowhead Pharmaceuticals, Inc. and Amgen Inc. announced a license and collaboration for development of Arrowhead's preclinical program which uses an RNAi conjugated with a GalNAc for the same target as AKCEA-APO(a)-L<sub>Rx</sub>. It is possible that other competitors may produce, develop, and commercialize drugs, or utilize other approaches, to treat patients with CVD. Under its strategic collaboration agreement with Alnylam Pharmaceuticals, Inc., or Alnylam, Ionis received an exclusive, royalty-bearing license to Alnylam's chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against Apo(a),

which means that Alnylam agreed not to use the exclusively-licensed technology to develop or commercialize an oligonucleotide against Apo(a).

AKCEA-ANGPTL3-L<sub>Rx</sub> may compete with a monoclonal antibody that binds to ANGPTL3 that Regeneron Pharmaceuticals, Inc. is developing, currently in Phase 2 development for the treatment of homozygous familial hypercholesterolemia and severe forms of hyperlipidemia. Additionally, many patients with familial hyperlipidemias are treated using diet and statins, which have limited effect in these patients.

AKCEA-APOCIII-L<sub>Rx</sub> may compete with gemcabene, an oral small molecule that reduces ApoC-III, that Gemphire Therapeutics, Inc. is developing to treat patients with triglycerides above 500 mg/dL. Gemphire is conducting a Phase 2 study of gemcabene in patients with severely high triglycerides. We are aware of other approaches such as RNA interference, or RNAi, that are in preclinical development for ApoC-III-driven cardiometabolic disease.

### **Intellectual Property**

We have in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, our other drugs in development and, more generally, the development and commercialization of oligonucleotide therapeutics. Our objective is to continue to develop and strengthen our proprietary position to further protect our drugs.

We obtained our rights to the patents covering volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub> and our other drugs in development and our rights in Ionis' proprietary technology platform and know-how under our development, commercialization and license agreement with Ionis. We seek to expand our portfolio of patents and patent applications by filing and prosecuting existing patent rights and filing additional patent applications.

We seek patent protection in significant markets and/or countries for each drug in development. We also seek to maximize patent term. The patent exclusivity period for a drug will prevent generic drugs from entering the market. Patent exclusivity depends on a number of factors including initial patent term and available patent term extensions based upon delays caused by the regulatory approval process.

### ***ApoC-III, Volanesorsen and AKCEA-APOCIII-L<sub>Rx</sub> Intellectual Property***

We have an exclusive license under Ionis' ApoC-III patent estate to develop and commercialize volanesorsen and the LICA follow-on drug AKCEA-APOCIII-L<sub>Rx</sub>. The ApoC-III patent estate includes patent claims in the United States drawn to the use of antisense compounds complementary to the mRNA of human ApoC-III including compounds designed to the region targeted by volanesorsen and AKCEA-APOCIII-L<sub>Rx</sub> (US 7,598,227), which excluding any additional term adjustments or patent term extensions, expires in 2023. Similar claims covering compounds complementary to any site on human ApoC-III have granted in Australia.

The ApoC-III patent estate also includes issued patent claims to the specific antisense sequence and chemical composition of volanesorsen in the United States (US 7,750,141), Australia, and Europe (EP1622597). The issued claims in the United States should protect volanesorsen from generic competition in the United States until at least 2023. In addition, depending upon the timing, duration and specifics of FDA regulatory review, this patent may be eligible for patent term restoration to recapture a portion of the term lost during such review. We are also pursuing additional patent applications directed to methods of using volanesorsen and other ApoC-III

compounds for treating various disorders including FCS in jurisdictions worldwide. Claims drawn to methods of using ApoC-III specific inhibitors, and specifically compounds designed to target the same sequence as volanesorsen and AKCEA-APOCIII-L<sub>Rx</sub>, for treating FCS have issued in the United States (US 9,593,333) and, will expire in 2034, excluding any additional term adjustments or patent term extensions.

The ApoC-III patent estate also includes issued patent claims covering the specific chemical composition of AKCEA-APOCIII-L<sub>Rx</sub> in the United States (US 9,163,239). The claims should protect AKCEA-APOCIII-L<sub>Rx</sub> from generic competition until at least 2034. We are pursuing additional patent coverage for AKCEA-APOCIII-L<sub>Rx</sub> in jurisdictions worldwide.

#### ***Apo(a) and AKCEA-APO(a)-L<sub>Rx</sub> Intellectual Property***

We have an exclusive license under Ionis' Apo(a) patent estate to develop and commercialize AKCEA-APO(a)-L<sub>Rx</sub>. The Apo(a) patent estate includes issued patent claims to the specific antisense sequence and chemical composition of AKCEA-APO(a)-L<sub>Rx</sub> in the United States (US 9,181,550). The issued claims directed to the composition should protect AKCEA-APO(a)-L<sub>Rx</sub> from generic competition in the United States until at least 2034. In addition, patent term restoration may be available to recapture a portion of the term lost during FDA regulatory review. We are also pursuing additional patent applications designed to protect the AKCEA-APO(a)-L<sub>Rx</sub> composition and additional dosing and methods of use in jurisdictions worldwide.

#### ***ANGPTL3 and AKCEA-ANGPTL3-L<sub>Rx</sub> Intellectual Property***

We have an exclusive license under Ionis' ANGPTL3 patent estate to develop and commercialize AKCEA-ANGPTL3-L<sub>Rx</sub>. The ANGPTL3 patent estate includes issued patent claims drawn to the use of antisense compounds complementary to ANGPTL3 RNA for inhibiting the production of ANGPTL3 (US 8,653,047). The ANGPTL3 patent estate also includes issued patent claims covering the specific antisense sequence and chemical composition of AKCEA-ANGPTL3-L<sub>Rx</sub> in the United States (US 9,382,540). The issued claims directed to the chemical composition should protect AKCEA-ANGPTL3-L<sub>Rx</sub> from generic competition until at least 2035. We are pursuing additional patent claims designed to protect the sequence and chemical composition of AKCEA-ANGPTL3-L<sub>Rx</sub> in jurisdictions worldwide.

## **Trade Secrets**

In addition to the protections afforded by patents and other regulatory protections, we may rely, in some circumstances, on trade secrets to protect our technology. Trade secrets may be useful to protect proprietary know-how that is not patentable or which we elect not to patent. Trade secrets may also be useful for processes or improvements for which patents are difficult to enforce. We also protect our drugs and the proprietary technology platform by confidentiality agreements with employees, consultants, advisors, contractors, and collaborators. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems.

## **Manufacturing**

We believe we have sufficient manufacturing capacity, through Ionis, to meet our current development needs, including the Phase 3 clinical studies for volanesorsen. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs. Ionis has agreed to supply the API and the finished drug product for the clinical studies for each of the drugs in our pipeline through the end of 2017. Ionis also has agreed to supply the API and, through its outside vendors, the finished drug product for at least the first two years of volanesorsen's commercial launch. Ionis has long-standing and strong relationships with third party vendors who can supply us with both API and finished drug product, and are currently supplying API and finished drug product to other of Ionis' partners. Ionis also has long-standing and strong relationships with the vendors who supply the key raw materials to Ionis to make our drugs and to the other major oligonucleotide contract manufacturers. We also believe that with anticipated benefits from increases in scale and improvements in chemistry, through Ionis or third parties, we will be able to manufacture our antisense drugs at commercially reasonable prices.

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides like antisense drugs. As a result, Ionis dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since Ionis can use variants of the same nucleotide building blocks and the same type of equipment to produce their oligonucleotide drugs, they found that the same techniques used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up their manufacturing capabilities, Ionis has greatly reduced the cost of producing oligonucleotide drugs. For example, Ionis has significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing its capacity to make the drugs. Through both Ionis' internal research and development programs and collaborations with outside vendors, we may benefit from even greater efficiency and further cost reductions. In addition, if Novartis exercises its option to license AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>, Novartis will be responsible for the long term supply of drug substance and finished drug product for the licensed drug.

For LICA-conjugated drugs, to date, Ionis has manufactured itself or through a contract manufacturing organization only limited supplies of LICA for their own and our own nonclinical and clinical studies. LICA enables lower doses than unconjugated oligonucleotides. Along with Ionis' expertise in optimizing manufacturing of oligonucleotides, we believe this will enable the development of new processes to scale up manufacturing of these LICA conjugated drugs at commercially competitive prices.

## Government Regulation and Approval

### *United States—FDA Process*

In the United States, the FDA regulates drugs. The Federal Food, Drug and Cosmetic Act, or FDCA, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of drugs. To obtain regulatory approvals in the United States and in foreign countries, and subsequently comply with applicable statutes and regulations, we will need to spend substantial time and financial resources.

### *Approval Process*

The FDA must approve any new unapproved drug or a drug with certain changes to a previously approved drug before a manufacturer can market it in the United States. If a company does not comply with applicable United States requirements it may be subject to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending applications, Warning or Untitled Letters, clinical holds, drug recalls, drug seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution. The steps we must complete before we can market a drug include:

- completion of preclinical laboratory tests, animal studies, and formulation studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical studies start. The sponsor must update the IND annually;
- approval of the study by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical study begins;
- performance of adequate and well-controlled human clinical studies to establish the safety and efficacy of the drug for each indication to FDA's satisfaction;
- submission to the FDA of an NDA;
- potential review of the drug application by an FDA advisory committee, where appropriate and if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities to assess compliance with current good manufacturing practices, cGMP, or regulations; and
- FDA review and approval of the NDA.

It generally takes companies many years to satisfy the FDA approval requirements, but this varies substantially based upon the type, complexity, and novelty of the drug or disease. Preclinical tests include laboratory evaluation of a drug's chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the drug. The conduct of the preclinical tests must comply with federal regulations and requirements, including GLP. The company submits the results of the preclinical testing to the FDA as part of an IND along with other information, including information about the drug's chemistry, manufacturing and controls, and a proposed clinical study protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after submitting the initial IND.

The FDA requires a 30-day waiting period after the submission of each IND before a company can begin clinical testing in humans in the United States. If the FDA has neither commented on nor questioned the IND within this 30-day period, the IND sponsor may begin the proposed clinical study. However, the FDA may, within the 30-day time period, raise concerns or questions relating to one or more proposed clinical studies and place the clinical study on a clinical hold. In such a case, the company and the FDA must resolve any outstanding concerns before the company begins the

clinical study. Accordingly, the submission of an IND may or may not be sufficient for the FDA to permit the sponsor to start a clinical study. The company must also make a separate submission to an existing IND for each successive clinical study conducted during drug development.

### *Clinical Studies*

Clinical studies involve administering the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. The company must conduct clinical studies:

- in compliance with federal regulations;
- in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical study sponsors, administrators, and monitors; as well as; and
- under protocols detailing the objectives of the trial, the safety monitoring parameters, and the effectiveness criteria.

The company must submit each protocol involving testing on United States patients and subsequent protocol amendments to the FDA as part of the IND. The FDA may order the temporary, or permanent, discontinuation of a clinical study at any time, or impose other sanctions, if it believes that the sponsor is not conducting the clinical study in accordance with FDA requirements or presents an unacceptable risk to the clinical study patients. The sponsor must also submit the study protocol and informed consent information for patients in clinical studies to an IRB for approval. An IRB may halt the clinical study, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Companies generally divide the clinical investigation of a drug into three or four phases.

- *Phase 1.* The company evaluates the drug in healthy human subjects or patients with the target disease or condition. These studies typically evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational new drug in humans, the side effects associated with increasing doses, and if possible, gain early evidence on effectiveness.
- *Phase 2.* The company administers the drug to a limited patient population to evaluate dosage tolerance and optimal dosage, identify possible adverse side effects and safety risks and preliminarily evaluate efficacy.
- *Phase 3.* The company administers the drug to an expanded patient population, generally at geographically dispersed clinical study sites, to generate enough data to statistically evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational drug and to provide an adequate basis for product approval.
- *Phase 4.* In some cases, the FDA may condition approval of an NDA for a drug on the company's agreement to conduct additional clinical studies after approval. In other cases, a sponsor may voluntarily conduct additional clinical studies after approval to gain more information about the drug. We typically refer to such post-approval studies as Phase 4 clinical studies.

While companies usually conduct these phases sequentially, they are sometimes overlapped or combined. A combined phase trial, such as a Phase 1/2 or a Phase 2/3 trial, is one that combines elements of objectives from two ordinarily sequential phases of development. For example, in a Phase 1/2 trial, the objectives may include both dose-finding and initial efficacy. In a Phase 2/3 trial, dosing regimen or population selection objectives are combined with confirmation of the safety and efficacy of the administration schedule in the intended population.



A pivotal study is a clinical study that adequately meets regulatory agency requirements to evaluate a drug's efficacy and safety to justify the approval of the drug. Generally, pivotal studies are Phase 3 studies, but the FDA may accept results from Phase 2 studies if the study design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations in which there is an unmet medical need and the results are sufficiently robust.

The FDA, the IRB or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee, may oversee some clinical studies. This group provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study. We may also suspend or terminate a clinical study based on evolving business objectives and the competitive climate.

#### *Submission of an NDA*

After we complete the required clinical testing, we can prepare and submit an NDA to the FDA, who must approve the NDA before we can start marketing the drug in the United States. An NDA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the drug's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical studies on a drug, or from a number of alternative sources, including studies initiated by investigators. To support marketing authorization, the data we submit must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug to the FDA's satisfaction.

The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved new drug application are also subject to annual drug and establishment user fees. The FDA typically increases these fees annually. Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages and user-fee waivers.

The FDA has 60 days from its receipt of an NDA to determine whether it will accept the application for filing based on the agency's threshold determination that the application is sufficiently complete to permit substantive review. Once the FDA accepts the filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Under the Prescription Drug User Fee Act, the FDA has a goal of responding to standard review NDAs within ten months after the 60-day filing review period, but this timeframe is often extended. The FDA reviews most applications for standard review drugs within ten to 12 months and most applications for priority review drugs within six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment, or provide a treatment where no adequate therapy exists.

The FDA may also refer applications for novel drugs that present difficult questions of safety or efficacy, to an advisory committee. This is typically a panel that includes clinicians and other experts that will review, evaluate, and recommend whether the FDA should approve the application. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP, and will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the drug unless compliance with cGMP is satisfactory and

the NDA contains data that provide evidence that the drug is safe and effective in the indication studied.

#### *The FDA's Decision on an NDA*

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter indicates that the FDA has completed its review of the application, and the agency has determined that it will not approve the application in its present form. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional clinical data and/or other significant, expensive and time-consuming requirements related to clinical studies, preclinical studies and/or manufacturing. The FDA has committed to reviewing resubmissions of the NDA addressing such deficiencies in two or six months, depending on the type of information included. Even if we submit such data the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Also, the government may establish additional requirements, including those resulting from new legislation, or the FDA's policies may change, which could delay or prevent regulatory approval of our drugs under development.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for REMS can materially affect the potential market and profitability of the drug. Moreover, the FDA may condition approval on substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, the FDA may withdraw drug approvals if the company fails to comply with regulatory standards or identifies problems following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before we can implement the change. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing new NDAs. As with new NDAs, FDA often significantly extends the review process with requests for additional information or clarification.

#### *Expedited review and accelerated approval programs*

A sponsor may seek approval of its drug candidate under programs designed to accelerate FDA's review and approval of NDAs. For example, the FDA may grant Fast Track Designation to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if the application meets relevant criteria. Based on results of the Phase 3 clinical study(ies) submitted in an NDA, upon the request of an applicant, the FDA may grant the NDA a priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. The FDA grants priority review where there is evidence that the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If the criteria for priority review are not met, the application is subject to the standard FDA review period of ten months after FDA accepts the application for filing. Priority review

designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve an NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. The FDA generally requires post-marketing studies or completion of ongoing studies after marketing authorization to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, a sponsor may seek FDA designation of its drug candidate as a breakthrough therapy if the drug can, alone or in combination with one or more other drugs, treat a serious or life threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

#### *Post-approval Requirements*

The FDA regulates drugs that we manufacture or distribute pursuant to FDA approvals and has specific requirements pertaining to recordkeeping, periodic reporting, drug sampling and distribution, advertising and promotion and reporting of adverse experiences with the drug. After approval, the FDA must provide review and approval for most changes to the approved drug, such as adding new indications or other labeling claims. There also are continuing, annual user fee requirements for any marketed drugs and the establishments who manufacture our drugs, as well as new application fees for supplemental applications with clinical data.

In some cases, the FDA may condition approval of an NDA for a drug on the sponsor's agreement to conduct additional clinical studies after approval. In other cases, a sponsor may voluntarily conduct additional clinical studies after approval to gain more information about the drug. We typically refer to such post-approval studies as Phase 4 clinical studies.

Drug manufacturers are subject to periodic unannounced inspections by the FDA and state agencies for compliance with cGMP requirements. There are strict regulations regarding changes to the manufacturing process, and, depending on the significance of the change, it may require prior FDA approval before we can implement it. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical quantities of our drugs, and expect to rely in the future on third parties for the production of commercial quantities. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a drug or the failure to comply with applicable requirements may result in restrictions on a drug, manufacturer or holder of an approved NDA, including withdrawal or recall of the drug from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing.

The FDA may withdraw approval if a company does not comply with regulatory requirements and maintain standards or if problems occur after the drug reaches the market. If a company or the FDA discovers previously unknown problems with a drug, including adverse events of unanticipated severity or frequency, issues with manufacturing processes or the company's failure to comply with regulatory requirements, the FDA may revise to the approved labeling to add new safety information; impose post-marketing studies or other clinical studies to assess new safety risks; or impose distribution or other restrictions under a REMS program. Other potential consequences may include:

- restrictions on the marketing or manufacturing of the drug, complete withdrawal of the drug from the market or drug recalls;
- fines, warning letters or holds on post-approval clinical studies;
- the FDA refusing to approve pending NDAs or supplements to approved NDAs, or suspending or revoking drug license approvals;
- drug seizure or detention, or refusal to permit the import or export of drugs; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of drugs that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. We could be subject to significant liability if we violated these laws and regulations.

#### *Orphan Drug Designation*

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making the drug for this type of disease or condition will be recovered from sales in the United States.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. In addition, if a drug receives FDA approval for the indication for which it has orphan designation, the drug has orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the drug with orphan exclusivity.

#### *Pediatric Information*

Under the Pediatric Research Equity Act, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which the FDA has granted an orphan designation.

#### *U.S. Patent Term Restoration*

Patent term can also be extended based on the amount of time the patented drug spends in regulatory review for drug approval. The length of time between drug launch and patent expiration is significantly less than the full 20-year patent term because companies often obtain the patents relating to a drug early in development and the development path for regulatory approval is long. In the United States, The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly

known as the Hatch-Waxman Act) permits a patent holder to seek a patent extension, commonly called patent term restoration, for a patent on a drug governed by the FDCA. The length of patent term restoration is related to the length of time the drug is under regulatory review. Patent term restoration can be a maximum of 5 years and cannot extend the remaining term of a patent beyond a total of 14 years from the date of drug approval. Only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug in that jurisdiction.

#### *Abbreviated New Drug Applications for Generic Drugs*

In 1984, with passage of the Hatch-Waxman Act, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order to approve an ANDA, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is bioequivalent to the RLD. Under the statute, a generic drug is bioequivalent to an RLD if “the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the listed drug...”

Upon approval of an ANDA, the FDA indicates that the generic drug is “therapeutically equivalent” to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication “Approved Drug Products with Therapeutic Equivalence Evaluations,” also referred to as the “Orange Book.” Physicians and pharmacists consider an “AB” therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA’s designation of an “AB” rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

The FDCA provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations that were conducted by or for the applicant and are essential to the approval of the application, and are not bioavailability or bioequivalence studies. This three-year exclusivity period often protects changes to a previously approved drug, such as a new dosage form, route of administration, combination or indication.

#### *Hatch-Waxman Patent Certification and the 30-month Stay*

Upon approval of an NDA or a supplement thereto, NDA sponsors must list with the FDA each patent with claims that cover the applicant’s drug or a method of using the drug. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference drug in the Orange Book, except for patents covering methods of use for which the

ANDA applicant is not seeking approval. Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new drug.

A certification that the new drug will not infringe the already approved drug's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the FDA will not approve the ANDA application until all the listed patents claiming the referenced drug have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

#### *Disclosure of Clinical Study Information*

Sponsors of clinical studies of FDA-regulated products, including drugs, are required to register and disclose certain clinical study information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical study is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical studies after completion. Disclosure of the results of these studies can be delayed until the new drug or new indication being studied has been approved. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

#### *Healthcare Reform*

In the United States and foreign jurisdictions, the legislative landscape continues to evolve. There have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the United States federal and state levels that seek to reduce healthcare costs. In March 2010, the Patient Protection and Affordable Care Act, or PPACA, was enacted, which includes measures that have significantly changed health care financing by both governmental and private insurers. The provisions of the PPACA of importance to the pharmaceutical and biotechnology industry are, among others, the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;



- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations, unless the drug is subject to discounts under the 340B drug discount program;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- new requirements under the federal Physician Payments Sunshine Act for drug manufacturers to report information related to payments and other transfers of value made to physicians and teaching hospitals as well as ownership or investment interests held by physicians and their immediate family members; and
- a new requirement to annually report certain drug samples that manufacturers and distributors provide to licensed practitioners, or to pharmacies of hospitals or other healthcare entities.

Since its enactment there have been judicial and Congressional challenges to or proposals to amend certain aspects of PPACA. We expect there will be additional challenges and amendments to it in the future.

In addition, other health reform measures have been proposed and adopted in the United States since PPACA was enacted. For example, as a result of the Budget Control Act of 2011, providers are subject to Medicare payment reductions of 2% per fiscal year through 2025 unless additional Congressional action is taken. Further, the American Taxpayer Relief Act of 2012 reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments from providers from three to five years. More recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs.

#### *European Union—EMA Process*

In the European Union, drugs follow a similar demanding process as that we described above for the United States and the ICH Common Technical Document is the basis for applications. Prior to submitting a European Marketing Authorization Application, or MAA, it is necessary to gain approval of a detailed Pediatric Investigation Plan, or PIP, with the European Medicines Agency's Pediatric Committee, or PDCO. After gaining PIP approval, EU regulatory authorities can authorize the drug using either the centralized authorization procedure or national authorization procedures.

### *Centralized Procedure*

Under the centralized procedure, after the EMA issues an opinion, the European Commission issues a single marketing authorization valid across the European Union, as well as Iceland, Liechtenstein and Norway. The centralized procedure is compulsory for human drugs that are: derived from biotechnology processes, such as genetic engineering; contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions; and officially designated orphan drugs. For drugs that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the EMA, as long as the drug concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.

### *National Authorization Procedures*

There are also two other possible routes to authorize medicinal products in several countries, which are available for products that fall outside the scope of the centralized procedure:

- Decentralized procedure. Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one European Union country of a medicinal product that has not yet been authorized in any European Union country and that does not fall within the mandatory scope of the centralized procedure.
- Mutual recognition procedure. In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, in accordance with the national procedures of that country. Thereafter, further marketing authorizations can be sought from other European Union countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

### *Good Manufacturing Practices*

Like the FDA, the EMA, the competent authorities of the European Union Member States and other regulatory agencies regulate and inspect equipment, facilities and processes used in the manufacturing of drugs prior to approving a drug. If, after receiving clearance from regulatory agencies, a company makes a material change in manufacturing equipment, location or process, additional regulatory review and approval may be required. Once we or our partners commercialize drugs, we will be required to comply with cGMP, and drug-specific regulations enforced by, the European Commission, the EMA and the competent authorities of European Union Member States following drug approval. Also like the FDA, the EMA, the competent authorities of the European Union Member States and other regulatory agencies also conduct regular, periodic visits to re-inspect equipment, facilities, and processes following the initial approval of a drug. If, as a result of these inspections, the regulatory agencies determine that our or our partners' equipment, facilities, or processes do not comply with applicable regulations and conditions of drug approval, they may seek civil, criminal or administrative sanctions and/or remedies against us, including the suspension of our manufacturing operations or the withdrawal of our drug from the market.

### *Data and Market Exclusivity*

Similar to the United States, there is a process to authorize generic versions of innovative drugs in the European Union. Generic competitors can submit abridged applications to authorize generic versions of drugs authorized by EMA through a centralized procedure referencing the innovator's data and demonstrating bioequivalence to the reference drug, among other things. New drugs in the European Union can receive eight years of data exclusivity coupled with two years of market exclusivity, and a potential one-year extension, if the marketing authorizations holder obtains an authorization for one or more new therapeutic indications that demonstrates "significant clinical

benefit” in comparison with existing therapies. This system is usually referred to as “8+2.” Abridged applications cannot rely on an innovator’s data until after expiry of the eight-year date exclusivity term, meaning that a competitor can file an application for a generic drug but the drug cannot be marketed until the end of the market exclusivity term.

#### *Other International Markets—Drug Approval Process*

In some international markets (such as China or Japan), although data generated in United States or European Union studies may be submitted in support of a marketing authorization application, regulators may require additional clinical studies conducted in the host territory, or studying people of the ethnicity of the host territory, prior to the filing or approval of marketing applications within the country.

#### *Pricing and Reimbursement*

Significant uncertainty exists as to the coverage and reimbursement status of any drugs for which we may obtain regulatory approval. In the United States and in other countries, sales of any drugs for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug may be separate from the process for setting the reimbursement rate that the payor will pay for the drug. Third-party payors may limit coverage to specific drugs on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Moreover, a payor’s decision to provide coverage for a drug does not imply that an adequate reimbursement rate will be approved. Additionally, coverage and reimbursement for drugs can differ significantly from payor to payor. One third-party payor’s decision to cover a particular drug does not ensure that other payors will also provide coverage for the drug, or will provide coverage at an adequate reimbursement rate. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of drugs and services, in addition to their safety and efficacy. To obtain coverage and reimbursement for any drug that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies to demonstrate the medical necessity and cost-effectiveness of our drug. These studies will be in addition to the studies required to obtain regulatory approvals. If third-party payors do not consider a drug to be cost-effective compared to other available therapies, they may not cover the drug after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its drugs at a profit.

The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic drugs for branded prescription drugs. By way of example, the PPACA contains provisions that may reduce the profitability of drugs, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies’ share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for our drugs.

In the European Community, governments influence the price of drugs through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those drugs to consumers. Some jurisdictions operate positive and negative list systems under which drugs may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical studies that compare the cost effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new drugs. In addition, in some countries, cross border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any drugs for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, the focus on cost containment measures in the United States and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if we attain favorable coverage and reimbursement status for one or more drugs for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

### *Sales and Marketing*

Numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the U.S. Department of Health and Human Services, the U.S. Department of Justice, and similar foreign, state and local government authorities, regulate sales, promotion and other activities following drug approval. As described above, the FDA regulates all advertising and promotion activities for drugs under its jurisdiction both prior to and after approval. Only those claims relating to safety and efficacy that the FDA has approved may be used in labeling. Physicians may prescribe legally available drugs for uses that are not described in the drug's labeling and that differ from those we tested and the FDA approved. Such off-label uses are common across medical specialties, and often reflect a physician's belief that the off-label use is the best treatment for the patients. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. If we do not comply with applicable FDA requirements we may face adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA. Promotion of off-label uses of drugs can also implicate the false claims laws described below.

In the United States sales, marketing and scientific/educational programs must also comply with various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. Due to the breadth of the statutory provisions, limited statutory exceptions and regulatory safe harbors, and the absence of guidance in the form of regulations and very few court decisions addressing industry practices, it is possible that our practices might be challenged under anti-kickback or similar laws. Moreover, recent healthcare reform legislation has strengthened these laws. For example, the PPACA among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes to clarify that a person or entity does not need to have actual knowledge of this statute or specific intent to violate it. In addition, PPACA clarifies that the government may assert that a claim that includes items or services resulting from a violation of the federal anti-kickback statute constitutes a

false or fraudulent claim for purposes of the false claims statutes. False claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment, to third-party payors (including Medicare and Medicaid) claims for reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Our activities relating to the sale and marketing of our drugs may be subject to scrutiny under these laws. Violations of fraud and abuse laws may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties also can be imposed upon executive officers and employees, including criminal sanctions against executive officers under the so-called “responsible corporate officer” doctrine, even in situations where the executive officer did not intend to violate the law and was unaware of any wrongdoing.

Given the significant penalties and fines that can be imposed on companies and individuals if convicted, allegations of such violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals can bring similar actions. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing attention being given to them by law enforcement authorities. Other healthcare laws that may affect our ability to operate include the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; analogous state laws governing the privacy and security of health information, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, and the Physician Payments Sunshine Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members. Further, there are an increasing number of state laws that require manufacturers to make reports to states on pricing and marketing information. Many of these laws contain ambiguities as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

Similar rigid restrictions are imposed on the promotion and marketing of drugs in the European Union and other countries. Even in those countries where we may not be directly responsible for the promotion and marketing of our drugs, if our potential international distribution partners engage in inappropriate activity it can have adverse implications for us.

#### *The Foreign Corrupt Practices Act*

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party, or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Activities

that violate the FCPA, even if they occur wholly outside the United States, can result in criminal and civil fines, imprisonment, disgorgement, oversight, and debarment from government contracts

### **Employees**

As of March 31, 2017, we had 30 full-time employees, 17 of whom were engaged in development activities, nine of whom were engaged in commercialization activities and four of whom were engaged in general and administrative functions. Ionis provides additional personnel to support our research and development and administrative functions. During the first three months of 2017, Ionis provided approximately 29 full time equivalents to support us and our programs. Ionis employees supporting our programs reside at Ionis' facilities in Carlsbad, California.

None of our employees are represented by any collective bargaining agreements. We believe that we maintain good relations with our employees.

### **Facilities**

Our corporate headquarters is located in Cambridge, Massachusetts. We currently occupy approximately 9,200 square feet of office space. Our lease expires for 6,100 square feet at the end of July 2018 and our lease for the remaining 3,100 square feet expires in April 2020. We believe our existing facility meets our current needs. We will need additional space in the future as we continue to build our development, commercial, and support teams. We believe we can find suitable additional space in the future on commercially reasonable terms.

### **Legal Proceedings**

From time to time, we may be involved in various claims and legal proceedings relating to claims arising out of our operations. We are not currently a party to any legal proceedings that, in the opinion of our management, are likely to have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.



## MANAGEMENT

### Executive Officers and Directors

The following table sets forth certain information regarding our executive officers and directors as of March 31, 2017:

<u>Name</u>	<u>Age</u>	<u>Position</u>
<i>Executive Officers</i>		
Paula Soteropoulos . . . . .	49	President, Chief Executive Officer and Director
Jeffrey M. Goldberg . . . . .	44	Chief Operating Officer
Elizabeth L. Hougen . . . . .	55	Chief Financial Officer
Louis St. L. O’Dea, MB BCh BAO. FRCP(C) . . . . .	66	Chief Medical Officer
<i>Non-Employee Directors</i>		
Stanley T. Crooke, M.D., Ph.D. . . . .	72	Chairman of the Board of Directors
B. Lynne Parshall, J.D. . . . .	63	Director
Edward Fitzgerald* . . . . .	62	Director
Christopher Gabrieli . . . . .	57	Director
Elaine Hochberg . . . . .	60	Director
Sandford D. Smith . . . . .	70	Director

\* Mr. Fitzgerald joined our board of directors in May 2017.

**Paula Soteropoulos**, Ms. Soteropoulos joined Akcea as President and Chief Executive Officer and as a member of our board of directors in January 2015. Prior to joining Akcea, Ms. Soteropoulos was a member of the executive leadership team of Moderna Therapeutics Inc., a private biotechnology company, serving as the Cardiometabolic Business Unit General Manager and Senior Vice President of Strategic Alliances from July 2013 to December 2014. Prior to Moderna, Ms. Soteropoulos spent 21 years at Genzyme Corporation in various leadership positions driving strategy, sales and marketing, business development, manufacturing process development, strategic capacity planning, and supply chain development. Since July 2013, Ms. Soteropoulos has served on the supervisory board of uniQure N.V., a public biotechnology company. Ms. Soteropoulos also serves on the advisory board of the Tufts University Chemical and Biological Engineering Department. Our board of directors believes that Ms. Soteropoulos is uniquely suited to serve on our board of directors because of her experience in the biotechnology industry and her daily insight into corporate matters as our President and Chief Executive Officer.

**Jeffrey M. Goldberg**, Mr. Goldberg joined Akcea as Chief Operating Officer in January 2015. Prior to joining Akcea, from December 2012 to September 2014, Mr. Goldberg was a member of the executive leadership team at Proteostasis Therapeutics, Inc., a now public biotechnology company focusing on neurology and orphan diseases, where he served as Vice President of Business Operations. Prior to that, Mr. Goldberg spent over 11 years in positions of increasing responsibility with Genzyme and Sanofi S.A., most recently as Associate Vice President, Project Head, within Sanofi Oncology.

**Elizabeth L. Hougen**, Ms. Hougen has served as Chief Financial Officer to Akcea since January 2015 under the services agreement between Akcea and Ionis. Ms. Hougen has served as Senior Vice President, Finance and Chief Financial Officer of Ionis since January 2013 and currently serves in this role. From January 2007 to December 2012, Ms. Hougen served as Ionis’ Vice President, Finance and Chief Accounting Officer, and from May 2000 to January 2007, she served

as Ionis' Vice President, Finance. Prior to joining Ionis in 2000, Ms. Hougen was Executive Director, Finance and Chief Financial Officer for Molecular Biosystems, Inc., a public biotechnology company.

**Louis St. L. O'Dea, MB BCh BAO. FRCP(C)**, Dr. O'Dea joined Akcea as Chief Medical Officer in January 2016. Prior to joining Akcea, Dr. O'Dea was Chief Medical Officer at Oxford Immunotec Global PLC, a private diagnostics company, from June 2014 to January 2016, overseeing medical affairs and clinical development. Prior to Oxford, Dr. O'Dea was Chief Medical Officer and Head of Regulatory Affairs at Moderna from January 2012 to June 2014. Before Moderna, Dr. O'Dea had positions including Chief Medical Officer at Radius Health, Inc., a public biopharmaceuticals company, an academic position at McGill University, and worldwide Head of Clinical Development for Endocrine and Metabolic products at Serono.

**Stanley T. Crooke, M.D., Ph.D.**, Dr. Crooke has served as a member of our board of directors since January 2015. Dr. Crooke is a founder of Ionis and has been Chief Executive Officer and a Director since January 1989. He was elected Chairman of Ionis' board of directors in February 1991. Prior to founding Ionis, from 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories. He is currently a member of the board of directors of BIO, a biotechnology industry association. He is the named inventor on some of the key patents in the field of RNA-targeted therapeutics, and has over 30 years of drug discovery and development experience. Our board of directors believes Dr. Crooke is uniquely suited to serve on our board of directors primarily because, as the Chief Executive Officer and founder of Ionis, he has dedicated over 26 years to discovering and developing Ionis' antisense technology platform.

**B. Lynne Parshall, J.D.**, Ms. Parshall has served as a member of our board of directors since January 2015. Ms. Parshall has served as a Director of Ionis since September 2000. She has been the Ionis Chief Operating Officer since December 2007 and previously served as the Chief Financial Officer from June 1994 to December 2012. She also served as the Ionis Corporate Secretary through 2014 and has served in various executive roles since November 1991. Prior to joining Ionis, Ms. Parshall practiced law at Cooley LLP, outside counsel to Ionis and Akcea, where she was a partner from 1986 to 1991. Ms. Parshall is currently a member of the board of directors of Cytokinetics Inc., a public biopharmaceutical company. She was a member of the board of directors of Regulus Therapeutics Inc., a public biopharmaceutical company, from January 2009 to June 2015. She is also a member of the American, California and San Diego bar associations. In addition, Ms. Parshall has over 30 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field. Our board of directors believes Ms. Parshall is uniquely suited to serve on our board of directors primarily because, as the Chief Operating Officer and an executive of Ionis for over 20 years, she has valuable experience and expertise.

**Edward Fitzgerald**, Mr. Fitzgerald has served as a member of our board of directors since May 2017. He has been an independent business advisor since April 2016. From June 2010 to April 2016, Mr. Fitzgerald served as Executive Vice President, Chief Financial Officer and Treasurer of ARIAD Pharmaceuticals, Inc., an international biopharmaceutical company, and was its Senior Vice President, Chief Financial Officer and Treasurer from May 2002 to June 2010. He was Senior Vice President, Chief Financial Officer and Secretary of AltaRex, Inc., a development stage biotechnology company, from 1998 to April 2002. He held management positions at BankBoston Corporation from 1992 to 1997 in its Mergers & Acquisitions Group and its Consumer Lending Group. He was a partner in the Audit and Business Advisory Practice of Arthur Andersen & Co. from 1989 to 1992. Our board of directors believes that Mr. Fitzgerald is uniquely suited to serve on our board of directors because of his background and extensive experience in executive management and financial accounting and reporting, particularly in the biotechnology and pharmaceutical industry.

**Christopher Gabrieli**, Mr. Gabrieli has served as a member of our board of directors since April 2016. Since June 2014, Mr. Gabrieli has served as Chief Executive Officer of Empower Schools, a non-profit education innovation organization, and since May 2014, Mr. Gabrieli has served as a Partner Emeritus at Bessemer Venture Partners, a venture capital fund. Previously, from 1987 to April 2014, Mr. Gabrieli was a Partner at Bessemer, where he led their life sciences practice and made a founding investment in Ionis. Mr. Gabrieli served on Ionis' board of directors from 1989 to 2006. During his time at Bessemer, he invested in over thirty life science and health care companies, including several that became publicly traded. Mr. Gabrieli is also the Chairman of the Massachusetts Board of Higher Education and a part-time Lecturer at the Harvard Graduate School of Education. Our board of directors believes that Mr. Gabrieli is uniquely suited to serve on our board of directors because of his substantial experience as an investor in the life sciences industry.

**Elaine Hochberg**, Ms. Hochberg has served as a member of our board of directors since March 2017. Currently, Ms. Hochberg is a managing partner of Elaran, LLC, a business strategy and management firm. Ms. Hochberg served in various senior leadership positions at Forest Laboratories, Inc. from June 1997 to June 2014 when the company was sold to Actavis. Her positions included Executive Vice President, International, Strategic Planning and Government Affairs from December 2013 to June 2014, Executive Vice President, US Sales and Marketing, Chief Commercial Officer from 2010 to November 2013, Senior Vice President, Marketing, Chief Commercial Officer, from 2007 to 2010, Senior Vice President, Marketing from 1999 to 2007 and Vice President, Marketing from 1997 to 1999. Ms. Hochberg began her pharmaceutical career in July of 1985 at Sandoz Pharmaceuticals (now Novartis). In April of 1991, she joined Wyeth-Ayerst Laboratories (now Pfizer) where she held several positions of increasing responsibility, ultimately serving as Assistant Vice-President, Marketing of the company's Vaccines and Pediatrics division. She also serves on the boards of several nonprofit organizations in the New York City area. Our board of directors believes that Ms. Hochberg is uniquely suited to serve on our board of directors because of her over 30 years of experience leading commercial organizations for life science companies.

**Sandford ("Sandy") D. Smith**, Mr. Smith has served as a member of our board of directors since March 15, 2017. For the past 20 years, he has focused on drugs and therapies for rare genetic diseases. Since December 2011, Mr. Smith has served as Founder and Chairman of Global Biolink Partners, a consulting firm advising public biopharmaceutical companies on commercial strategy and international business models. From July 2015 to January 2016, Mr. Smith served as interim Chief Executive Officer of Aegerion Pharmaceuticals, Inc., a biotechnology company, and following Aegerion's merger with Novilion Therapeutics, Inc., he served as Novilion's Vice Chair until March 2017. From 1996 to 2011, Mr. Smith held various positions at Sanofi-Genzyme (formerly Genzyme Corporation), most recently leading the integration of Genzyme's international business into Sanofi's global organization. Prior to that, he served as Executive Vice President of Genzyme Corporation, and President of Genzyme International. From 1986 to 1996, Mr. Smith was President, Chief Executive Officer and a member of the Board of Directors of RepliGen Corporation. From 1977 to 1985, Mr. Smith held various positions at Bristol-Myers Squibb, most recently serving as Vice President of Business Development and Strategic Planning for the Pharmaceutical and Nutritional Division. He currently serves on the boards of Cytokinetics Inc., Apricus Biosciences and Neuralstem Inc., each a publicly traded biopharmaceutical company. Our board of directors believes that Mr. Smith is uniquely suited to serve on our board of directors because of his substantial experience in strategic executive roles for publicly traded life sciences companies.

## **Board Composition**

Our business and affairs are organized under the direction of our board of directors, or the Board, which currently consists of seven members. Our Board's primary responsibilities are to

provide oversight, strategic guidance, counseling and direction to our management. Our Board meets on a regular basis and additionally as required. In accordance with the terms of our certificate of incorporation and bylaws that will become effective upon the closing of this offering, our Board will be elected annually to a one-year term.

Our Board has undertaken a review of the independence of our directors and considered whether any director has a material relationship with us that could compromise his or her ability to exercise independent judgment in carrying out his or her responsibilities. Based upon information requested from and provided by each director concerning such director's background, employment and affiliations, including family relationships, our Board has determined that four of our directors, Messrs. Fitzgerald, Gabrieli and Smith, and Ms. Hochberg, are independent as defined by Rule 5605(a)(2) of the Nasdaq Marketplace Rules. In making these determinations, our Board considered the current and prior relationships that each non-employee director has with our company and all other facts and circumstances that our Board deemed relevant in determining their independence, including the beneficial ownership of our capital stock by each non-employee director and the transactions involving them described in "Certain relationships and related person transactions."

There are no family relationships among any of our directors or executive officers.

### **Board Leadership Structure**

Dr. Crooke is our current Board Chairman, and after we complete this offering, Mr. Gabrieli will serve as our Board Chairman. As a general policy, our Board believes that separation of the positions of Chairman and Chief Executive Officer reinforces the independence of the Board from management, creates an environment that encourages objective oversight of management's performance and enhances the effectiveness of the Board as a whole. As such, Ms. Soteropoulos serves as our President and Chief Executive Officer while Dr. Crooke serves as our Chairman of the Board, but is not an officer. We expect and intend the positions of Chairman of the Board and Chief Executive Officer to continue to be held by two individuals in the future.

### **Board Committees**

Our Board has established three committees: an Audit Committee, a Compensation Committee and a Nominating, Governance and Review Committee. Below is a description of each committee of our Board. Each of the committees has authority to engage legal counsel or other experts or consultants as it deems appropriate to carry out its responsibilities.

#### **Audit Committee**

The Audit Committee of the Board oversees our corporate accounting and financial reporting process. For this purpose, the Audit Committee performs several functions.

The Audit Committee:

- reviews the annual and quarterly financial statements and oversees the annual and quarterly financial reporting processes, including sessions with the auditors in which Akcea's employees and management are not present;
- selects and hires our independent auditors;
- oversees the independence of our independent auditors;
- evaluates our independent auditors' performance; and
- has the authority to hire its own outside consultants and advisors, if necessary.

In addition to the responsibilities listed above, the Audit Committee has the following functions:

- reviewing our annual budget with management and, if acceptable, recommending the budget to the Board for approval;
- setting and approving changes to our investment policy;
- receiving and considering our independent auditors' comments as to the audit of the financial statements and internal controls, adequacy of staff and management performance and procedures in connection with internal controls;
- reviewing and, if appropriate, approving related person transactions;
- establishing and enforcing procedures for the receipt, retention and treatment of complaints regarding accounting or auditing improprieties; and
- pre-approving all audit and non-audit services provided by our independent auditors that are not prohibited by law.

Our Audit Committee is composed of Messrs. Fitzgerald, and Gabrieli and Ms. Parshall. Mr. Fitzgerald serves as the chairperson of our Audit Committee and Mr. Fitzgerald and Ms. Parshall are our financial experts. Under Rule 10A-3 under the Securities Exchange Act of 1934, as amended, or the Exchange Act, we are permitted to phase in our compliance with the independent audit committee requirements set forth in Nasdaq Marketplace Rule 5605(c) and Rule 10A-3 under the Exchange Act as follows: (1) one independent member at the time of listing, (2) a majority of independent members within 90 days of listing and (3) all independent members within one year of listing. Our board of directors has determined that each of Messrs. Fitzgerald and Gabrieli is an independent director under Nasdaq Marketplace Rules and under Rule 10A-3 under the Exchange Act. Within one year of our listing on the Nasdaq Global Select Market, we expect that Ms. Parshall will have resigned from our Audit Committee and that any new directors added to the Audit Committee will be independent under Nasdaq Marketplace Rules and Rule 10A-3.

All Audit Committee members must be financially literate and at least one member must be a "financial expert," as defined by SEC regulations. Our Board has determined that the Audit Committee's financial experts are Mr. Fitzgerald and Ms. Parshall.

Our Audit Committee will operate under a written charter, to be effective immediately prior to the completion of this offering, that satisfies the applicable rules of the Securities and Exchange Commission and the listing standards of the Nasdaq Stock Market.

### **Compensation Committee**

Our Compensation Committee is composed of Mr. Smith, Ms. Hochberg and Dr. Crooke. Mr. Smith serves as the chairperson of our Compensation Committee. We are permitted to phase in our compliance with the independent compensation committee requirements set forth in Nasdaq Marketplace Rule 5605(d) as follows: (1) one independent member at the time of listing, (2) a majority of independent members within 90 days of listing and (3) all independent members within one year of listing. Our board of directors has determined that each of Ms. Hochberg and Mr. Smith is an independent director under Nasdaq Marketplace Rules, a non-employee director as defined in Rule 16b-3 under the Exchange Act and an outside director as that term is defined in Section 162(m) of the Internal Revenue Code of 1986, as amended, or the Code. Within one year of our listing on the Nasdaq Global Select Market, we expect that Dr. Crooke will have resigned from our Compensation Committee and that any new directors added to the Compensation Committee will be independent under Nasdaq Marketplace Rules, as well as non-employee directors as defined in Rule 16b-3 under the Exchange Act and outside directors as that term is defined in Section 162(m) of the Code.



The primary function of the Compensation Committee of the Board is to review, modify (as needed) and approve our overall compensation strategy and policies and approve the compensation and other terms of employment of our executive officers, including our Chief Executive Officer. The Compensation Committee has full access to all of our books, records, facilities and personnel, and authority to obtain, at our expense, advice and assistance from internal and external legal, accounting or other advisors and consultants and other external resources that the Compensation Committee considers necessary or appropriate in the performance of its duties. In particular, the Compensation Committee has the sole authority to retain independent compensation consultants to help the Compensation Committee evaluate executive and director compensation, including the authority to approve the consultants' reasonable fees and other retention terms.

We also have a Non-Management Stock Option Committee that, as delegated by the Compensation Committee, may award stock options and other share awards to employees who are below director level in accordance with guidelines adopted by the Compensation Committee. The Non-Management Stock Option Committee has one member, Ms. Soteropoulos.

Our Compensation Committee will operate under a written charter, to be effective immediately prior to the completion of this offering, that satisfies the applicable rules of the SEC and the listing standards of the Nasdaq Stock Market.

#### **Nominating, Governance and Review Committee**

Our Nominating, Governance and Review Committee is composed of Ms. Parshall and Messrs. Gabrieli and Smith. Ms. Parshall serves as chairperson of the Nominating, Governance and Review Committee. We are permitted to phase in our compliance with the independent nominating committee requirements set forth in Nasdaq Marketplace Rule 5605(e) as follows: (1) one independent member at the time of listing, (2) a majority of independent members within 90 days of listing and (3) all independent members within one year of listing. Our Board has determined that Messrs. Gabrieli and Smith are independent director under Nasdaq Marketplace Rules. Within one year of our listing on the Nasdaq Global Select Market, we expect that Ms. Parshall will have resigned from our Nominating, Governance and Review Committee and that any new directors added to the Nominating, Governance and Review Committee will be independent under Nasdaq Marketplace Rules.

The Nominating, Governance and Review Committee of the Board is responsible for:

- interviewing, evaluating, nominating and recommending individuals for membership on our Board, and considering proposed changes to the Board for approval;
- managing risks associated with the independence of the Board and potential conflicts of interests at the Board level, and periodically reviewing our policies and procedures and making recommendations when appropriate; and
- performing such other functions as may be necessary or convenient for the efficient discharge of the foregoing.

Our Nominating, Governance and Review Committee will operate under a written charter, to be effective immediately prior to the completion of this offering, that satisfies the applicable rules of the SEC and the listing standards of the Nasdaq Stock Market.

#### **Compensation Committee Interlocks and Insider Participations**

None of the members of our Compensation Committee is, or has at any time during the past year been, one of our officers or employees. None of our executive officers currently serves or in the



past year has served as a member of the board of directors or compensation committee of any entity that has one or more executive officers serving on our Board or Compensation Committee.

### **Limitation on Director and Officer Liability and Indemnification**

Our certificate of incorporation that will be in effect when we complete this offering limits the liability of our directors for monetary damages to the fullest extent permitted by Delaware law. Consequently, our directors will not be personally liable to us or our stockholders for monetary damages for any breach of fiduciary duties as directors, except liability for:

- any breach of the director's duty of loyalty to us or our stockholders;
- any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the Delaware General Corporation Law; or
- any transaction from which the director derived an improper personal benefit.

Our certificate of incorporation and bylaws that will be in effect when we complete this offering require us to indemnify our directors and officers to the fullest extent permitted by Delaware law. Our bylaws also obligate us to advance expenses incurred by a director or officer in advance of the final disposition of any action or proceeding, and permit us to obtain insurance on behalf of any officer, director, employee or other agent for any liability arising out of his or her actions in that capacity regardless of whether we would otherwise be permitted to indemnify him or her under the provisions of Delaware law.

We have entered and expect to continue to enter into agreements to indemnify our directors, executive officers and other employees as determined by our board of directors. With specified exceptions, these agreements indemnify for related expenses including, among other things, attorneys' fees, witness fees, damages, judgments, fines and settlement amounts incurred by any of these individuals (including expenses of a derivative action) in connection with any proceeding, whether actual or threatened, to which any of these individuals may be made a party by reason of the fact that these individuals are or were a director or an executive officer of us or any of our affiliated enterprises, provided these individuals acted in good faith and in a manner they reasonably believed to be in, or not opposed to, our best interests and, with respect to any criminal proceeding, we have no reasonable cause to believe his or her conduct was unlawful. The indemnification agreements also contain procedures that apply if these individuals seek indemnification. We believe that our bylaws and indemnification agreements are necessary to attract and retain qualified persons as directors and officers. We also maintain directors' and officers' liability insurance.

The limitation of liability and indemnification provisions in our certificate of incorporation and bylaws may discourage stockholders from bringing a lawsuit against our directors and officers for breach of their fiduciary duty. They may also reduce the likelihood of derivative litigation against our directors and officers, even though an action, if successful, might benefit us and other stockholders. Further, a stockholder's investment may be negatively affected to the extent that we pay the costs of settlement and damage awards against directors and officers as required by these indemnification provisions. Currently, there is no pending litigation or proceeding involving any of our directors, officers or employees for which indemnification is sought, and we are not aware of any threatened litigation that may result in claims for indemnification.

## **Code of Business Conduct and Ethics**

We have adopted a Code of Business Conduct and Ethics, or the Code of Conduct, that will be applicable to all of our employees, executive officers and directors immediately prior to the completion of this offering. Following the completion of this offering, the Code of Conduct will be available on our website at [www.akceatx.com](http://www.akceatx.com). The Nominating, Governance and Review Committee of our Board will be responsible for overseeing the Code of Conduct and must approve any waivers of the Code of Conduct for employees, executive officers and directors. We expect that any amendments to the Code of Conduct, or any waivers of its requirements, will be disclosed on our website.

## **Rule 10b5-1 Sales Plans**

Our directors and executive officers may adopt written plans, known as Rule 10b5-1 plans, in which they will contract with a broker to buy or sell shares of our common stock on a periodic basis. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the director or executive officer when entering into the plan, without further direction from them. The director or executive officer may amend a Rule 10b5-1 plan in some circumstances and may terminate a plan at any time. Our directors and executive officers also may buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material nonpublic information subject to compliance with the terms of our insider trading policy. Prior to 180 days after the date of this offering, subject to early termination, the sale of any shares under such plan would be subject to the lock-up agreement that the director or executive officer has entered into with the underwriters.

## **Director Compensation**

Directors who are also our employees do not receive cash or equity compensation for service on our Board in addition to the compensation payable for their service as our employees. In addition, our non-employee directors who are affiliated with Ionis do not receive cash or equity compensation for service on our Board. In 2015, all of our directors were employed by us or by Ionis, and we therefore did not pay any cash or equity compensation to our directors for Board service. Through December 31, 2016, we paid Mr. Gabrieli \$23,400 for his service on our Board and, in October 2016, we granted him an option to purchase up to 52,837 shares of our common stock.

In January 2017, we paid Mr. Gabrieli \$8,750 for his service on our Board and, in April 2017, we paid each of Mr. Gabrieli and Ms. Hochberg \$8,750 and Mr. Smith \$11,664 for his and her respective service on our Board. In June 2017, we granted each of Messrs. Fitzgerald and Smith and Ms. Hochberg an option to purchase up to 52,837 shares of common stock.

Following the completion of this offering, we intend to provide cash and equity compensation to certain non-employee members of our Board, including Messrs. Fitzgerald, Gabrieli and Smith and Ms. Hochberg, who are not affiliated with Ionis. We refer to the individual non-employee members of our Board who our Compensation Committee determines will receive such compensation as our "Eligible Directors." Following the completion of this offering, we intend to provide cash compensation in the form of an annual retainer of \$35,000 to each of our Eligible Directors. We will also pay additional retainers of \$25,000 to the chairperson of our Board, \$15,000 to the chairperson of our Audit Committee, \$7,500 to other Eligible Directors who serve on our Audit Committee, \$10,000 to the chairperson of our Compensation Committee, \$5,000 to other Eligible Directors who serve on our Compensation Committee, \$7,500 to the chairperson of our Nominating, Governance and Review Committee and \$3,750 to other Eligible Directors who serve on our Nominating, Governance and Review Committee. We will also reimburse our non-employee directors for travel,

lodging and other reasonable expenses incurred in attending meetings of our Board and committees of the Board.

Following the completion of this offering, we will grant each new Eligible Director an option to purchase 52,837 shares of our common stock on the date of his or her initial election to the Board. In addition, on the date of each annual meeting of our stockholders following this offering, each Eligible Director will be eligible to receive an option to purchase 26,418 shares of our common stock. Such initial and annual options will have an exercise price per share equal to the fair market value of our common stock on the date of grant.

Each initial option and annual option granted to such Eligible Directors described above will vest and become exercisable in equal annual installments over the four years following the date of grant, such that the option is fully vested on the fourth anniversary of the date of grant, subject to the Eligible Director continuing to provide services to us through such dates. Further, upon a change of control of our company, vesting of all unvested options held by our Eligible Directors will accelerate in full. The term of each option granted to an Eligible Director will be 10 years. We will grant the options under our 2015 Plan, the terms of which are described in more detail under “—Equity benefit plans—2015 equity incentive plan.”

## EXECUTIVE COMPENSATION

Our named executive officers for the year ended December 31, 2016, which consist of our principal executive officer and our two other most highly compensated executive officers, are:

- Paula Soteropoulos, our President and Chief Executive Officer;
- Jeffrey M. Goldberg, our Chief Operating Officer; and
- Dr. Louis St. L. O'Dea, our Chief Medical Officer.

### Summary Compensation Table

The following table sets forth information regarding the compensation of our named executive officers during the years ended December 31, 2015 and 2016.

Name and Principal Position	Year	Salary(\$)	Bonus\$(1)	Option Awards\$(2)	Non-Equity Incentive Plan Compensation	All Other Compensation\$(3)	Total(\$)
Paula Soteropoulos President and Chief Executive Officer	2015	400,000	276,000	7,102,948	—	26,376	7,805,324
	2016	412,600	340,395	2,630,877	—	25,555	3,409,427
Jeffrey M. Goldberg Chief Operating Officer	2015	307,653	171,120	1,818,857	—	25,527	2,323,157
	2016	319,982	220,788	416,203	—	24,895	981,868
Dr. Louis St. L. O'Dea(4) Chief Medical Officer	2016	397,708	286,350	2,835,661	—	24,554	3,544,273

- (1) We present bonuses in the years they were earned, not in the year paid. Bonuses represent discretionary compensation for achievements and are not necessarily paid in the year they are earned. In January 2016, we paid bonuses for 2015 performance. We paid bonuses for 2016 performance in January 2017. For more information, see “—Bonus Opportunity” below.
- (2) Reflects the full grant date fair value of options granted during the year as measured pursuant to Financial Accounting Standard Board Accounting Standards Codification Topic 718 (ASC 718) as stock-based compensation in our financial statements. Unlike the calculations contained in our financial statements, this calculation does not give effect to any estimate of forfeitures related to service-based vesting, but assumes that the named executive officer will perform the requisite service for the award to vest in full. The assumptions we used in valuing options are described in note 5, *Stockholders' Equity (Deficit)*, to our consolidated financial statements included in this prospectus.
- (3) Includes accidental death and dismemberment, basic life, medical, dental and vision insurance, parking and transportation reimbursement and 401(k) matching contributions, each of which are available to all employees.
- (4) Dr. O'Dea's bonus for 2016 includes a \$40,000 sign on bonus paid in January 2016. Dr. O'Dea joined us in January 2016 and as such received no compensation in 2015.

### Narrative Disclosure to Summary Compensation Table

#### Annual Base Salary

The compensation of our named executive officers is generally determined and approved by our Board. Base salary is guaranteed to all employees as wages for hours worked. It represents consideration for the performance of job responsibilities. This portion of total cash compensation is not at risk and may increase as a result of how well an individual performs his or her job responsibilities. The 2017 base salaries that became effective for our named executive officers as of January 1, 2017 were as follows:

NAME	2017 BASE SALARY (\$)
Paula Soteropoulos(1)	424,978
Jeffrey M. Goldberg.	349,943
Dr. Louis St. L. O'Dea(2)	426,620

- (1) After the completion of this offering, Ms. Soteropoulos' base salary will increase to \$449,978.
- (2) After the completion of this offering, Dr. O'Dea's base salary will increase to \$450,000.

### ***Bonus Opportunity***

A component of an executive officer's compensation, as well as the compensation of our employees at the director level and above, is a discretionary performance-based cash payment through our Performance MBO program. Our Performance MBO program rewards employees for reaching specific objectives and for the judgment they use in making decisions, while an employee's base salary compensates the employee for his or her continued service and performance. We do not guarantee a Performance MBO as compensation. It is totally at risk. As such, a Performance MBO represents an opportunity for reward based upon the individual's level of accountability and depends on the relative success of both Akcea and the individual.

We calculate the actual amount of each executive officer's respective Performance MBO based on the following formula:

Base Salary (x) Target MBO % (x) Company Performance Factor (x) Individual Performance Factor = Performance MBO Amount

The multipliers in this formula create a structure where we award bonuses based on both Akcea's performance and individual performance. Performance MBOs are limited by a maximum Company Performance Factor, maximum Individual Performance Factor and Target MBO Percentage:

For 2015, the Target MBO percentages were: 50% for Ms. Soteropoulos and 40% for Mr. Goldberg. For 2015, the maximum potential Company Performance Factor was 200% and the maximum potential Individual Performance Factor was 160%. The actual Company Performance Factor for 2015 was 120%.

For 2016, the Target MBO percentages were: 50% for Ms. Soteropoulos, 40% for Mr. Goldberg and 40% for Dr. O'Dea. For 2016, the maximum potential Company Performance Factor was 200% and the maximum potential Individual Performance Factor was 160%. The actual Company Performance Factor for 2016 was 150%.

Since we were a wholly owned subsidiary of Ionis in 2015 and 2016, Ionis' Compensation Committee set the Company Performance Factor based on the following process:

- Ionis' achievement of the approved corporate objectives for the year, which included specific objectives for Akcea. At the end of 2015 and 2016, the Ionis Compensation Committee met to evaluate Ionis' overall performance. Ionis' Compensation Committee measured Ionis' performance based upon the achievement of goals that were set at the beginning of the year and agreed upon by our Board and upper management.
- Ionis' Compensation Committee reviewed the Company Performance Factor history for Ionis from the prior ten years to form a comparison for Ionis' current year's successes and/or failures.

Next, the members of our Board approved each executive officer's Individual Performance Factor based on the individual's performance.

Once the elements of the formula above have been determined, we use that formula to calculate each executive officer's Performance MBO.

### **Equity-based Incentive Awards**

We use stock options to give all employees, including our executive officers, an economic interest in the long-term appreciation of our common stock. We believe awarding stock options provides a way to align employee interests with those of upper management and our stockholders because as our stock price increases, so too does the employee's compensation.

We grant existing employees options upon commencement of employment with us and new options annually to provide a continuing financial incentive in our long-term success. We set the size of the equity awards based on individual and company performance during the previous year.

The stock option vesting schedule is typically over a 4-year period at the rate of 25% at the end of the first year and then at the rate of approximately 2.08% per month for 36 months thereafter during the optionee's employment.

Prior to this offering, we have granted all equity awards pursuant to the 2015 Plan, the terms of which are described below under "—Equity Benefit Plans," or pursuant to the Ionis 2011 Equity Incentive Plan. All options are granted with a per share exercise price not less than the fair market value of a share of our common stock or Ionis' common stock, as applicable, on the date of the grant of such award. For additional information regarding awards granted to our named executive officers in 2016, see "—Outstanding Equity Awards at Fiscal Year-end" below.

### **Offer Letters with Our Named Executive Officers**

Below are written descriptions of our offer letter agreements with each of Ms. Soteropoulos, Mr. Goldberg and Dr. O'Dea. Each of our named executive officers' employment is "at will" and may be terminated at any time.

*Paula Soteropoulos.* We entered into an offer letter agreement with Ms. Soteropoulos effective January 1, 2015 for the position of President and Chief Executive Officer. Ms. Soteropoulos currently receives a base salary of \$424,978, which is subject to annual adjustment, and which will increase to \$449,978 upon the completion of this offering. Pursuant to her agreement, Ms. Soteropoulos was also entitled to a stock option grant as described under "—Outstanding Equity Awards at Fiscal year-end" below. Ms. Soteropoulos is also eligible to participate in our employee benefit plans, subject to the terms of those plans.

*Jeffrey M. Goldberg.* We entered into an offer letter agreement with Mr. Goldberg effective January 5, 2015 for the position of Chief Operating Officer. Mr. Goldberg currently receives a base salary of \$349,943, which is subject to annual adjustment. Pursuant to his agreement, Mr. Goldberg was also entitled to a stock option grant as described under "—Outstanding Equity Awards at Fiscal Year-end" below. Mr. Goldberg is also eligible to participate in our employee benefit plans, subject to the terms of those plans.

*Dr. Louis St. L. O'Dea.* We entered into an offer letter agreement with Dr. O'Dea effective January 18, 2016 for the position of Chief Medical Officer. Dr. O'Dea currently receives a base salary of \$426,620, which is subject to annual adjustment, and which will increase to \$450,000 upon the completion of this offering. Pursuant to his agreement, Dr. O'Dea was also entitled to a stock option grant as described under "—Outstanding Equity Awards at Fiscal Year-end" below. Dr. O'Dea is also eligible to participate in our employee benefit plans, subject to the terms of those plans.

Once we complete this offering, we intend to enter into employment agreements with our executive officers, other than Ms. Hougén, that are generally consistent with employment agreements for publicly traded biopharmaceutical companies in Boston Massachusetts, which may



include among other things, a combination of cash severance payments, continued healthcare, bonus payouts, and accelerated vesting for stock awards in the case of a termination without cause, a termination following a change in control or a voluntary termination for good reason.

**Potential Payments Upon Termination or Change in Control**

We are currently party to change in control severance letter agreements with each of Ms. Soteropoulos, Mr. Goldberg and Dr. O’Dea which will terminate upon the completion of this offering. Ms. Hougen has served as our Chief Financial Officer since we founded our operations in January 2015 under the terms of the services agreement between us and Ionis. For additional information, please see “—Certain Relationships and Related Person Transactions—Related Person Transactions” below.

We expect that the employment agreements that we intend to enter into with our executive officers following the completion of this offering will include payments upon termination and/or a change in control under certain circumstances.

Regardless of the manner in which a named executive officer’s service terminates, each named executive officer is entitled to receive amounts earned during his or her term of service, including unpaid salary and unused vacation.

**Outstanding Equity Awards at Fiscal Year-End**

The following table sets forth certain information regarding equity awards granted to our named executive officers that remain outstanding as of December 31, 2016.

NAME	GRANT DATE	OPTION AWARDS(1)			
		NUMBER OF SECURITIES UNDERLYING UNEXERCISED OPTIONS (#) EXERCISABLE	NUMBER OF SECURITIES UNDERLYING UNEXERCISED OPTIONS (#) UNEXERCISABLE	OPTION EXERCISE PRICE (\$)(2)	OPTION EXPIRATION DATE
Paula Soteropoulos . . . . .	12/16/2015(3)	843,933	917,319	\$6.48	12/15/2025
	02/17/2016(4)	—	158,512	\$6.48	02/16/2026
Jeffrey M. Goldberg. . . . .	12/16/2015(5)	168,786	183,464	\$6.48	12/15/2025
	02/17/2016(4)	—	91,585	\$6.48	02/16/2026
Dr. Louis St. L. O’Dea . . . . .	02/17/2016(6)	—	704,500	\$6.48	02/16/2026

- (1) All of the option awards were granted under the 2015 Plan, the terms of which plan are described below under “—Equity benefit plans.”
- (2) All of the option awards were granted with a per share exercise price equal to the fair market value of one share of our common stock or Ionis common stock, as applicable, on the date of grant, as determined by our Board. Unless otherwise noted, all options granted provide for the following standard vesting schedule: 25% of the shares subject to the option vest on the one-year anniversary of the vesting commencement date and 1/48<sup>th</sup> of the total shares subject to the option vest on the monthly anniversary of the vesting commencement date over the next three years.
- (3) The shares vest according to the standard vesting schedule, measured from January 1, 2015.
- (4) The shares vest according to the standard vesting schedule, measured from January 4, 2016.
- (5) The shares vest according to the standard vesting schedule, measured from January 5, 2015.
- (6) The shares vest according to the standard vesting schedule, measured from January 18, 2016.

In June 2017, we granted Ms. Soteropoulos, Mr. Goldberg and Dr. O’Dea options to purchase 308,219, 52,837 and 105,675 shares of common stock, respectively, at an exercise price of \$12.21 per share.

## **Perquisites, Health, Welfare and Retirement Benefits**

All of our current named executive officers are eligible to participate in Ionis' employee benefit plans on the same basis as all of our and Ionis' other employees. These benefits include medical, dental and vision insurance, EAP/WorkLife, basic life insurance, short-term disability/sick pay, long-term disability, vacation, holidays, a 401(k) plan with employer match, parking and transportation reimbursement and accidental death and dismemberment insurance. We do not provide perquisites or personal benefits to our named executive officers.

### **401(k) Plan**

All of our full-time employees in the United States, including our named executive officers, are eligible to participate in Ionis' 401(k) plan, which is a retirement savings defined contribution plan established in accordance with Section 401(a) of the Code. Pursuant to Ionis' 401(k) plan, employees may elect to defer their eligible compensation into the plan on a pre-tax basis, up to the statutorily prescribed annual limit of \$18,000 in 2017 (additional salary deferrals not to exceed \$6,000 are available to those employees 50 years of age or older) and to have the amount of this deduction contributed to Ionis' 401(k) plan. We currently provide a \$0.50 match for every dollar our employees elect to defer up to 6% of their eligible compensation. In general, eligible compensation for purposes of the 401(k) plan includes an employee's wages, salaries, fees for professional services and other amounts received for personal services actually rendered in the course of employment with us to the extent the amounts are includible in gross income, and subject to certain adjustments and exclusions required under the Code. The 401(k) plan currently does not offer the ability to invest in our securities or Ionis' securities.

### **Nonqualified Deferred Compensation**

None of our named executive officers participate in or have account balances in nonqualified defined contribution plans or other nonqualified deferred compensation plans maintained by us. Our Board may elect to provide our officers and other employees with nonqualified defined contribution or other nonqualified deferred compensation benefits in the future if it determines that doing so is in our best interests.

## **Equity Benefit Plans**

### ***2015 Equity Incentive Plan***

Our Board and stockholders initially adopted and approved our 2015 equity incentive plan, or the 2015 Plan, in December 2015. In May 2017 and in June 2017, the Board and stockholders, respectively, approved an amendment to the 2015 Plan, (the 2015 Plan, as amended, the "Amended 2015 Plan"), to be effective immediately prior to the closing of our initial public offering. The description set forth below reflects the 2015 Plan, as currently in effect. For a description of the terms of the Amended 2015 Plan, see "*—Amended 2015 Plan*" below.

The aggregate number of shares of common stock that may be issued pursuant to stock awards under the 2015 Plan is 6,340,508 shares. Additionally, the 2015 Plan provides that no more than 12,681,016 shares may be issued under the 2015 Plan pursuant to the exercise of incentive stock options, or ISOs.

If a stock award granted under the 2015 Plan expires or otherwise terminates without being exercised in full or is settled in cash, the shares of our common stock not acquired pursuant to the stock award again become available for subsequent issuance under the 2015 Plan. In addition, the following types of shares under the 2015 Plan may become available for the grant of new stock awards under the 2015 Plan: (a) shares that are forfeited to us because of a failure to meet a

contingency or condition required to vest such shares; (b) shares withheld to satisfy income or employment withholding taxes; and (c) shares used as consideration to exercise an option.

As of March 31, 2017, options to purchase 5,063,585 shares of common stock were outstanding, 1,276,923 shares of common stock remained available for grant, and no options had been exercised. As of March 31, 2017, the outstanding options were exercisable at a weighted average exercise price of \$6.48 per share.

In June 2017, we granted options to purchase up to an aggregate of 1,678,661 shares of common stock pursuant to the 2015 Plan at an exercise price of \$12.21 per share.

We have summarized the material terms of the 2015 Plan below. We filed the 2015 Plan as an exhibit to the registration statement of which this prospectus is a part.

*Administration.* Our Board, or a duly authorized committee thereof, has the authority to administer the 2015 Plan. Our Board has delegated its authority to administer the 2015 Plan to our compensation committee under the terms of the compensation committee's charter. Our Board may also delegate to one or more of our officers the authority to (1) designate officers and employees to be recipients of options, and (2) determine the number of shares of common stock to be subject to such stock awards. Subject to the terms of the 2015 Plan, our Board or the authorized committee, referred to herein as the plan administrator, determines recipients, dates of grant, the numbers and types of stock awards to be granted and the terms and conditions of the stock awards, including the period of their exercisability and vesting schedule applicable to a stock award. Subject to the limitations set forth below, the plan administrator will also determine the exercise price, strike price or purchase price of awards granted and the types of consideration to be paid for the award.

*Repricing, "cash-out" or cancellation and re-grant of stock awards without stockholder approval.* Under the 2015 Plan, our Board cannot reprice any outstanding options or stock appreciation rights by reducing the exercise price of the stock award or cancel any outstanding options or stock appreciation rights in exchange for cash or other stock awards without obtaining the approval of our stockholders within 12 months prior to the repricing or cancellation and re-grant event.

*Types of awards.* The 2015 Plan provides for the grant of ISOs, within the meaning of Section 422 of the Code, nonstatutory stock options, or NSOs, stock appreciation rights, restricted stock awards and restricted stock unit awards, or collectively, stock awards. Each award is set forth in a separate award agreement that indicates the type, terms and conditions of the award.

*Eligibility.* ISOs may be granted only to employees, including employees of a parent company or subsidiary. All other stock awards may be granted to employees, including officers, and to non-employee directors and consultants.

*Stock options.* Stock options are granted pursuant to stock option agreements. The exercise price for an option cannot be less than 100% of the fair market value of the common stock subject to the option on the date of grant. Options granted under the 2015 Plan will vest at the rate specified in the option agreement. A stock option agreement may provide for early exercise, rights of repurchase, and rights of first refusal. We may repurchase unvested shares of our common stock issued in connection with an early exercise.

The plan administrator will determine acceptable consideration for the purchase of common stock issued upon the exercise of a stock option, which may include (1) cash, check, bank draft or money order, (2) a broker-assisted cashless exercise, (3) the tender of shares of our common stock previously owned by the optionee, (4) a net exercise arrangement, (5) deferred payment arrangement and (6) other legal consideration approved by the plan administrator.

Generally, an optionee may not transfer a stock option other than by will or the laws of descent and distribution or a domestic relations order. An optionee may, however, designate a beneficiary who may exercise the option following the optionee's death.

The plan administrator determines the term of stock options granted under the 2015 Plan, up to a maximum of 10 years. Unless the terms of an optionee's stock option agreement provides otherwise, if an optionee's service relationship with us, or any of our affiliates, ceases for any reason other than disability or death or for cause (if such termination occurs prior to our initial public offering), the optionee may generally exercise any vested options for a period of three months following the cessation of service. The option term may be extended if exercise of the option following such a termination of service is prohibited by applicable securities laws. If an optionee's service relationship with us, or any of our affiliates, ceases due to a termination for cause prior to our initial public offering, the option shall terminate immediately. If an optionee's service relationship with us, or any of our affiliates, ceases due to disability or death, or an optionee dies within a certain period following cessation of service, the optionee or a beneficiary may generally exercise any vested options for a period of 12 months in case of disability and 18 months in case of death. In no event may an option be exercised beyond the expiration of its term.

*Tax limitations on incentive stock options.* The aggregate fair market value, determined at the time of grant, of our common stock with respect to ISOs that are exercisable for the first time by an optionee during any calendar year under all of our stock plans may not exceed \$100,000. Options or portions thereof that exceed such limit will generally be treated as NSOs. No ISO may be granted to any person who, at the time of the grant, owns or is deemed to own stock possessing more than 10% of our total combined voting power or that of any of our affiliates unless (1) the option exercise price is at least 110% of the fair market value of the stock subject to the option on the date of grant, and (2) the term of the ISO does not exceed five years from the date of grant.

*Restricted stock awards.* Restricted stock awards are granted pursuant to restricted stock award agreements adopted by the plan administrator. Restricted stock awards may be granted in consideration for (1) services rendered to us or our affiliates or (2) any other form of legal consideration. Common stock acquired under a restricted stock award may, but need not, be subject to a share repurchase option in our favor in accordance with a vesting schedule to be determined by the plan administrator. Rights to acquire shares under a restricted stock award may be transferred only upon such terms and conditions as set by the plan administrator.

*Restricted stock unit awards.* Restricted stock unit awards are granted pursuant to restricted stock unit award agreements adopted by the plan administrator. We may grant restricted stock unit awards in consideration for any form of legal consideration. We may settle a restricted stock unit award by cash, delivery of stock, a combination of cash and stock, or in any other form of consideration the stock plan administrator deems appropriate or that is set forth in the restricted stock unit award agreement. Additionally, dividend equivalents may be credited in respect of shares covered by a restricted stock unit award. Except as otherwise provided in the applicable award agreement, restricted stock units that have not vested will be forfeited upon the participant's cessation of continuous service for any reason.

*Stock appreciation rights.* Stock appreciation rights are granted pursuant to stock appreciation grant agreements adopted by the plan administrator. The plan administrator determines the strike price for a stock appreciation unit, which generally cannot be less than 100% of the fair market value of our common stock on the date of grant. Upon the exercise of a stock appreciation unit, we will pay the participant an amount equal to the product of (1) the excess of the per share fair market value of our common stock on the date of exercise over the strike price, multiplied by (2) the number of shares of common stock with respect to which the stock appreciation unit is exercised. A stock

appreciation unit granted under the 2015 Plan vests at the rate specified in the stock appreciation grant agreement as determined by the plan administrator.

The plan administrator determines the term of stock appreciation rights granted under the 2015 Plan, up to a maximum of 10 years. Unless the terms of a participant's stock appreciation grant agreement provides otherwise, stock appreciation rights granted under the 2015 Plan are generally subject to the same term and termination provisions as stock options granted under the 2015 Plan.

*Corporate transactions.* If a corporate transaction occurs where the acquiring or surviving corporation does not assume, continue or substitute stock awards granted under the 2015 Plan, outstanding stock awards under the 2015 Plan and held by participants whose continuous service with us has not terminated prior to such transaction will be subject to accelerated vesting such that 100% of such award will become vested and exercisable or payable, as applicable, prior to the effective time of the corporate transaction and such outstanding stock awards under the 2015 Plan will be terminated if not exercised (if applicable) prior to the effective time of the corporate transaction. However, the plan administrator may provide that if a stock award will terminate if not exercised prior to a corporate transaction, the participant will receive a payment in lieu of exercise equal to the value of the excess, if any, of (i) the value of the property the participant would have received upon exercise of the stock award over (ii) any exercise price payable in connection with such exercise.

Under the 2015 Plan, a corporate transaction is generally the consummation of (i) a sale or other disposition of all or substantially all of our consolidated assets, (ii) a sale or other disposition of at least 90% of our outstanding securities, (iii) a merger, consolidation or similar transaction following which we are not the surviving corporation, or (iv) a merger, consolidation or similar transaction following which we are the surviving corporation but the shares of our common stock outstanding immediately prior to such transaction are converted or exchanged into other property by virtue of the transaction.

Under the 2015 Plan, a stock award may be subject to additional acceleration of vesting and exercisability upon or after a change in control transaction as may be provided in the stock award agreement or other written agreement with the participant, but in the absence of such provision, no such acceleration will occur.

*Amendment and termination of the 2015 Plan.* Our Board has the authority to amend or terminate the 2015 Plan at any time. However, except as otherwise provided in the 2015 Plan, no amendment or termination of the 2015 Plan may impair any rights under awards already granted to a participant unless agreed to by the affected participant. We will obtain stockholder approval of any amendment to the 2015 Plan as required by applicable law and listing requirements. If not terminated earlier by the Board, the 2015 Plan will terminate on December 15, 2025.

### ***Amended 2015 Plan***

The material terms of the Amended 2015 Plan are the same as the terms of the 2015 Plan described above, except for the provisions described below.

*Share reserve.* The aggregate number of shares of common stock that may be issued pursuant to stock awards under the Amended 2015 Plan is 8,500,000 shares, which is the sum of (i) 6,340,508 shares originally approved by the Company's stockholders in December 2015 under the 2015 Plan and (ii) 2,159,492 new shares. Additionally, the Amended 2015 Plan provides that no more than 17,000,000 shares may be issued under the Amended 2015 Plan pursuant to the exercise of ISOs.



*Stock options.* Unless the terms of an optionee's stock option agreement provides otherwise, if an optionee's service relationship with us, or any of our affiliates, ceases for any reason other than disability or death, the optionee may generally exercise any vested options for a period of three months following the cessation of service.

*Corporate transaction.* Under the Amended 2015 Plan, a corporate transaction is generally the consummation of (i) a sale or other disposition of all or substantially all of our consolidated assets, (ii) a sale or other disposition of at least 90% of our outstanding securities (other than a distribution of the shares by Ionis to the Ionis stockholders), (iii) a merger, consolidation or similar transaction following which we are not the surviving corporation, or (iv) a merger, consolidation or similar transaction following which we are the surviving corporation but the shares of our common stock outstanding immediately prior to such transaction are converted or exchanged into other property by virtue of the transaction.

### **2017 Employee Stock Purchase Plan**

Our Board initially adopted the 2017 Employee Stock Purchase Plan, or the ESPP, in May 2017, and our stockholders approved the ESPP in June 2017. The ESPP will become effective upon the closing of this offering. The purpose of the ESPP is to secure the services of new employees and retain the services of new and existing employees while providing incentives for such individuals to exert maximum efforts toward our success and that of our affiliates.

*Share reserve.* Following this offering, the ESPP authorizes the issuance of 500,000 shares of our common stock pursuant to purchase rights granted to our employees or to employees of any of our designated affiliates. The number of shares of our common stock reserved for issuance will automatically increase on January 1 of each calendar year, from January 1, 2018 (assuming the ESPP becomes effective before such date) through January 1, 2027, by the lesser of (a) 1% of the total number of shares of our common stock outstanding on December 31 of the preceding calendar year, (b) 500,000 shares, or (c) a number determined by our Board that is less than (a) and (b). The ESPP is intended to qualify as an "employee stock purchase plan" within the meaning of Section 423 of the Code. As of the date hereof, no shares of our common stock have been purchased under the ESPP.

*Administration.* Our Board has delegated its authority to administer the ESPP to our compensation committee. The ESPP is implemented through a series of offerings of purchase rights to eligible employees. Under the ESPP, we may specify offerings with durations of not more than 27 months, and may specify shorter purchase periods within each offering. Each offering will have one or more purchase dates on which shares of our common stock will be purchased for employees participating in the offering. An offering may be terminated under certain circumstances.

*Payroll deductions.* Generally, all regular employees, including executive officers, employed by us or by any of our designated affiliates, may participate in the ESPP and may contribute, normally through payroll deductions, up to 15% of their earnings for the purchase of our common stock under the ESPP. Unless otherwise determined by our Board, common stock will be purchased for accounts of employees participating in the ESPP at a price per share equal to the lower of (a) 85% of the fair market value of a share of our common stock on the first date of an offering or (b) 85% of the fair market value of a share of our common stock on the date of purchase.

*Limitations.* Employees may have to satisfy one or more of the following service requirements before participating in the ESPP, as determined by our Board: (a) customarily employed for more than 20 hours per week, (b) customarily employed for more than five months per calendar year or (c) continuous employment with us or one of our affiliates for a period of time (not to exceed two years). No employee may purchase shares under the ESPP at a rate in excess of \$25,000 worth of



our common stock based on the fair market value per share of our common stock at the beginning of an offering for each year such a purchase right is outstanding. Each participant in the ESPP will be required to hold the shares of common stock acquired pursuant to the ESPP for not less than six months prior to disposing of such shares. Finally, no employee will be eligible for the grant of any purchase rights under the ESPP if immediately after such rights are granted, such employee has voting power over 5% or more of our outstanding capital stock measured by vote or value pursuant to Section 424(d) of the Code.

*Minimum holding period.* Participants must hold the shares that they purchase under the ESPP for a period of at least six months.

*Changes to capital structure.* If a change in our capital structure occurs through such actions as a stock split, merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or similar transaction, the Board will make appropriate adjustments to (a) the number of shares reserved under the ESPP, (b) the maximum number of shares by which the share reserve may increase automatically each year and (c) the number of shares and purchase price of all outstanding purchase rights.

*Corporate transactions.* In the event of certain significant corporate transactions, including a sale of all our assets, the sale or disposition of at least 50% of our outstanding securities (other than a distribution of shares of our common stock held by Ionis to Ionis' stockholders), or the consummation of a merger or consolidation where we do not survive the transaction, any then-outstanding rights to purchase our stock under the ESPP may be assumed, continued or substituted for by any surviving or acquiring entity (or its parent company). If the surviving or acquiring entity (or its parent company) elects not to assume, continue or substitute for such purchase rights, then the participants' accumulated payroll contributions will be used to purchase shares of our common stock within 10 business days prior to such corporate transaction, and such purchase rights will terminate immediately. Under the ESPP, a corporate transaction is generally the consummation of (i) a sale or other disposition of all or substantially all of our consolidated assets, (ii) a sale or other disposition of at least 50% of our outstanding securities (other than a distribution of the shares by Ionis to the Ionis stockholders), (iii) a merger, consolidation or similar transaction following which we are not the surviving corporation, or (iv) a merger, consolidation or similar transaction following which we are the surviving corporation but the shares of our common stock outstanding immediately prior to such transaction are converted or exchanged into other property by virtue of the transaction.

*Plan amendments, termination.* Our Board has the authority to amend or terminate our ESPP. If our Board determines that the amendment or terminating of an offering is in our best interests and the best interests of our stockholders, then our Board may terminate any offering on any purchase date, establish a new purchase date with respect to any offering then in progress, amend our ESPP and the ongoing offering to reduce or eliminate detrimental accounting treatment or terminate any offering and refund the participants' contributions. We will obtain stockholder approval of any amendment to our ESPP as required by applicable law or listing requirements.

## CERTAIN RELATIONSHIPS AND RELATED PERSON TRANSACTIONS

### Related Person Transactions

The following is a summary of transactions since our incorporation to which we have been a participant in which the amount involved exceeded or will exceed \$120,000, and in which any of our then directors, executive officers or holders of more than 5% of any class of our capital stock at the time of such transaction, or any members of their immediate family, had or will have a direct or indirect material interest, other than compensation arrangements which are described in “Executive Compensation.”

#### *Indemnification agreements*

We have entered into or intend to enter into indemnification agreements with each of our directors and executive officers. These agreements contain provisions that require us, among other things, to indemnify these directors and executive officers against certain liabilities that may arise because of their status or service as directors or executive officers and advance their expenses incurred as a result of any proceeding against them related to activities for which we agree to indemnify the directors and executive officers.

#### *Offer letter agreements and change in control severance agreements*

We have entered into offer letter agreements and change in control severance agreements with our executive officers, other than Ms. Hougen. For more information regarding these agreements with Ms. Soteropoulos, Dr. O’Dea and Mr. Goldberg, see “Executive Compensation—Narrative Disclosure to Summary Compensation Table.” Ms. Hougen has served as our Chief Financial Officer since January 2015 under the terms of the services agreement between us and Ionis. For more information, see “—Services agreement” below.

#### *Stock option grants to executive officers and independent directors*

We have granted stock options to certain of our executive officers and our independent directors. For more information regarding the stock options and stock awards granted to our named executive officers see “Executive and Director Compensation—Equity Benefit Plans.”

#### *Series A convertible preferred stock financing*

In December 2015, we issued and sold to Ionis, a holder of more than 5% of our capital stock, an aggregate of 28,884,540 shares of Series A convertible preferred stock for a total purchase price of \$100,000,000, plus the grant of the rights and licenses we received under our development, commercialization and license agreement with Ionis.

#### *Development, commercialization and license agreement with Ionis*

In December 2015, we entered into a development, commercialization and license agreement with Ionis in which Ionis granted exclusive rights to us to develop and commercialize volanesorsen, AKCEA-APOCIII-L<sub>Rx</sub>, AKCEA-APO(a)<sub>Rx</sub>, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-ANGPTL3<sub>Rx</sub> and AKCEA-ANGPTL3-L<sub>Rx</sub>, which are collectively referred to as the Lipid Drugs. As a part of the grant to us from Ionis, Ionis has granted an exclusive license to certain patents to develop and commercialize products containing the Lipid Drugs. Ionis also granted us a non-exclusive license to the Ionis antisense platform technology, including its LICA technology, for us to develop and commercialize products containing the Lipid Drugs. Ionis also granted us non-exclusive rights under its manufacturing technology to manufacture the Lipid Drugs in our own facility, or at a contract manufacturer. As a part of this agreement both companies agreed not to work with any other parties

to develop or commercialize other drugs that are designed to inhibit any of the Lipid Drug targets so long as we are developing or commercializing the Lipid Drugs.

We and Ionis share development responsibilities for the Lipid Drugs. We pay Ionis for the research and development expenses it incurs on our behalf, which include both external and internal expenses. A Joint Steering Committee, or JSC, comprising two senior members from each company, sets the development strategy for the Lipid Drugs by mutual agreement. A regulatory sub-committee, established by the JSC and having equal membership from each company, will set the regulatory strategy for each of the Lipid Drugs by mutual agreement. If the regulatory sub-committee cannot agree on an issue related to the regulatory strategy for any one of the Lipid Drugs, we will submit the disputed issues to a mutually agreed-upon regulatory expert, we will share the costs of the expert and the expert's decision will be binding. At the time of this agreement, we agreed to the initial membership of a cardiometabolic advisory board that will advise the JSC on matters related to the development of the Lipid Drugs. We will provide Ionis notice of all meetings of this advisory board and Ionis personnel will have the ability to attend these meetings.

As we commercialize each of the Lipid Drugs, we will pay Ionis royalties ranging from the mid-teens to the mid-twenties on sales related to the Lipid Drugs that we sell. If we sell a Lipid Drug for a Rare Disease Indication (defined in our agreement as less than 500,000 patients worldwide or an indication that required a Phase 3 program of less than 1,000 patients and less than 2 years of treatment), we will pay a higher royalty rate to Ionis than we do if we sell a Lipid Drug for a Broad Disease Patient Population (defined in our agreement as more than 500,000 patients worldwide or an indication that required a Phase 3 program of 1,000 or more patients and 2 or more years of treatment). Other than with respect to the drugs licensed to Novartis under the strategic collaboration, option and license agreement, if our annual sales reach \$500.0 million, \$1.0 billion and \$2.0 billion, we will be obligated to pay Ionis sales milestones in the amount of \$50.0 million for each sales milestone reached by each Lipid Drug. If and when triggered, we will pay Ionis each of these sales milestones over the subsequent 12 quarters in equal payments.

To sublicense one or more Lipid Drugs licensed to us under this agreement, we will need to mutually agree on the terms of the sublicense with Ionis. If we sublicense any one of the Lipid Drugs to a commercial partner, we will share 50% of any revenue from the commercial partner with Ionis, excluding (i) money received from our partner specifically designated to fund future research and development costs and (ii) money we are obligated to spend in support of commercialization of a Lipid Drug in a co-commercialization arrangement. Regarding our Novartis collaboration, we paid Ionis \$15.0 million of the \$75.0 million upfront option payment we received from Novartis. We will share with Ionis 50% of any additional payments we receive from Novartis, excluding money received specifically designated to fund future development costs and money we are obligated to spend to co-commercialize a drug.

We may terminate this agreement if Ionis is in material breach of the agreement. Ionis may terminate this agreement if we are in material breach of the agreement. In each circumstance the party that is in breach will have an opportunity to cure the breach prior to the other party terminating this agreement.

In the first quarter of 2017, we entered into letter agreements with Ionis to reflect the agreed upon payment terms with respect to the upfront option payment that we received from Novartis and to allocate the premium that Novartis paid for Ionis' common stock in connection with our strategic collaboration.

In April 2017, Ionis granted us a right of first negotiation with respect to Ionis development candidates that are designed to treat a rare cardiometabolic disease or a rare inherited metabolic

disease, where we have the capability and financial and other resources to develop and commercialize the development candidate and Ionis does not have an agreement with a third party that would preclude granting us this right. If we exercise our right of first negotiation for an eligible development candidate, we and Ionis will negotiate in good faith the terms of an exclusive license for us to develop and commercialize the development candidate. If we and Ionis cannot agree to the terms of such a license, Ionis may grant a license to a third party on terms no more favorable than Ionis last offered to us. This right of first negotiation expires in April 2024.

#### *Services agreement with Ionis*

In December 2015, we entered into a services agreement with Ionis. Under the services agreement, Ionis provides us certain services, including, without limitation, general and administrative support services and development support services. Ionis has allocated a certain percentage of personnel to perform the services that it provides to us based on its good faith estimate of the required services. We pay Ionis for these allocated costs, which reflect the Ionis full-time equivalent, or FTE, rate for the applicable personnel, plus out-of-pocket expenses such as occupancy costs associated with the FTEs allocated to providing us these services.

In addition, as long as Ionis continues to consolidate our financials, we will comply with Ionis' policies and procedures and internal controls.

The initial term of this services agreement will end at the conclusion of 2017, however, so long as Ionis determines it should consolidate our financials, we will continue to obtain the following services from Ionis:

- investor relations services,
- human resources and personnel services,
- risk management and insurance services,
- tax related services,
- corporate record keeping services,
- financial and accounting services,
- credit services, and
- COO/CFO/CBO oversight.

However, if we want to provide for our own human resources and personnel services, and doing so does not negatively impact Ionis' internal controls and procedures for financial reporting, we can negotiate in good faith with Ionis for a reduced scope of services related to human resources and personnel services. When Ionis determines it should no longer consolidate our financials, we may mutually agree with Ionis in writing to extend the term in six month increments.

Following the completion of this offering, we can establish our own benefits programs or can continue to use Ionis' benefits, however, we must provide Ionis a minimum advance notice to opt-out of using Ionis' benefits.

We paid Ionis an aggregate of \$35.7 million under the license agreement and services agreement for the year ended December 31, 2015 and had an aggregate outstanding payable to Ionis under the license agreement and services agreement of \$9.2 million as of December 31, 2015. We paid Ionis an aggregate of \$48.5 million under the license agreement and services agreement for the year ended December 31, 2016 and had an aggregate outstanding payable to Ionis under the license agreement and services agreement of \$24.4 million as of December 31, 2016. In the first quarter of 2017, we made (i) a payment of \$24.4 million to Ionis to satisfy our outstanding intercompany payable through December 31, 2016 and (ii) a payment of \$18.0 million to Ionis for the

estimated intercompany expenses we expected to incur for the first quarter of 2017. In May 2017, we paid Lonis a \$15.0 million sublicense fee from the upfront payment we received from Novartis.

#### *Line of credit agreement with Lonis*

In January 2017, we entered into a line of credit agreement with Lonis, pursuant to which Lonis agreed to advance funds to us up to a maximum aggregate principal amount of \$150.0 million. The amounts we borrow under the line of credit bear interest at an annual interest rate of 4%, compounded monthly. As of the date of this prospectus, we had borrowed an aggregate of \$106.0 million pursuant to the line of credit, which together with accrued interest will automatically convert upon completion of this offering into an aggregate of 13,438,339 Lonis Conversion Shares, based on the initial public offering price of \$8.00 per share.

The line of credit agreement includes customary affirmative and negative covenants including, among others, that we will run our business in the ordinary course and that we will not change our business to a business other than developing and commercializing drugs. The line of credit provides that each of the following events is an event of default, which may result in acceleration of the amounts payable under the line of credit:

- We fail to timely pay amounts due and payable under the line of credit;
- Any representation or warranty we made under the line of credit proves to have been incorrect or misleading in any material respect;
- We fail to perform or observe certain terms, covenants or agreements under the line of credit and do not cure such failure where curable;
- We dissolve, liquidate, terminate our operations, stop generally paying our debts, become insolvent or enter bankruptcy proceedings.

#### *Lonis participation in this offering*

Lonis has agreed to purchase 3,125,000 shares of common stock in this offering at the initial public offering price for an aggregate purchase price of \$25.0 million. The underwriters will not receive any underwriting discounts or commissions on the shares purchased by Lonis.

#### *Investor rights agreement with Lonis*

In December 2015, in connection with our Series A convertible preferred stock financing, we entered into an Investor Rights Agreement with Lonis, which provides for rights that Lonis will retain as a stockholder after this offering. As long as Lonis owns at least 50% of our stock, we will need to obtain Lonis' approval to issue equity or debt securities in our company in a financing valued at over \$10.0 million. In addition, we will need to obtain Lonis' approval to in-license a product, acquire a product or acquire another company, until the earlier of (i) five years following this offering or (ii) the date when Lonis no longer is required to record its share of our profits and losses.

While Lonis is consolidating the financials of our company, we are required to:

- use the same auditors and tax advisors as Lonis;
- use Lonis' financial systems;
- provide to Lonis monthly, quarterly and annual financials, including footnotes; and
- provide to Lonis certifications required by Lonis' internal controls.

*provided, however,* in each case we will work with Lonis to augment Lonis' financial systems and advisors, if needed, to support our global commercialization activities.

Pursuant to the Investor Rights Agreement, Ionis will have the right to demand one S-3 registration per year if it is at least in the amount of \$15.0 million. Ionis will have the right to “piggy-back” on all of our registrations or any other demand registration of another investor. We and Ionis will share the underwriter cutback on a pro-rata basis for these registrations. Ionis will agree to not sell its shares for a specified period of time not to exceed 180 days, if our officers and directors are similarly restricted. Ionis’ agreement to customary restrictions on the sale of shares will be conditioned on our compliance with these registration rights. We will approve any 10b5-1 trading plans to sell our shares held by Ionis if the trading plan does not violate securities laws.

Ionis has advised us that it does not have any current plans to sell or distribute to its stockholders the shares of our common stock that it beneficially owns, although it may elect to do so in the future.

#### *Strategic Collaboration with Novartis*

In January 2017, we initiated a strategic collaboration with Novartis. For additional information, please see “Business—Our Strategic Collaboration with Novartis” above. Pursuant to the stock purchase agreement with Novartis, we have agreed to provide Novartis the same registration rights as we have provided Ionis. Novartis has agreed that it will not sell any of these shares until the earlier of January 5, 2020 or six months after we stop developing a drug under the agreement, and if Novartis wishes to sell such shares after this initial period, then Novartis may only sell a limited number of shares each day.

#### **Related Person Transaction Policy**

Prior to this offering, we have not had a formal policy regarding approval of transactions with related parties. In connection with this offering, we have adopted a related person transaction policy that sets forth our procedures for the identification, review, consideration and approval or ratification of related person transactions. For purposes of our policy only, a related person transaction is a transaction, arrangement or relationship, or any series of similar transactions, arrangements or relationships, in which we and any related person are, were or will be participants in which the amount involved exceeds \$120,000. Transactions involving compensation for services provided to us as an employee or director are not covered by this policy. A related person is any executive officer, director or beneficial owner of more than 5% of any class of our voting securities, including any of their immediate family members and any entity owned or controlled by such persons.

Under the policy, if a transaction has been identified as a related person transaction, including any transaction that was not a related person transaction when originally consummated or any transaction that was not initially identified as a related person transaction prior to consummation, our management must present information regarding the related person transaction to our audit committee, or, if audit committee approval would be inappropriate, to another independent body of our board of directors, for review, consideration and approval or ratification. The presentation must include a description of, among other things, the material facts, the interests, direct and indirect, of the related persons, the benefits to us of the transaction and whether the transaction is on terms that are comparable to the terms available to or from, as the case may be, an unrelated third party or to or from employees generally. Under the policy, we will collect information that we deem reasonably necessary from each director, executive officer and, to the extent feasible, significant stockholder to enable us to identify any existing or potential related person transactions and to effectuate the terms of the policy.

In addition, under our Code of Conduct, which we intend to adopt in connection with this offering, our employees and directors will have an affirmative responsibility to disclose any transaction or relationship that reasonably could be expected to give rise to a conflict of interest.



In considering related person transactions, our audit committee, or other independent body of our board of directors, will take into account the relevant available facts and circumstances including, but not limited to:

- the risks, costs and benefits to us;
- the impact on a director's independence in the event that the related person is a director, immediate family member of a director or an entity with which a director is affiliated;
- the availability of other sources for comparable services or products; and
- the terms available to or from, as the case may be, unrelated third parties or to or from employees generally.

The policy requires that, in determining whether to approve, ratify or reject a related person transaction, our audit committee, or other independent body of our board of directors, must consider, in light of known circumstances, whether the transaction is in, or is not inconsistent with, our best interests and those of our stockholders, as our audit committee, or other independent body of our board of directors, determines in the good faith exercise of its discretion.

All of the transactions described above were entered into prior to the adoption of the written policy, but all were approved by our board of directors considering similar factors to those described above.

## PRINCIPAL STOCKHOLDERS

The following table sets forth the beneficial ownership of our common stock as of March 31, 2017, as adjusted to reflect the sale of common stock offered by us in this offering, for:

- each person, or group of affiliated persons, who is known by us to beneficially own more than 5% of our common stock;
- each of our named executive officers;
- each of our directors; and
- all of our executive officers and directors as a group.

The percentage of beneficial ownership prior to the offering shown in the table is based upon 28,884,540 shares, on an as converted to common stock basis, outstanding as of March 31, 2017. The percentage of beneficial ownership after this offering shown in the table is based on 64,197,879 shares of common stock outstanding after the closing of this offering, assuming the sale of 15,625,000 shares of common stock by us, no exercise of the underwriters' option to purchase additional shares, the issuance of 13,438,339 Ionis Conversion Shares and the sale of 6,250,000 Novartis Private Placement Shares.

We have determined beneficial ownership in accordance with the rules of the SEC. These rules generally attribute beneficial ownership of securities to persons who possess sole or shared voting power or investment power with respect to those securities. In addition, the rules take into account shares of common stock issuable pursuant to the exercise of stock options that are either immediately exercisable or exercisable on or before May 30, 2017, the 60th day after March 31, 2017. These shares are deemed to be outstanding and beneficially owned by the person holding those shares for the purpose of computing the percentage ownership of that person, but not for the purpose of computing the percentage ownership of any other person. Unless otherwise indicated, the persons or entities identified in this table have sole voting and investment power with respect to all shares shown as beneficially owned by them, subject to applicable community property laws.

Except as otherwise noted below, the address for persons listed in the table is c/o Akcea Therapeutics, Inc., 55 Cambridge Parkway, Cambridge, Massachusetts 02142.

<u>Beneficial owner</u>	<u>Shares beneficially owned prior to this offering</u>		<u>Shares beneficially owned following this offering</u>	
	<u>Shares</u>	<u>%</u>	<u>Shares</u>	<u>%</u>
<b>5% or greater stockholders:</b>				
Ionis Pharmaceuticals, Inc.(1) . . . . .	28,884,540	100.0%	45,447,879	70.8%
Novartis Pharma AG(2) . . . . .	—	—	6,250,000	9.7
<b>Directors and named executive officers:</b>				
Stanley T. Crooke, M.D., Ph.D.(3) . . . . .	—	—	—	—
B. Lynne Parshall, J.D.(3) . . . . .	—	—	—	—
Edward Fitzgerald(4) . . . . .	—	—	—	—
Christopher Gabrieli . . . . .	13,209	*	13,209	*
Elaine Hochberg . . . . .	—	—	—	—
Sandford D. Smith . . . . .	—	—	—	—
Paula Soteropoulos(5) . . . . .	1,067,025	3.7	1,067,025	1.7
Jeffrey M. Goldberg(5) . . . . .	228,375	*	228,375	*
Louis St. L. O’Dea MB BCh BAO. FRCP(C)(5) . . . . .	234,833	*	234,833	*
All current executive officers and directors as a group (9 persons)(3)(4)(5) . . . . .	1,543,442	5.3%	1,543,442	2.4%

\* Represents beneficial ownership of less than 1%.

- (1) The address of Ionis is 2855 Gazelle Court Carlsbad, California 92010. Shares beneficially owned following this offering include the issuance of 13,438,339 Ionis Conversion Shares, based on the initial public offering price of \$8.00 per share, and Ionis’ purchase of 3,125,000 shares of common stock in this offering.
- (2) The address of Novartis is Lichtstrasse 35, 4002, Basel, Switzerland. Shares beneficially owned following this offering reflects the issuance of 6,250,000 Novartis Private Placement Shares, based on the initial public offering price of \$8.00 per share.
- (3) Dr. Crooke and Ms. Parshall are directors and executive officers of Ionis and Ms. Hougen is an executive officer of Ionis. Each of these individuals may influence voting and disposition of the shares of common stock held by Ionis.
- (4) Mr. Fitzgerald joined our board of directors in May 2017.
- (5) Represents shares of common stock issuable upon the exercise of options.

## DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock, certain provisions of our amended and restated certificate of incorporation and amended and restated bylaws, as each will be in effect upon the completion of this offering, and certain provisions of Delaware law are summaries. You should also refer to the amended and restated certificate of incorporation and the amended and restated bylaws, which are filed as exhibits to the registration statement of which this prospectus is part, as well as the relevant provisions of the Delaware General Corporation Law. We refer in this section to our amended and restated certificate of incorporation and amended and restated bylaws that we intend to adopt in connection with this offering as our certificate of incorporation and bylaws, respectively.

### **General**

Upon the completion of this offering, our certificate of incorporation will authorize us to issue up to 100,000,000 shares of common stock, \$0.001 par value per share, and 10,000,000 shares of preferred stock, \$0.001 par value per share, all of which shares of preferred stock will be undesignated. Our board of directors may establish the rights, preference and privileges of the preferred stock from time to time.

### **Common Stock**

#### ***Outstanding Shares***

On March 31, 2017, after giving effect to the conversion of all outstanding Series A convertible preferred stock into shares of common stock, there were 28,884,540 shares of common stock issued and outstanding, held of record by one stockholder. Options to purchase 5,063,585 shares of common stock were also outstanding as of March 31, 2017 at a weighted-average exercise price of \$6.48 per share.

After the completion of this offering there will be 64,197,879 shares of common stock outstanding after giving effect to the sale of the shares offered in this offering, the issuance of 13,438,339 Ionis Conversion Shares and the sale of 6,250,000 Novartis Private Placement Shares.

### ***Voting***

The holders of common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders, including the election of directors. Under our certificate of incorporation and bylaws, our stockholders will not have cumulative voting rights. Accordingly, the holders of a majority of the shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election.

Under our stock purchase agreement with Novartis, Novartis has agreed that until Novartis holds less than 7.5% of our outstanding common stock, Novartis will vote the shares it purchased in this private placement consistent with the recommendation of our Board of Directors, except Novartis has retained the sole discretion to vote such shares regarding proposals we submit to our stockholders related to:

- any transaction which would result in our change of control;
- any issuance of our common stock that represents more than 20% of our then outstanding common stock;
- the entry into any licensing, partnering, partnership, collaboration, research and development, joint venture or other commercial agreement;
- the payment of any dividends to any of our stockholders; and
- our liquidation or dissolution.

### ***Dividends***

Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of common stock are entitled to receive ratably any dividends declared by our board of directors out of legally available funds for that purpose. See “Dividend Policy.”

### ***Liquidation***

If there is a liquidation, dissolution or winding up of the Company, holders of our common stock are entitled to share ratably in the net assets legally available for distribution to stockholders after payment of all of our debts and other liabilities, subject to the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

### ***Rights and Preferences***

Holders of our common stock have no preemptive, conversion or subscription rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

### ***Preferred Stock***

All currently outstanding shares of Series A convertible preferred stock will be converted to common stock upon the completion of this offering. Any accrued dividends on the preferred stock will not be converted into common stock. We will not be obligated to pay any accrued dividends on the preferred stock converted upon the completion of this offering.

Following the completion of this offering, our certificate of incorporation authorizes our board of directors to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility for possible future acquisitions and other corporate purposes, will affect, and may negatively affect, the rights of holders of common stock. It is not possible to state the actual effect on the rights of holders of common stock if we issue any shares of preferred stock until the board of directors determines the specific rights attached to that preferred stock. The effects of issuing preferred stock could include one or more of the following:

- restricting dividends on the common stock;
- diluting the voting power of the common stock;
- impairing the liquidation rights of the common stock; or
- delaying or preventing changes in control or management of our company.

We have no present plans to issue any shares of preferred stock.

### ***Registration Rights***

Pursuant to an investor rights agreement, Ionis will have the right to demand one S-3 registration per year if it is at least in the amount of \$15.0 million. Ionis will have the right to “piggy-back” on all of our registrations or any other demand registration of another investor. As of

March 31, 2017, after giving effect to the conversion of all outstanding shares of Series A convertible preferred stock into shares of our common stock in connection with the completion of the offering, the issuance of 13,438,339 Ionis Conversion Shares and Ionis' purchase of 3,125,000 shares of common stock in this offering, there would have been an aggregate of 45,447,879 shares of common stock entitled to these registration rights.

Pursuant to the stock purchase agreement with Novartis, we have agreed to provide Novartis the same registration rights as we have provided Ionis. We will issue and sell 6,250,000 Novartis Private Placement, all of which will be entitled to these registration rights.

### **Corporate Opportunities**

Our certificate of incorporation will provide that, to the fullest extent permitted by law, the doctrine of "corporate opportunity" will not apply to business opportunities that are presented to Ionis or its subsidiaries (other than us or our subsidiaries) or any of their officers, directors, agents or stockholders unless, in the case of our directors or officers, the business opportunity is expressly offered to the director or officer in writing solely in his or her capacity as a director or officer of our Company. This means that if certain of our directors or officers that are also directors or officers of Ionis are presented with a business opportunity that we might otherwise desire to pursue, they will be free to present that opportunity instead to Ionis unless it is clear that the opportunity was directed expressly to us.

### **Anti-takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws**

#### ***Undesignated Preferred Stock***

As discussed above, our board of directors will have the ability to issue preferred stock with voting or other rights or preferences that could make it more difficult to effect a change of control of us. These and other provisions may deter hostile takeovers or delay changes in control or management of our company.

#### ***Limits on Ability of Stockholders to Act by Written Consent or Call a Special Meeting***

Until Ionis no longer beneficially owns a majority of the total voting power of the outstanding shares of all classes of capital stock entitled to vote generally in the election of directors, our certificate of incorporation will allow stockholders to take action by written consent in lieu of an annual or special meeting if that consent is in writing, states the action to be taken, and is signed by the holders of outstanding capital stock having not less than the minimum number of votes that would be necessary to authorize or take such action at a meeting at which all shares entitled to vote thereon were present and voted. Thereafter, stockholders will only be able to take action at an annual or special meeting called in accordance with our bylaws.

Our bylaws will provide that only the chairperson of the board, our chief executive officer or a majority of our board of directors can call special meetings of the stockholders.

#### ***Requirements for Advance Notification of Stockholder Nominations and Proposals***

Our bylaws will have advance notice procedures for stockholder proposals and for nominating director candidates, other than nominations made by or at the direction of our board of directors or a committee of our board of directors. These provisions may have the effect of preventing stockholder-proposed business from being conducted at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from soliciting proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.



### ***Delaware Anti-Takeover Statute***

We are subject to Section 203 of the Delaware General Corporation Law regulating corporate takeovers. In general, Section 203 prohibits a publicly held Delaware corporation from engaging, under specified circumstances, in a business combination with an interested stockholder for a period of three years following the date the person became an interested stockholder unless:

- prior to the date of the transaction, our board of directors approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, calculated as provided under Section 203; or
- at or after the date of the transaction, the business combination is approved by our board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least two-thirds of the outstanding voting stock that is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation's outstanding voting stock. We expect the existence of this provision to have an anti-takeover effect with respect to transactions our board of directors does not approve in advance. We anticipate that Section 203 may also discourage takeover attempts that might result in a premium over the market price for the shares of common stock held by stockholders.

### ***Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws***

Provisions of our amended and restated certificate of incorporation and amended and restated bylaws, which will become effective upon the closing of this offering, may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our common stock. Among other things, our amended and restated certificate of incorporation and amended and restated bylaws:

- permit our board of directors to issue up to 10,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate (including the right to approve an acquisition or other change in our control);
- provide that the authorized number of directors may be changed only by resolution of the board of directors;
- provide that a majority of directors then in office, even if less than a quorum, may fill all vacancies, including newly created directorships, except as otherwise required by law;
- except while Ionis beneficially owns a majority of the total voting power of the outstanding shares of all classes of capital stock entitled to vote, require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner and also specify requirements as to the form and content of a stockholder's notice; and

- do not provide for cumulative voting rights, which means the holders of a majority of the shares of common stock entitled to vote in any election of directors may elect all of the directors standing for election, if they should so choose.

Amending any of these provisions, with the exception of the ability of our board of directors to issue shares of preferred stock and designate any rights, preferences and privileges thereto, would require approval by the holders of at least 66⅔% of our then outstanding common stock.

The combination of these provisions will make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of us by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to reduce our vulnerability to hostile takeovers and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of delaying changes in our control or management. As a consequence, these provisions may also inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts. We believe that the benefits of these provisions, including increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure our company, outweigh the disadvantages of discouraging takeover proposals, because negotiation of takeover proposals could result in an improvement of their terms.

### **Choice of Forum**

Our certificate of incorporation will provide that the Court of Chancery of the State of Delaware will be the exclusive forum for:

- any derivative action or proceeding brought on our behalf;
- any action asserting a breach of fiduciary duty;
- any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or bylaws; and
- any action asserting a claim against us that is governed by the internal affairs doctrine.

Several lawsuits have been filed in Delaware challenging the enforceability of similar choice of forum provisions and it is possible that a court determines such provisions are not enforceable.

### **Transfer Agent and Registrar**

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent's address is 6201 15<sup>th</sup> Avenue, Brooklyn, New York 11219.

### **Listing**

Our common stock has been approved for listing on the Nasdaq Global Select Market under the trading symbol "AKCA."

## SHARES ELIGIBLE FOR FUTURE SALE

Immediately prior to this initial public offering, there was no public market for our common stock. Sales of substantial amounts of shares of our common stock in the public market could adversely affect prevailing market prices of our common stock. Some shares of our common stock will not be available for sale for a certain period of time after this offering because they are subject to contractual and legal restrictions on resale, some of which are described below. Sales of substantial amounts of shares of our common stock in the public market after these restrictions lapse, or the perception that these sales could occur, could adversely affect the prevailing market price and our ability to raise equity capital in the future.

### Sales of Restricted or Control Securities

Based on our shares outstanding as of March 31, 2017, after this offering, 64,197,879 shares of our common stock will be outstanding, or 66,541,629 shares if the underwriters exercise their option to purchase additional shares in full. Of these shares, 12,500,000 of the shares sold in this offering to investors other than Ionis will be freely tradable without restriction under the Securities Act, unless otherwise purchased by our “affiliates,” as that term is defined in Rule 144 under the Securities Act. The remaining 51,697,879 shares of our common stock that will be outstanding after this offering, including all Ionis Conversion Shares, shares purchased by Ionis in this offering and Novartis Private Placement Shares, are “restricted securities” or “control securities” within the meaning of Rule 144 under the Securities Act. Restricted or control securities may be sold in the public market only if they are registered under the Securities Act or are sold pursuant to an exemption from registration under Rule 144 or Rule 701 under the Securities Act, which are summarized below. Subject to the lock-up agreements described below, shares held by non-affiliates that are not restricted securities or that have been owned for more than one year may be sold without regard to the provisions of Rule 144.

### Lock-up Agreements

We, Ionis, Novartis, our officers, our directors and substantially all of our option holders have agreed with the underwriters not to dispose of or hedge any of the shares of our common stock or securities convertible into or exchangeable for shares of our common stock during the period from the date of this prospectus continuing through the date that is 180 days after the date of this prospectus, except with the prior written consent of Cowen and Company, LLC. These agreements are described below under “Underwriting.” In addition, Novartis has agreed separately that it will not sell any of the Novartis Private Placement Shares until the earlier of January 5, 2020 or six months following our decision to discontinue the development of AKCEA-APO(a)-L<sub>Rx</sub> or AKCEA-APOCIII-L<sub>Rx</sub>. If Novartis wishes to sell such shares after this initial period, then Novartis will be subject to volume limitations.

### Rule 144

In general, under Rule 144, beginning 90 days after the date of this prospectus, a person who is not our affiliate and has not been our affiliate at any time during the preceding three months will be entitled to sell any shares that such person has beneficially owned for at least six months, including the holding period of any prior owner other than one of our affiliates, without regard to volume limitations.

In addition, under Rule 144, a person may sell shares of our common stock acquired from us immediately upon the closing of this offering, without regard to volume limitations or the availability of public information about us, if:

- the person is not our affiliate and has not been our affiliate at any time during the preceding three months; and
- the person has beneficially owned the shares to be sold for at least one year, including the holding period of any prior owner other than one of our affiliates.

Beginning 90 days after the date of this prospectus, and subject to the lock up agreements described above, our affiliates who have beneficially owned shares of our common stock for at least six months, including the holding period of any prior owner other than one of our affiliates, would be entitled to sell within any three-month period a number of shares that does not exceed the greater of:

- 1% of the number of shares of our common stock then outstanding, which will equal approximately 641,978 shares immediately after this offering; and
- the average weekly trading volume in our common stock on the Nasdaq Global Select Market during the four calendar weeks preceding the date of filing of a Notice of Proposed Sale of Securities Pursuant to Rule 144 with respect to the sale.

Sales under Rule 144 by our affiliates are also subject to manner of sale provisions and notice requirements and to the availability of current public information about us.

#### **Rule 701**

Any of our employees, officers or directors who acquired shares under a written compensatory plan or contract may be entitled to sell them in reliance on Rule 701. Rule 701 permits affiliates to sell their Rule 701 shares under Rule 144 without complying with the holding period requirements of Rule 144. Rule 701 further provides that non-affiliates may sell these shares in reliance on Rule 144 without complying with the holding period, public information, volume limitation or notice provisions of Rule 144. All holders of Rule 701 shares are required to wait until 90 days after the date of this prospectus before selling those shares. As of March 31, 2017, no shares of our outstanding common stock had been issued in reliance on Rule 701 as a result of exercises of stock options and issuance of restricted stock. Further, any shares issued under Rule 701 are subject to lock-up agreements and will only become eligible for sale when the 180-day lock-up agreements expire.

#### **Form S-8 Registration**

As of March 31, 2017, options to purchase an aggregate 5,063,585 of our common stock were outstanding. As soon as practicable after the completion of this offering, we intend to file with the SEC one or more registration statements on Form S-8 under the Securities Act to register the shares of our common stock that are issuable pursuant to our equity incentive plans, including pursuant to outstanding options. See “Executive Compensation—Equity Benefit Plans” for a description of our equity incentive plans. These registration statements will become effective immediately upon filing. Shares covered by these registration statements will then be eligible for sale in the public markets, subject to vesting restrictions, any applicable lock-up agreements described below and Rule 144 limitations applicable to affiliates.

#### **Registration Rights**

Upon the completion of this offering, Ionis and Novartis, the holders of 51,697,879 shares of our common stock will be entitled to specified rights with respect to the registration of the offer and sale of their shares under the Securities Act. Registration of the offer and sale of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act immediately upon the effectiveness of the registration. See “Description of Capital Stock—Registration Rights” for additional information.

## MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following summary describes the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion does not address all aspects of U.S. federal income taxes that may be relevant to Non-U.S. Holders in light of their particular circumstances, does not deal with foreign, state and local tax consequences and does not address U.S. federal tax consequences other than income taxes, including the effects of any applicable gift or estate tax or the Medicare contribution tax. Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended, or the Code, such as financial institutions, insurance companies, tax-exempt organizations, tax-qualified retirement plans, broker-dealers and traders in securities, commodities or currencies, U.S. expatriates, "controlled foreign corporations," "passive foreign investment companies," corporations that accumulate earnings to avoid U.S. federal income tax, persons that hold our common stock as part of a "straddle," "hedge," "conversion transaction," "synthetic security," integrated investment or other risk reduction strategy, holders deemed to sell our common stock under the constructive sale provisions of the Code, holders who hold or receive our common stock pursuant to the exercise of employee stock options or otherwise as compensation, holders who are subject to the alternative minimum tax, partnerships and other pass-through entities, including hybrid entities and partners and investors in such entities or an entity that is treated as a disregarded entity for U.S. federal income tax purposes (regardless of its place of organization or formation). Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them.

This discussion is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof. Such authorities may be repealed, revoked or modified, perhaps retroactively, so as to result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the U.S. Internal Revenue Service, or "the IRS", with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions. This discussion assumes that the Non-U.S. Holder holds our common stock as a "capital asset" within the meaning of Section 1221 of the Code (generally, property held for investment).

Persons considering the purchase of our common stock pursuant to this offering should consult their own tax advisors concerning the U.S. federal income tax consequences of acquiring, owning and disposing of our common stock in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local or foreign tax consequences and any U.S. federal non-income tax consequences.

For the purposes of this discussion, a "Non-U.S. Holder" is, for U.S. federal income tax purposes, a beneficial owner of our common stock that is not a partnership for U.S. federal income tax purposes and is not a U.S. Holder. A "U.S. Holder" means a beneficial owner of our common stock that is for U.S. federal income tax purposes (a) an individual who is a citizen or resident of the United States, (b) a corporation or other entity treated as a corporation created or organized in or under the laws of the United States, any state thereof or the District of Columbia, (c) an estate the income of which is subject to U.S. federal income taxation regardless of its source or (d) a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

## **Distributions on Our Common Stock**

Subject to the discussion below regarding back-up withholding and foreign accounts, distributions, if any, made on our common stock to a Non-U.S. Holder of our common stock to the extent made out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles) generally will constitute dividends for U.S. tax purposes and will be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide us or our paying agent with a properly executed IRS Form W-8BEN, or other appropriate form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent will then be required to provide certification to the applicable withholding agent, either directly or through other intermediaries. These certifications must be provided to us or our paying agent prior to the payment of dividends and must be updated periodically, or earlier if any information therein becomes outdated or is no longer correct. If you do not timely provide us or our paying agent the required certification but are eligible for a reduced rate of U.S. federal withholding tax under an income tax treaty, you should consult with your own tax advisor to determine if you are able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment that such holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to us or our paying agent (or, if stock is held through a financial institution or other agent, to such agent). In general, such effectively connected dividends will be subject to U.S. federal income tax, on a net income basis at the regular graduated U.S. federal income tax rates, unless a specific treaty exemption applies. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax," which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will first constitute a non-taxable return of capital and will reduce your basis in our common stock, but not below zero, and then will be treated as capital gain and taxed in the same manner as gain realized from a sale or other disposition of common stock as described in the next section.

## **Gain on Disposition of Our Common Stock**

Subject to the discussion below regarding backup withholding and foreign accounts, a Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (a) the gain is effectively connected with a trade or business of such holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment that such holder maintains in the United States), (b) the Non-U.S. Holder is a non-resident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (c) we are or have been a "United States real property holding corporation" within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder's holding period.



If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at regular graduated U.S. federal income tax rates, unless a specific treaty exemption applies, and corporate Non-U.S. Holders described in (a) above may be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual Non-U.S. Holder described in (b) above, you will be required to pay a flat 30% tax on the gain derived from the sale, which gain may be offset by U.S. source capital losses (even though you are not considered a resident of the United States). For purposes of (c) above, in general, we would be a United States real property holding corporation if the fair market value of our U.S. real property interests was equal to or exceeded 50% of the sum of the fair market value of our worldwide real property interests plus other assets used or held for use by us in a trade or business. We believe that we are not, and do not anticipate becoming, a United States real property holding corporation. However, because the determination of whether we are a United States real property holding corporation depends on the fair market value of our U.S. real property interests relative to the fair market value of our other business assets, there can be no assurance that we will not become a United States real property holding corporation in the future. Even if we are treated as a United States real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned, directly, indirectly and constructively, no more than 5% of our common stock at all times within the shorter of (i) the five-year period preceding the disposition or (ii) the holder's holding period and (2) our common stock is "regularly traded," as defined by applicable Treasury regulations, on an established securities market. We expect our common stock to be "regularly traded" on an established securities market, but there can be no assurance that our common stock will be so traded. If gain on the sale or other taxable disposition of our common stock were subject to taxation under (c) above, the Non-U.S. Holder would be subject to regular U.S. federal income tax with respect to such gain in generally the same manner as a U.S. person and may be subject to a withholding tax on the disposition.

### **Information Reporting Requirements and Backup Withholding**

Generally, we or certain financial middlemen must report information to the IRS with respect to any dividends we pay on our common stock, including the amount of any such dividends, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such dividends are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient's country of residence.

Dividends paid by us (or our paying agents) to a Non-U.S. Holder may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN or IRS Form W-8ECI or otherwise establishes an exemption, *provided* we do not have actual knowledge or reason to know such non-U.S. holder is a U.S. person, as defined in the Code. The current backup withholding rate is 28%.

Under current U.S. federal income tax law, U.S. information reporting and backup withholding requirements generally will apply to the proceeds from a disposition of our common stock effected by or through a U.S. office of any broker, U.S. or foreign, except that information reporting and such requirements may be avoided if the holder provides a properly executed IRS Form W-8BEN or otherwise meets documentary evidence requirements for establishing Non-U.S. Holder status or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. brokers. Information reporting and backup

withholding requirements may apply to a payment of disposition proceeds if the broker has actual knowledge, or reason to know, that the holder is a U.S. person, as defined in the Code.

If backup withholding is applied to you, you should consult with your own tax advisor to determine if you are able to obtain a tax benefit or credit with respect to such backup withholding.

### **Foreign Accounts**

A U.S. federal withholding tax of 30% may apply to dividends and the gross proceeds from a disposition of our common stock if the disposition occurs after December 31, 2018 to a foreign financial institution (as specifically defined for this purpose), including when the foreign financial institution holds our common stock on behalf of a Non-U.S. Holder, unless such institution enters into an agreement with the U.S. government to withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding U.S. account holders of such institution (which may include certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing these withholding and reporting requirements may be subject to different rules. This U.S. federal withholding tax of 30% currently applies to dividends and is scheduled to apply to the gross proceeds from a disposition of our common stock after December 31, 2018. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules. Under certain circumstances, a Non-U.S. Holder might be eligible for refunds or credits of such taxes. Holders are encouraged to consult with their own tax advisors regarding the possible implications of the legislation on their investment in our common stock.

## UNDERWRITING

We are offering the shares of common stock described in this prospectus through a number of underwriters. Cowen and Company, LLC, Stifel, Nicolaus & Company, Incorporated and Wells Fargo Securities, LLC are acting as book running managers of the offering and as representatives of the underwriters. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus, the number of shares of common stock listed next to its name in the following table:

<u>Name</u>	<u>Number of Shares</u>
Cowen and Company, LLC . . . . .	5,078,125
Stifel, Nicolaus & Company, Incorporated . . . . .	5,078,125
Wells Fargo Securities, LLC . . . . .	3,125,000
BMO Capital Markets Corp. . . . .	2,343,750
Total . . . . .	<u>15,625,000</u>

Ionis Pharmaceuticals, Inc., or Ionis, has agreed to purchase 3,125,000 shares of common stock in this offering at the initial public offering price. The underwriters will not receive any underwriting discounts or commissions on the shares purchased by Ionis.

The underwriters are committed to purchase all the common stock offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

The underwriters propose to offer the common stock directly to the public at the initial public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of \$0.336 per share. After the initial offering of the shares to the public, the offering price and other selling terms may be changed by the underwriters.

The underwriters have an option to buy up to 2,343,750 additional shares of common stock from us to cover sales of shares by the underwriters which exceed the number of shares specified in the table above. The underwriters have 30 days from the date of this prospectus to exercise this option to purchase additional shares. If any shares are purchased with this option to purchase additional shares, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock; provided that no underwriting fee will be paid with respect to shares purchased by Ionis. The underwriting fee is \$0.56 per share. The following table shows the per share and total underwriting discounts and commissions to be paid to

the underwriters assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Without option to purchase additional shares exercise	With full option to purchase additional shares exercise
Per share to public . . . . .	\$ 0.56	\$ 0.56
Total . . . . .	\$7,000,000	\$8,312,500

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately \$3.0 million. We have agreed to reimburse the underwriters up to \$35,000 for expenses relating to the clearance of this offering with the Financial Industry Regulatory Authority, Inc.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We have agreed that we will not (1) offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise dispose of, directly or indirectly, or file with the Securities and Exchange Commission a registration statement under the Securities Act relating to, any shares of our common stock or securities convertible into or exchangeable or exercisable for any shares of our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (2) enter into any swap or other arrangement that transfers all or a portion of the economic consequences associated with the ownership of any shares of common stock or any such other securities (regardless of whether any of these transactions are to be settled by the delivery of shares of common stock or such other securities, in cash or otherwise), in each case without the prior written consent of Cowen and Company, LLC for a period of 180 days after the date of this prospectus, other than (i) the shares of our common stock to be sold hereunder, (ii) any shares of our common stock issued upon the exercise of options granted under our existing equity incentive plans, (iii) any options or awards granted pursuant to our existing equity incentive plans; provided, that each recipient of such options or awards enter into a lock-up agreement with the underwriters with the terms described in the paragraph below, (iv) the filing of any registration statement on Form S-8 relating to our existing equity incentive plans and (v) any shares of our common stock or other securities issued in connection with a bona fide commercial or licensing relationship or acquisition of assets or equity securities of an unaffiliated third party; provided, that the aggregate number of shares issued in connection with any such transaction shall not exceed 10% of our shares of common stock outstanding following completion of this offering and provided, further, that each recipient of such shares or other securities enter into a lock-up agreement with the underwriters with the terms described in the paragraph below.

Ionis, Novartis, our directors and executive officers and substantially all of our option holders have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant to which each of these persons or entities, with limited exceptions, for a period of 180 days after the date of this prospectus, may not, without the prior written consent of Cowen and Company, LLC, (1) offer, pledge, announce the intention to sell, sell, contract to sell, sell any option

or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock (including, without limitation, common stock or such other securities which may be deemed to be beneficially owned by such directors, executive officers, managers and members in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant) or (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise, or (3) make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock.

The restrictions described in the immediately preceding paragraph do not apply to:

- common stock acquired in open market transactions after the completion of this offering, *provided* that no filing by any party (donor, donee, transferor or transferee) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, or other public announcement shall be required or shall be made voluntarily in connection with such transfer or distribution (other than a filing on a Form 5 made after the expiration of the restricted period under the lock-up agreement);
- transfers of shares of our common stock:
  - as a *bona fide* gift or gifts;
  - to any trust for the direct or indirect benefit of the party subject to the lock-up restrictions or the immediate family of such party, or if such party is a trust, to any beneficiary (including such beneficiary's estate) of such party, *provided* that any such transfer shall not involve a disposition for value; or
  - upon death by will or intestacy,*provided* that in the case of any transfer or distribution pursuant to the above three subclauses, each donee, heir, distributee or transferee will execute and deliver to the representatives of the underwriters a lock-up letter in the form of the original lock-up agreement, and *provided further* that no filing by any party (donor, donee, transferor or transferee) under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with such transfer or distribution (other than a filing on a Form 5 made after the expiration of the restricted period under the lock-up agreement);
- if the party subject to the lock-up restrictions is a corporation, partnership, limited liability company, trust or other business entity, transfers of our common stock (i) to another corporation, partnership, limited liability company, trust or other business entity that is a direct or indirect affiliate (as defined in Rule 405 promulgated under the Securities Act of 1933, as amended) of such party or (ii) distributions of shares of our common stock to members, stockholders or other equityholders of the such party; *provided* that each donee, heir, distributee or transferee will execute and deliver to the representatives of the underwriters a lock-up letter in the form of the original lock-up agreement, and *provided further* that no filing by any party (donor, donee, transferor or transferee) under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with such transfer or distribution (other than a filing on a Form 5 made after the expiration of the restricted period under the lock-up agreement);
- entering into a 10b5-1 Plan, *provided* that such plan does not provide for the transfer of our common stock during the restricted period under the lock-up agreement and no public announcement or filing under the Exchange Act regarding the establishment of such plan

- will be required of or voluntarily made by or on behalf of the party subject to the lock-up restrictions or us during the restricted period under the lock-up agreement;
- transfers of shares of our common stock in connection with the repurchase of securities issued pursuant to our equity incentive plans or pursuant to agreements under which we have the option to purchase such shares or a right of first refusal with respect to transfers of such shares;
  - in connection with the conversion of the outstanding preferred stock of into shares of our common stock, *provided* that the shares of our common stock so received shall be subject to the terms of the lock-up agreement;
  - pursuant to a bona fide third-party tender offer, merger, consolidation or other similar transaction made to all holders of our capital stock involving a change of control of Akcea, *provided* that in the event that such tender offer, merger, consolidation or other such transaction is not completed, the shares of our common stock held by the party subject to the lock-up restrictions shall remain subject to such restrictions; and
  - by operation of law, such as pursuant to a domestic relations order or in connection with a divorce settlement; *provided* that each donee, heir, distributee or transferee will execute and deliver to the representatives of the underwriters a lock-up letter in the form of the original lock-up agreement;

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

Our common stock has been approved for listing on the Nasdaq Global Select Market under the symbol "AKCA."

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be "covered" shorts, which are short positions in an amount not greater than the underwriters' option to purchase additional shares referred to above, or may be "naked" shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional shares, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the option to purchase additional shares. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act of 1933, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.



These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on the Nasdaq Global Select Market, in the over the counter market or otherwise.

Prior to this offering, there has been no public market for our common stock. The initial public offering price was determined by negotiations between us and the representatives of the underwriters. In determining the initial public offering price, we and the representatives of the underwriters considered a number of factors including:

- the information set forth in this prospectus and otherwise available to the representatives;
- our prospects and the history and prospects for the industry in which we compete;
- an assessment of our management;
- our prospects for future earnings;
- the general condition of the securities markets at the time of this offering;
- the recent market prices of, and demand for, publicly traded common stock of generally comparable companies; and
- other factors deemed relevant by the underwriters and us.

Neither we nor the underwriters can assure investors that an active trading market will develop for our common shares, or that the shares will trade in the public market at or above the initial public offering price.

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

### **European Economic Area**

In relation to each Member State of the European Economic Area (each, a "Relevant Member State"), no offer of common stock may be made to the public in that Relevant Member State other than:

- a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or
- c) in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of shares shall require the Company or the representative(s) to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a “qualified investor” within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

The Company, the representatives and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus has been prepared on the basis that any offer of shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly any person making or intending to make an offer in that Relevant Member State of shares which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for the Company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the Company nor the underwriters have authorized, nor do they authorize, the making of any offer of shares in circumstances in which an obligation arises for the Company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression “an offer to the public” in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression “Prospectus Directive” means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression “2010 PD Amending Directive” means Directive 2010/73/EU.

#### **Notice to Prospective Investors in the United Kingdom**

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are “qualified investors” (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19 (5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as “relevant persons”).

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom,

any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

### **Notice to Residents of Canada**

Our common stock may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of our common stock must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

### **Notice to Residents of France**

This prospectus has not been prepared in the context of a public offering of financial securities in France within the meaning of Article L.411-1 of the French Code Monétaire et Financier and Title I of Book II of the Règlement Général of the Autorité des marchés financiers, or the AMF, and therefore has not been and will not be filed with the AMF for prior approval or submitted for clearance to the AMF. Consequently, the shares of our common stock may not be, directly or indirectly, offered or sold to the public in France and offers and sales of the shares of our common stock may only be made in France to qualified investors (investisseurs qualifiés) acting for their own, as defined in and in accordance with Articles L.411-2 and D.411-1 to D.411-4, D.734-1, D.744-1, D.754-1 and D.764-1 of the French Code Monétaire et Financier. Neither this prospectus nor any other offering material may be released, issued or distributed to the public in France or used in connection with any offer for subscription on sale of the shares of our common stock to the public in France. The subsequent direct or indirect retransfer of the shares of our common stock to the public in France may only be made in compliance with Articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French Code Monétaire et Financier.

### **Notice to Residents of Germany**

Each person who is in possession of this prospectus is aware of the fact that no German securities prospectus (wertpapierprospekt) within the meaning of the securities prospectus act (*wertpapier-prospektgesetz*), or the act, of the federal republic of Germany has been or will be published with respect to the shares of our common stock. In particular, each underwriter has represented that it has not engaged and has agreed that it will not engage in a public offering in the federal republic of Germany (öffentliches angebot) within the meaning of the act with respect to any of the shares of our common stock otherwise than in accordance with the act and all other applicable legal and regulatory requirements.

### **Notice to Residents of Switzerland**

The shares common stock may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document does not constitute a prospectus within the meaning of, and has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to the shares or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company, the shares have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of shares will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA (FINMA), and the offer of shares has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of shares.

### **Notice to Residents of the Netherlands**

The offering of the shares of our common stock is not a public offering in The Netherlands. The shares of our common stock may not be offered or sold to individuals or legal entities in The Netherlands unless (1) a prospectus relating to the offer is available to the public, which has been approved by the Dutch Authority for the Financial Markets (Autoriteit Financiële Markten) or by the competent supervisory authority of another state that is a member of the European Union or party to the Agreement on the European Economic Area, as amended or (2) an exception or exemption applies to the offer pursuant to Article 5:3 of The Netherlands Financial Supervision Act (*Wet op het financieel toezicht*) or Article 53 paragraph 2 or 3 of the Exemption Regulation of the Financial Supervision Act, for instance due to the offer targeting exclusively “qualified investors” (*gekwalificeerde beleggers*) within the meaning of Article 1:1 of The Netherlands Financial Supervision Act.

### **Notice to Residents of Japan**

The shares have not been and will not be registered under the Financial Instruments and Exchange Act. Accordingly, the shares may not be offered or sold, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to or for the benefit of a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in

compliance with, the Financial Instruments and Exchange Act and any other applicable laws, regulations and ministerial guidelines of Japan.

### **Notice to Residents of Hong Kong**

The shares have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to “professional investors” as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a “prospectus” as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to our common stock has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to our common stock which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

### **Notice to Residents of Singapore**

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries’ rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

- a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;
- b) where no consideration is or will be given for the transfer;
- c) where the transfer is by operation of law;
- d) as specified in Section 276(7) of the SFA; or
- e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

## LEGAL MATTERS

The validity of the common stock offered hereby will be passed upon for us by Cooley LLP, Boston, Massachusetts. Certain legal matters in connection with this offering will be passed upon for the underwriters by Davis Polk & Wardwell LLP, Menlo Park, California.

## EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements at December 31, 2015 and 2016, and for each of the three years in the period ended December 31, 2016, as set forth in their report. We have included our consolidated financial statements in the prospectus and elsewhere in the registration statement in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

## WHERE YOU CAN FIND ADDITIONAL INFORMATION

We have filed with the Securities and Exchange Commission, or SEC, a registration statement on Form S-1 (including exhibits, schedules, and amendments) under the Securities Act of 1933, as amended, with respect to the shares of common stock offered by this prospectus. This prospectus, which constitutes part of the registration statements, does not contain all the information set forth in the registration statement and its exhibits. For further information about us and the shares of common stock to be sold in this offering, you should refer to the registration statement. Statements contained in this prospectus relating to the contents of any contract, agreement or other document are not necessarily complete and are qualified in all respects by the complete text of the applicable contract, agreement or other document, a copy of which has been filed as an exhibit to the registration statement. Whenever this prospectus refers to any contract, agreement, or other document, you should refer to the exhibits that are a part of the registration statement for a copy of the contract, agreement, or document.

You may read and copy all or any portion of the registration statement or any other information we file at the SEC's public reference room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You can request copies of these documents, upon payment of a duplicating fee, by writing to the SEC. Please call the SEC at 1-800-SEC-0330 for further information about the operation of the public reference rooms. Our SEC filings, including the registration statement, are also available to you on the SEC's Website (<http://www.sec.gov>).

Upon completion of this offering, we will become subject to the information and periodic reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Under the Exchange Act, we will file annual, quarterly and current reports, as well as proxy statements and other information with the SEC. These periodic reports, proxy statements, and other information will be available for inspection and copying at the SEC's Public Reference Room and the website of the SEC referred to above. We maintain a website at [www.akceatx.com](http://www.akceatx.com), at which you may access these materials free of charge as soon as reasonably practicable after they are electronically filed with, or furnished to, the SEC. The reference to our website address does not constitute incorporation by reference of the information contained on our website, and you should not consider the contents of our website in making an investment decision with respect to our common stock.



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## REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Akcea Therapeutics, Inc.

We have audited the accompanying consolidated balance sheets of Akcea Therapeutics, Inc. as of December 31, 2015 and 2016, and the related consolidated statements of operations, comprehensive loss, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Akcea Therapeutics, Inc. at December 31, 2015 and 2016, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

/s/ ERNST & YOUNG LLP

San Diego, California  
March 27, 2017,  
except for the second paragraph in Note 9, as to which the date is  
June 20, 2017

**Akcea Therapeutics, Inc.**  
**Consolidated Balance Sheets**  
(in thousands, except share and per share data)

	December 31,		March 31, 2017	
	2015	2016	Actual	Pro forma
			(unaudited)	
<b>Assets</b>				
Current assets:				
Cash and cash equivalents . . . . .	\$ 29,389	\$ 7,857	\$ 77,858	\$ 77,858
Short-term investments . . . . .	34,921	—	46,664	46,664
Prepaid amounts to Ionis . . . . .	—	—	3,005	3,005
Other current assets . . . . .	218	1,209	3,895	3,895
Total current assets . . . . .	64,528	9,066	131,422	131,422
Property, plant and equipment, net . . . . .	10	177	141	141
Licenses, net . . . . .	1,460	1,341	1,311	1,311
Deposits and other assets . . . . .	69	100	107	107
Total assets . . . . .	\$ 66,067	\$ 10,684	\$ 132,981	\$ 132,981
<b>Liabilities and Stockholders' Equity (Deficit)</b>				
Current liabilities:				
Accounts payable . . . . .	\$ 239	\$ 476	\$ 329	\$ 329
Payable to Ionis Pharmaceuticals, Inc. . . . .	9,198	24,355	15,000	15,000
Accrued compensation . . . . .	923	2,505	847	847
Accrued liabilities . . . . .	405	1,041	1,362	1,362
Current portion of deferred revenue . . . . .	—	—	61,928	61,928
Current portion of deferred rent . . . . .	2	33	34	34
Total current liabilities . . . . .	10,767	28,410	79,500	79,500
Long-term portion of deferred rent . . . . .	33	21	12	12
Line of credit with Ionis . . . . .	—	—	91,541	91,541
Long-term portion of deferred revenue . . . . .	—	—	36,870	36,870
Total liabilities . . . . .	10,800	28,431	207,923	207,923
Stockholders' equity (deficit):				
Series A convertible preferred stock, \$0.001 par value; 28,884,540 shares authorized, issued and outstanding at December 31, 2015, December 31, 2016 and March 31, 2017, respectively, actual; aggregate liquidation value of \$575,758, \$610,304 and \$619,458 as of December 31, 2015, December 31, 2016 and March 31, 2017, respectively; no shares authorized, issued or outstanding, pro forma (unaudited) . . . . .	100,000	100,000	100,000	—
Common stock, \$0.001 par value; 100,000,000 shares authorized and 0 shares issued and outstanding at December 31, 2015, December 31, 2016 and March 31, 2017, respectively, actual; 100,000,000 shares authorized, 28,884,540 shares issued and outstanding (unaudited), pro forma . . . . .	—	—	—	29
Additional paid-in capital . . . . .	46,787	56,936	60,116	160,087
Accumulated other comprehensive loss . . . . .	(75)	(21)	(43)	(43)
Accumulated deficit . . . . .	(91,445)	(174,662)	(235,015)	(235,015)
Total stockholders' equity (deficit) . . . . .	55,267	(17,747)	(74,942)	(74,942)
Total liabilities and stockholders' equity (deficit) .	\$ 66,067	\$ 10,684	\$ 132,981	\$ 132,981

See accompanying notes.

**Akcea Therapeutics, Inc.**  
**Consolidated Statements of Operations**  
(in thousands, except for share and per share data)

	Years Ended December 31,			Three Months Ended March 31,	
	2014	2015	2016	2016	2017
	(unaudited)				
Revenue: . . . . .					
Research and development revenue under collaborative agreements . . . . .	\$ —	\$ —	\$ —	\$ —	\$ 9,597
Total revenue . . . . .	<u>—</u>	<u>—</u>	<u>—</u>	<u>—</u>	<u>9,597</u>
Operating expenses:					
Research and development expenses . . . . .	29,028	50,885	68,459	11,796	64,794
General and administrative expenses . . . . .	995	10,553	15,053	4,253	4,676
Total operating expenses . . . . .	<u>30,023</u>	<u>61,438</u>	<u>83,512</u>	<u>16,049</u>	<u>69,470</u>
Loss from operations . . . . .	(30,023)	(61,438)	(83,512)	(16,049)	(59,873)
Other income:					
Investment income . . . . .	—	16	295	87	61
Interest expense . . . . .	—	—	—	—	(541)
Net loss . . . . .	<u>\$ (30,023)</u>	<u>\$ (61,422)</u>	<u>\$ (83,217)</u>	<u>\$ (15,962)</u>	<u>\$ (60,353)</u>
Net loss per share of preferred stock, basic and diluted . . . . .	<u>\$ (1.04)</u>	<u>\$ (2.13)</u>	<u>\$ (2.88)</u>	<u>\$ (0.55)</u>	<u>\$ (2.09)</u>
Weighted-average shares of preferred stock outstanding, basic and diluted . . . . .	<u>28,884,540</u>	<u>28,884,540</u>	<u>28,884,540</u>	<u>28,884,540</u>	<u>28,884,540</u>
Pro forma net loss per share, basic and diluted (unaudited) . . . . .			<u>\$ (2.88)</u>		<u>\$ (2.09)</u>
Pro forma weighted-average shares of common stock outstanding, basic and diluted (unaudited) . .			<u>28,884,540</u>		<u>28,884,540</u>

*See accompanying notes.*

**Akcea Therapeutics, Inc.**  
**Consolidated Statements of Comprehensive Loss**  
(in thousands)

	Years Ended December 31,			Three Months Ended March 31,	
	2014	2015	2016	2016	2017
				(unaudited)	
Net loss . . . . .	\$(30,023)	\$(61,422)	\$(83,217)	\$(15,962)	\$(60,353)
Unrealized (losses) gains on investments, net of tax . . . . .	—	(75)	75	70	(28)
Currency translation adjustment . . . . .	—	—	(21)	—	6
Comprehensive loss . . . . .	<u>\$(30,023)</u>	<u>\$(61,497)</u>	<u>\$(83,163)</u>	<u>\$(15,892)</u>	<u>\$(60,375)</u>

*See accompanying notes.*

**Akcea Therapeutics, Inc**  
**Consolidated Statements of Stockholders' Equity (Deficit)**  
(in thousands)

Description	Convertible preferred stock		Common stock		Additional paid in capital	Accumulated other comprehensive loss	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	Amount	Shares	Amount				
<b>Balance at December 31, 2013</b>	—	\$ —	—	—	\$ —	\$ —	\$ —	\$ —
Net loss	—	—	—	—	—	—	(30,023)	(30,023)
Ionis investment in Akcea	—	—	—	—	31,602	—	—	31,602
<b>Balance at December 31, 2014</b>	—	\$ —	—	—	\$31,602	\$ —	\$ (30,023)	\$ 1,579
Net loss	—	—	—	—	—	—	(61,422)	(61,422)
Ionis investment in Akcea	—	—	—	—	8,689	—	—	8,689
Change in unrealized losses, net of tax	—	—	—	—	—	(75)	—	(75)
Issuance of Series A convertible preferred stock	28,885	100,000	—	—	—	—	—	100,000
Stock-based compensation expense	—	—	—	—	6,496	—	—	6,496
<b>Balance at December 31, 2015</b>	28,885	\$100,000	—	—	\$46,787	\$(75)	\$ (91,445)	\$ 55,267
Net loss	—	—	—	—	—	—	(83,217)	(83,217)
Change in unrealized gains, net of tax	—	—	—	—	—	75	—	75
Currency translation adjustment	—	—	—	—	—	(21)	—	(21)
Stock-based compensation expense	—	—	—	—	10,149	—	—	10,149
<b>Balance at December 31, 2016</b>	28,885	\$100,000	—	—	\$56,936	\$(21)	\$(174,662)	\$ (17,747)
Net loss	—	—	—	—	—	—	(60,353)	(60,353)
Change in unrealized losses, net of tax	—	—	—	—	—	(28)	—	(28)
Currency translation adjustment	—	—	—	—	—	6	—	6
Stock-based compensation expense	—	—	—	—	3,180	—	—	3,180
<b>Balance at March 31, 2017 (unaudited)</b>	28,885	\$100,000	—	—	\$60,116	\$(43)	\$(235,015)	\$ (74,942)

*See accompanying notes.*



**Akcea Therapeutics, Inc.**  
**Consolidated Statements of Cash Flows**  
(In thousands)

	Years Ended December 31,			Three Months Ended March 31,	
	2014	2015	2016	2016	2017
Operating activities:					
Net loss	\$(30,023)	\$ (61,422)	\$(83,217)	\$(15,962)	\$(60,353)
Adjustments to reconcile net loss (used in) provided by operating activities:					
Depreciation	—	—	12	—	29
Amortization of licenses	119	119	119	36	30
Amortization of premium on investments, net	—	18	170	53	24
Non-cash interest expense for line of credit with Ionis	—	—	—	—	541
Stock-based compensation expense	—	6,496	10,149	3,189	3,180
Changes in operating assets and liabilities:					
Other current and long-term assets	—	(286)	64	85	(1,915)
Prepaid amounts to Ionis	—	—	—	—	(3,005)
Accounts payable	—	239	(54)	99	(463)
Payable to Ionis Pharmaceuticals, Inc.	—	9,198	15,157	11,904	(9,355)
Accrued compensation	—	923	1,582	(525)	(1,658)
Deferred rent	—	35	20	19	(9)
Accrued liabilities	—	405	637	34	331
Deferred revenue	—	—	—	—	98,798
Net cash (used in) provided by operating activities	<u>(29,904)</u>	<u>(44,275)</u>	<u>(55,361)</u>	<u>(1,068)</u>	<u>26,175</u>
Investing activities:					
Purchases of short-term investments	—	(35,975)	(16,638)	—	(49,465)
Proceeds from the sale of short-term investments	—	960	51,464	6,519	2,750
Purchases of property, plant and equipment	—	(10)	(179)	(4)	—
Net cash (used in) provided by investing activities	<u>—</u>	<u>(35,025)</u>	<u>34,647</u>	<u>6,515</u>	<u>(46,715)</u>
Financing activities:					
Proceeds from the issuance of Series A convertible preferred stock to Ionis Pharmaceuticals, Inc.	—	100,000	—	—	—
Proceeds from line of credit from Ionis	—	—	—	—	91,000
Offering costs paid	—	—	(818)	—	(459)
Capital contribution from Ionis Pharmaceuticals, Inc.	29,904	8,689	—	—	—
Net cash provided by (used in) financing activities	<u>29,904</u>	<u>108,689</u>	<u>(818)</u>	<u>—</u>	<u>90,541</u>
Net increase (decrease) in cash and cash equivalents	—	29,389	(21,532)	5,447	70,001
Cash and cash equivalents at beginning of period	—	—	29,389	29,389	7,857
Cash and cash equivalents at end of period	<u>\$ —</u>	<u>\$ 29,389</u>	<u>\$ 7,857</u>	<u>\$ 34,836</u>	<u>\$ 77,858</u>
<b>Supplemental disclosures of non-cash financing activities:</b>					
Unpaid deferred offering costs	<u>\$ —</u>	<u>\$ —</u>	<u>\$ 291</u>	<u>\$ —</u>	<u>\$ 319</u>

See accompanying notes.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements**

**1. Organization and Significant Accounting Policies**

***Organization***

Akcea Therapeutics, Inc., referred to as Akcea or the Company, was incorporated in Delaware in December 2014. It was organized and is wholly owned by Ionis Pharmaceuticals, Inc., or Ionis, to complete development of and commercialize Ionis' drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. The consolidated financial statements include the accounts of Akcea and its wholly owned subsidiaries, Akcea Therapeutics UK Ltd., or Akcea UK, which Akcea formed in August 2016 and Akcea Intl Ltd., or Akcea Intl, which Akcea formed in February 2017. Akcea, Akcea UK and Akcea Intl are collectively referred to in these consolidated financial statements as the Company. All intercompany transactions and balances have been eliminated in consolidation.

***Basis of Presentation***

For comparative purposes, the Company derived its full year 2014 financial results on a standalone basis from Ionis' financial statements and accounting records. The 2014 results reflect amounts attributable to the Company's business, including the costs Ionis incurred for the drugs the Company exclusively licensed from Ionis under the development, commercialization and license agreement with Ionis, which the Company refers to as the license agreement. Under this agreement, Ionis charges the Company external and internal research and development expenses Ionis incurs on the Company's behalf. External research and development expenses charged to the Company include costs for contract research organizations, or CROs, costs to conduct nonclinical and clinical studies on its drugs, costs to acquire and evaluate clinical study data such as investigator grants, patient screening fees and laboratory work, and fees paid to consultants. Ionis charges these costs to the Company at the same costs that Ionis incurs. Internal development expenses include costs for the work that Ionis' development employees perform for the Company. Ionis charges the Company a full-time equivalent rate that covers personnel-related expenses, including salaries and benefits, plus an allocation of facility-related expenses, including rent, utilities, insurance and property taxes, for those research and development employees who work either directly or indirectly on the development of the Company's drugs. Ionis calculates the facility-related expenses based on the full-time equivalents it charges to the Company as a percentage of the total full-time equivalents at Ionis. The Company also pays Ionis for the active pharmaceutical ingredient, or API, and drug product the Company uses in its nonclinical and clinical studies for all of its drugs. Ionis manufactures the API for the Company and charges the Company a price per gram consistent with the price Ionis charges its pharmaceutical partners, which includes the cost for direct materials, direct labor and overhead required to manufacture the API.

The Company also has a services agreement with Ionis that provides it with certain services, including, without limitation, general and administrative support services and development support services. The Company pays Ionis for its share of the internal and external expenses for each of these functions based on the Company's relative use of each function, plus an allocation of facility-related expenses. To reflect the Company's cost of doing business, the financial statements for 2014 and 2015 have been prepared as if the license and services agreements were in place for the entirety of both annual periods.

Akcea has calculated its income tax amounts using a separate return methodology and has presented these amounts as if it were a separate taxpayer from Ionis in each jurisdiction for each period the Company presented.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

Akcea's management believes that the allocations and results are reasonable for all periods presented. However, allocations may not be indicative of the actual expense Akcea would have incurred had it operated as an independent, publicly traded company for the periods presented.

Akcea's agreements with Ionis are discussed in note 3, *Development, Commercialization and License Agreement and Services Agreement with Ionis*.

***Unaudited Interim Financial Information***

The accompanying interim balance sheet as of March 31, 2017, the statements of operations, comprehensive loss and cash flows for the three months ended March 31, 2016 and 2017, the statements of stockholders' equity (deficit) for the three months ended March 31, 2017 and the related footnote disclosures for these periods are unaudited. These unaudited interim financial statements have been prepared in accordance with accounting principles generally accepted in the United States, or U.S. GAAP. In management's opinion, the unaudited interim financial statements have been prepared on the same basis as the audited financial statements and include all adjustments, which include only normal recurring adjustments, necessary for the fair presentation of the Company's financial position as of March 31, 2017 and its results of operations and comprehensive loss and its cash flows for the three months ended March 31, 2016 and 2017. The results for the three months ended March 31, 2017 are not necessarily indicative of the results expected for the full fiscal year or any other interim period.

***Unaudited Pro Forma Balance Sheet and Net Loss Per Share Information***

The unaudited pro forma balance sheet information as of March 31, 2017 assumes the conversion of 28,884,540 shares of Series A convertible preferred stock into 28,884,540 shares of the Company's common stock upon completion of the Company's initial public offering, or IPO. The pro forma balance sheet was prepared as though the completion of the IPO contemplated by this prospectus occurred on March 31, 2017. Shares of common stock issued in the IPO and the concurrent private placement and any related net proceeds are excluded from the pro forma information.

The unaudited pro forma net loss per share information for the three months ended March 31, 2017 assumes the conversion of 28,884,540 shares of Series A convertible preferred stock into 28,884,540 shares of the Company's common stock at the beginning of the period presented.

***Liquidity***

From inception through March 31, 2017, Akcea has devoted substantially all of its efforts to developing its drugs and building its infrastructure. The Company is subject to a number of risks and uncertainties, including, but not limited to, the need to obtain adequate additional funding, possible failure of clinical studies, the need to obtain marketing authorization for its drugs, competitors developing new technological innovations, the need to successfully commercialize and gain market acceptance of its drugs, and protection of its proprietary technology. The Company's transition to profitability is dependent upon the successful development, approval and commercialization of its drugs and the achievement of a level of revenue adequate to support its operating activities. Akcea may never achieve profitability, and unless and until it does, it will continue to need to raise additional capital or obtain financing from other sources, such as strategic collaborations or partnerships, debt or Ionis. The consolidated financial statements have been prepared assuming that Akcea will be able to continue as a going concern through May 9, 2018 and that, if necessary, Ionis

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

will continue to fund Akcea through that date. There can be no assurances, however, that additional funding will be available on terms acceptable to Akcea, or at all.

***Basic and Diluted Net Loss Per Share***

The Company issued 28,884,540 shares of Series A convertible preferred stock in December 2015. The Company has used the Series A convertible preferred stock to calculate basic net loss per share because there was no common stock outstanding in any period presented, and the Series A convertible preferred stock represents the lowest subordinated form of outstanding equity. For purposes of calculating diluted net loss per share, the Company considered the conversion of the Series A convertible preferred stock using its 1:1 conversion ratio and the potential dilutive effect of employee stock options.

For comparative purposes, the Company has also used a total of 28,884,540 outstanding shares of Series A convertible preferred stock to calculate net loss per share prior to December 2015. Additionally, because the Series A convertible preferred stock is the only outstanding form of equity, cumulative accruing dividends on the Series A convertible preferred stock have no effect on net loss available to these stockholders. As it incurred a net loss for the years ended December 31, 2015 and 2016 and for the first three months of 2016 and 2017, the Company did not include dilutive common equivalent shares, which consisted of 127,339; 4,371,578; 3,530,084; and 5,063,585 weighted average outstanding common stock options, respectively, in the computation of diluted net loss per share because the effect would have been anti-dilutive. The Company did not have any stock options outstanding for the year ended December 31, 2014.

***Revenue Recognition***

The Company will recognize revenue when it has satisfied all contractual obligations and it is reasonably assured of collecting the resulting receivable. The Company may be entitled to bill its customers and receive payment from its customers in advance of recognizing the revenue. In the instances in which the Company receives payment from its customers in advance of recognizing revenue, the Company will include the amounts in deferred revenue on its consolidated balance sheet.

Research and development revenue under collaborative agreements

*Arrangements with multiple deliverables*

The Company's strategic collaboration, option and license agreement, or collaboration agreement, with Novartis, which it entered into in January 2017, contains multiple elements, or deliverables, including options to obtain licenses to drugs, research and development services, and manufacturing services. Therefore, the Company accounted for the collaboration under the multiple deliverables guidance.

*Multiple agreements*

When the Company enters into separate agreements at or near the same time with the same partner, the Company must first evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. The Company evaluates whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement,

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

and whether elements in one arrangement are essential to another arrangement. The Company's evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, in the first quarter of 2017, the Company and Ionis entered into two separate agreements with Novartis at the same time: a collaboration agreement and a stock purchase agreement, or SPA.

The Company entered into the collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. Under the collaboration agreement, the Company received a \$75.0 million upfront payment. For each drug, the Company is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and delivering active pharmaceutical ingredient, or API. Under the collaboration agreement, Novartis has an exclusive option to develop and commercialize AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. If Novartis exercises an option for one of these drugs, it will pay the Company a license fee and will assume all further global development, regulatory and commercialization activities for the licensed drug. Akcea is also eligible to receive a development milestone payment, milestone payments if Novartis achieves pre-specified regulatory milestones, commercial milestones and tiered royalties on net sales from each drug under the collaboration.

Under the SPA, Novartis purchased 1.6 million shares of Ionis' common stock for \$100.0 million in the first quarter of 2017 and paid a premium over the weighted average trading price at the time of purchase. Additionally, Novartis agreed to purchase up to \$50.0 million of the Company's common stock in a separate private placement concurrent with the completion of this offering at a price per share equal to the initial offering price, subject to a number of conditions. If the Company does not complete this offering or a similar offering by the 15 month anniversary of the SPA, or if the Company completes an offering that does not meet the specified criteria for Novartis to invest, then Novartis is required to purchase \$50.0 million of Ionis' common stock at a premium over the weighted average trading price of Ionis' common stock at the time of purchase.

The Company evaluated the Novartis agreements to determine whether it should treat the agreements separately or as a single arrangement. The Company considered that the agreements were negotiated concurrently and in contemplation of one another. Additionally, the same individuals were involved in the negotiations of both agreements. Based on these facts and circumstances, the Company concluded that it should treat both agreements as a single arrangement, which the Company refers to as the Novartis collaboration. The Company evaluated the provisions of the agreements on a combined basis.

*Identifying deliverables and units of accounting*

The Company evaluates the deliverables in a collaboration agreement to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to the customer, the Company will account for the deliverables as separate units of accounting. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a stand-alone basis. For example, the Company's Novartis collaboration and SPA have multiple elements. The Company evaluated the deliverables in the Novartis collaboration when it entered into the agreements and determined that certain deliverables have stand-alone value.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

The Company identified the following four separate units of accounting under the collaboration, each with stand-alone value:

- Development activities for AKCEA-APO(a)-L<sub>Rx</sub>;
- Development activities for AKCEA-APOCIII-L<sub>Rx</sub>;
- API for AKCEA-APO(a)-L<sub>Rx</sub>; and
- API for AKCEA-APOCIII-L<sub>Rx</sub>.

The development activities and the supply of API each have stand-alone value because Novartis or another third party could provide these items without the Company's assistance.

*Measurement and allocation of arrangement consideration*

The Company's Novartis collaboration provides for various types of payments to the Company including upfront payments, milestone payments, licensing fees, royalties on product sales and payments for the purchase of common stock. The Company first evaluated the total consideration under both the collaboration agreement and SPA and determined how much of the total consideration was attributable to elements that Akcea is delivering under the collaboration. The Company determined that Akcea's portion of the total allocable arrangement consideration for the Novartis collaboration was \$108.4 million.

The Company determined that Akcea's portion of the allocable arrangement consideration for the Novartis collaboration was \$108.4 million, comprised of the following:

- \$75.0 million from the upfront payment received;
- \$28.4 million for the premium paid by Novartis, which represents the excess of the fair value Ionis received from Novartis' purchase of Ionis' stock at a premium in the first quarter of 2017; and
- \$5.0 million for the potential premium Novartis will pay if Novartis purchases Ionis' stock in the future at a premium.

Akcea will recognize the \$75.0 million upfront payment plus the premium paid by Novartis from its purchase of Ionis' stock and the potential premium if Novartis purchases Ionis' stock in the future as revenue because Akcea is the party providing the services and API under the collaboration agreement.

The Company will initially allocate the amount of consideration that is fixed or determinable at the time the agreement is entered into and exclude contingent consideration. The Company allocates the consideration to each unit of accounting based on the relative selling price of each deliverable. The Company uses the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BEBP. BEBP reflects the Company's best estimate of what the selling price would be if the Company regularly sold the deliverable on a stand-alone basis. The Company recognizes the revenue allocated to each unit of accounting as it delivers the related goods or services. If the Company determines that it should treat certain deliverables as a single unit of accounting, then it will recognize the revenue ratably over the Company's estimated period of performance.



**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

The Company allocated the consideration based on the relative BESP of each unit of accounting. The Company estimated the selling price of the development services over the expected period during which it will perform these services. The significant inputs it used to determine the selling price of the development services included:

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

For purposes of determining BESP of the services the Company will perform and the API it will deliver under the Company's Novartis collaboration, accounting guidance required it to include a markup for a reasonable profit margin.

Based on the units of accounting under the Novartis collaboration, the Company allocated the \$108.4 million of allocable consideration as follows:

- \$64.0 million for development services for AKCEA-APO(a)-L<sub>Rx</sub>;
- \$40.1 million for development services for AKCEA-APOCIII-L<sub>Rx</sub>;
- \$1.5 million for the delivery of AKCEA-APO(a)-L<sub>Rx</sub> API; and
- \$2.8 million for the delivery of AKCEA-APOCIII-L<sub>Rx</sub> API.

*Timing of revenue recognition*

The Company recognizes revenue as it delivers each item under its Novartis collaboration as it provides services and the related revenue is realizable and earned. The Company also recognizes revenue over time. The Company's Novartis collaboration agreement includes a development project plan outlining the activities the agreement requires each party to perform during the collaboration. The Company estimated its period of performance when the agreement was entered into because the agreement did not clearly define such information. The Company then recognizes revenue for development services ratably over such period. The Company made estimates of its time to complete its obligations under its Novartis collaboration agreement, and in certain instances the timing of satisfying these obligations may change as the development plans for the Company's drugs progress. If the Company's estimates and judgments change over the course of the Novartis collaboration agreement, it may affect the timing and amount of revenue that the Company will recognize in future periods. Any changes in estimates are recognized on prospective basis.

The following are the periods over which the Company is recognizing revenue for each of its units of accounting under the Novartis collaboration:

- The Company is recognizing the amount attributed to the development services for AKCEA-APO(a)-L<sub>Rx</sub> over the period of time it is performing the services, currently estimated to be through August 2018;
- The Company is recognizing the amount attributed to the development services for AKCEA-APOCIII-L<sub>Rx</sub> over the period of time it is performing the services, currently estimated to be through May 2019;
- The Company will recognize the amount attributed to the AKCEA-APO(a)-L<sub>Rx</sub> API supply when it delivers API to Novartis; and

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

- The Company will recognize the amount attributed to the AKCEA-APOCIII-L<sub>Rx</sub> API supply when it delivers API to Novartis.

*Milestone payments*

The Company's Novartis collaboration agreement contains contractual milestone payments that relate to the achievement of pre-specified development, regulatory and commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of the Company's drugs, which the Company describes in more detail in the following paragraphs.

The designation of a development candidate is the first stage in the life-cycle of the Company's drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

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

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

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

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

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

Development milestones in the Company's Novartis collaboration agreement or potential future collaborations may include the following types of events:

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

Regulatory milestones in the Company's Novartis collaboration agreement or potential future collaborations may include the following types of events:

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

Commercialization milestones in the Company's Novartis agreement or potential future collaborations may include the following types of events:

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

The Company will assess whether a substantive milestone exists at the inception of the collaboration agreement. When a substantive milestone is achieved, the Company will recognize revenue related to the milestone payment immediately. In evaluating if a milestone is substantive the Company will consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

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

If any of these conditions are not met, the Company will not consider the milestone to be substantive and it will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. The Company has determined that all milestones under its Novartis collaboration are substantive milestones.

*Option to license*

When the Company has a multiple element arrangement that includes an option to obtain a license, it will evaluate if the option is a deliverable at the inception of the arrangement. The Company does not consider the option to be a deliverable if it concludes that it is substantive and not priced at a significant and incremental discount. The Company will consider an option substantive if, at the inception of the arrangement, the Company is at risk as to whether the collaboration partner will choose to exercise its option to obtain the license. In those circumstances, the Company does not include the associated license fee in the allocable consideration at the inception of the agreement. Rather, the Company accounts for the license fee when the partner exercises its option. Under the Novartis collaboration, the Company concluded that the option to license is a substantive option. Therefore, the Company did not include any amounts in the initial allocable consideration at the inception of the collaboration. The Company will recognize any future exercise of an option to license a drug under the Novartis agreement in full in the period in which the option is exercised.

Refer to note 7, *Strategic Collaboration with Novartis*, where the Company discusses its Novartis collaboration agreement in more detail.

***Research and Development Expenses***

Akcea's research and development expenses include wages, benefits, facilities, supplies, external services, clinical study and manufacturing costs and other expenses that are directly related to its research and development activities. Akcea expenses research and development costs as it incurs them.

If Akcea makes payments for research and development services prior to the services being rendered, it records those amounts as prepaid assets on its balance sheet and it expenses them as the services are provided.

*Sublicensing Expenses*

The Company incurs sublicense fee expenses under its development, commercialization and license agreement and services agreement with Ionis related to the drugs it has licensed under the agreement. The Company includes its sublicense fee expenses in its research and development expenses on its consolidated results of operations since the applicable drugs are not yet approved

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

for marketing. The Company recognizes its sublicense fee expenses in the period they are incurred. For example, in the first quarter of 2017, the Company incurred \$48.4 million of sublicense fee expenses related to its collaboration with Novartis, of which \$33.4 million of these expenses were non-cash and were related to the premium Novartis paid and the potential premium Novartis may pay on Ionis' stock in the future. Under the Novartis collaboration, the Company will recognize \$108.4 million of revenue over the period of its performance and \$48.4 million of sublicensing expense in the first quarter of 2017. The \$48.4 million is comprised of the following:

- \$15.0 million for the portion of the \$75.0 million upfront payment the Company received upon initiating the Novartis collaboration, which will be paid in cash to Ionis;
- \$28.4 million for the premium paid by Novartis for its purchase of Ionis' stock in the first quarter of 2017, which is a non-cash expense. The Company determined the fair value of the premium by calculating the stated premium and applying a discount for lack of marketability because Ionis initially issued unregistered shares to Novartis; and
- \$5.0 million for the potential premium Novartis will pay if it purchases Ionis' stock in the future at a premium, which is a non-cash expense. The Company determined the fair value of the potential premium at the inception of the collaboration by calculating the value of the future premium based upon the stated premium, adjusting for the probability of an Akcea IPO occurring by the 15 month anniversary of the SPA and applying a discount for lack of marketability because Ionis will issue unregistered shares to Novartis if it purchases Ionis' common stock.

The Company will pay 50% of all future license fees, milestone payments and royalties it receives to Ionis as a sublicense fee.

***Estimated Liability for Research and Development Costs***

The Company records accrued liabilities related to expenses for which vendors or service providers have not yet billed it. These liabilities are for products or services that the Company has received and specifically relate to ongoing nonclinical studies and clinical studies. These costs primarily include third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. Akcea has drugs in concurrent nonclinical studies and clinical studies at several sites throughout the world. To ensure that it has adequately provided for ongoing nonclinical and clinical research and development costs during the period in which it incurs such costs, Akcea maintains an accrual to cover these costs. The Company updates its estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in the Company's consolidated financial statements. Akcea's historical accrual estimates have not been materially different from its actual amounts.

***License***

As part of the Company's founding in 2015, Akcea obtained an exclusive license from Ionis for specific patents that Ionis owns and maintains related to Akcea's drug pipeline. The Company recorded its license from Ionis as a capital contribution using the carryover basis of Ionis' historical cost for the related patents. For comparative purposes, the Company has assumed that it obtained the license as of January 1, 2014. Akcea is amortizing its capitalized license over its estimated useful life, which is the term of the underlying individual patents owned by Ionis. The weighted average remaining amortizable life of Akcea's license from Ionis is 13.2 years at December 31,

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

2016. The value of the license recorded on the Company's consolidated balance sheet at December 31, 2015 was \$1.5 million, The value of the license recorded on the Company's consolidated balance sheets at December 31, 2016 and March 31, 2017 was \$1.3 million at each period end. Accumulated amortization related to this license was \$238,000, \$357,000 and \$387,000 at December 31, 2015 and 2016 and March 31, 2017, respectively.

The Company estimated amortization expense for its license from Ionis in each of the next five years is as follows:

<u>Years Ending December 31, (in thousands)</u>	<u>Amortization</u>
2017 . . . . .	\$119
2018 . . . . .	\$119
2019 . . . . .	\$119
2020 . . . . .	\$119
2021 . . . . .	\$118

For additional detail of Akcea's license agreement with Ionis see note 3, *Development, Commercialization and License Agreement and Services Agreement with Ionis*.

**Concentration of Credit Risk**

Financial instruments that potentially subject Akcea to concentrations of credit risk consist primarily of its cash, cash equivalents and short-term investments. The Company places its cash equivalents and short-term investments with reputable financial institutions. The Company primarily invests its excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or Fitch, respectively. The Company has established guidelines relative to diversification and maturities that are designed to maintain safety and liquidity. Akcea periodically reviews and modifies these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

**Cash, Cash Equivalents and Short-Term Investments**

Akcea considers all liquid investments with maturities of three months or less when it purchases them to be cash equivalents. Akcea's short-term investments have initial maturities of greater than three months from date of purchase. The Company classifies its short-term investments as available-for-sale and carries them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. Akcea records unrealized gains and losses as a separate component of comprehensive income (loss) and includes net realized gains and losses in gain (loss) on investments on its consolidated statement of operations. The Company uses the specific identification method to determine the cost of securities sold.

**Property, Plant and Equipment**

Akcea carries its leasehold improvements and equipment at cost and depreciates it using the straight-line method over its estimated useful life. At December 31, 2015 and 2016 and March 31, 2017, Akcea's equipment consisted of computer equipment that has an estimated useful life of three years. At December 31, 2016 and March 31, 2017, Akcea's leasehold improvements consisted of improvements to its office facility that have an estimated useful life of two years.



**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

***Fair Value of Financial Instruments***

Akcea has estimated the fair value of its financial instruments. The amounts reported for cash equivalents, accounts payable and accrued expenses approximate fair value because of their short maturities. Akcea reports its investment securities at their estimated fair value based on quoted market prices for identical or similar instruments.

***Operating Leases***

Akcea leases its office space in a building in Cambridge, Massachusetts under a non-cancelable operating lease, which commenced in April 2015 and was subsequently amended and expanded in February 2016 and March 2017. A portion of the Company's lease currently has a three-year term and expires in July 2018 and a portion of it expires in April 2020.

Annual future minimum payments under its operating lease for its office space in Cambridge, Massachusetts are as follows (in thousands) for each year indicated:

	<b>Cambridge Office Space Operating Lease</b>
2017 .....	\$ 590
2018 .....	486
2019 .....	251
2020 .....	63
Total minimum payments .....	\$1,390

Rent expense for the year ended December 31, 2015 and 2016 was \$183,000 and \$435,000, respectively. Rent expense for the three months ended March 31, 2016 and 2017 was \$99,000 and \$155,000, respectively. Akcea recognizes rent expense on a straight-line basis over the lease term for the lease of its office space, which resulted in a deferred rent balance of \$35,000, \$54,000 and \$46,000 at December 31, 2015 and 2016 and March 31, 2017, respectively.

***Use of Estimates***

The preparation of financial statements in conformity with U.S. GAAP requires Akcea's management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

***Stock-Based Compensation Expense***

Akcea measures stock-based compensation expense for equity-classified stock option awards based on the estimated fair value of the award on the date of grant. Akcea recognizes the value of the portion of the award that the Company ultimately expects to vest as stock-based compensation expense over the requisite service period in its statements of operations. The Company reduces stock-based compensation expense for estimated forfeitures at the time of grant and revises the expense in subsequent periods if actual forfeitures differ from those estimates.

Akcea values its stock option awards using the Black-Scholes model. The determination of the grant date fair value of options using an option pricing model is affected principally by the

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

Company's estimated common stock fair value and requires management to make a number of other assumptions, including: the expected life of the option, the volatility of the underlying stock, the risk-free interest rate and expected dividends.

Akcea recognizes compensation expense for option awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach, also known as the graded-vesting method, an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

***Income Taxes***

Akcea is included in Ionis' consolidated U.S. federal income tax return filing. For these consolidated financial statements, the Company is using the separate return method, which determines income taxes as if Akcea were a separate taxpayer from Ionis. Since Ionis is the taxpayer, the estimated taxes payable under this method as current income tax expense were not recognized as liabilities in the Company's consolidated balance sheets, but were recorded to Akcea's additional paid-in capital account.

Akcea has not determined the amount of tax attributes, including net operating losses and tax credit carryovers, that will transfer over to Akcea if it were to deconsolidate from Ionis. An analysis will be performed at a future date if necessary.

***Accumulated Other Comprehensive Loss***

Akcea's accumulated other comprehensive loss is comprised of unrealized gains and losses on investments, net of taxes, adjustments Akcea made to reclassify realized gains and losses on investments from other accumulated comprehensive loss to the Company's consolidated statement of operations and foreign currency translation adjustments.

***Translation of Foreign Currency***

Akcea UK operates in the United Kingdom and it is using the British pound sterling as its functional currency. When Akcea consolidates Akcea UK's financial results, it translates Akcea UK's assets and liabilities using the exchange rate at the balance sheet date and Akcea UK's income and expense items using the average exchange rate for the period. Akcea translates Akcea UK's capital accounts at the historical exchange rate in effect at the date of the transaction. Akcea records adjustments resulting from the translation of Akcea UK's financial statements as a separate component of stockholders' equity (deficit) in accumulated other comprehensive income.

***Segment Information***

Akcea operates as a single segment because the Company's chief decision maker reviews operating results on an aggregate basis and manages the Company's operations as a single operating segment.

***Fair Value Measurements***

Akcea uses a three-tier fair value hierarchy to prioritize the inputs used in the Company's fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes Akcea's money market funds and

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

treasury securities classified as available-for-sale securities; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes Akcea's fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring Akcea to develop its own assumptions. Akcea has not held any Level 3 investments. The Company's securities have been classified as Level 1 or Level 2. Akcea obtains the fair value of its Level 2 investments from its custodian bank and from a professional pricing service. Akcea validates the fair value of its Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During 2015 and 2016, there were no transfers between the Company's Level 1 and Level 2 investments. Akcea recognizes transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer. Akcea did not have any Level 3 investments or liabilities at December 31, 2015 and 2016 and at March 31, 2017.

At December 31, 2016, the Company held \$7.1 million of money market fund investments which are Level 1 investments and are considered cash equivalents. The following tables present the major security types the Company held at December 31, 2015 and March 31, 2017 that are regularly measured and carried at fair value. The tables segregate each security by the level within the fair value hierarchy of the valuation techniques the Company utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2015	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents(1) . . . . .	\$29,284	\$29,284	\$ —
Corporate debt securities(2) . . . . .	28,928	—	28,928
Debt securities issued by U.S. government agencies(2) . . . . .	5,993	—	5,993
Total . . . . .	\$64,205	\$29,284	\$34,921

(1) Included in cash and cash equivalents on Akcea's consolidated balance sheet.

(2) Included in short-term investments on Akcea's consolidated balance sheet.

	At March 31, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents(1) . . . . .	\$ 73,811	\$73,811	\$ —
Corporate debt securities(2) . . . . .	47,384	—	47,384
Total . . . . .	\$121,195	\$73,811	\$47,384

(1) Included in cash and cash equivalents on Akcea's consolidated balance sheet.

(2) At March 31, 2017, \$0.7 million was included in cash and cash equivalents on Akcea's consolidated balance sheet, with the difference included in short-term investments on Akcea's consolidated balance sheet.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

***Impact of Recently Issued Accounting Standards***

In May 2014, the Financial Accounting Standards Board, or FASB, issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. This new guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance as originally issued is effective for annual and interim periods, beginning after December 15, 2016. In July 2015, the FASB issued updated accounting guidance to allow for an optional one-year deferral from the original effective date. As a result, the Company will adopt this guidance beginning on January 1, 2018. The guidance allows the Company to select one of two methods of adoption, either the full retrospective approach, meaning the guidance would be applied to all periods presented, or modified retrospective approach, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to the Company's opening accumulated deficit balance. Prior to 2017, Akcea had not generated revenue. In January 2017, Akcea entered into a strategic collaboration agreement with Novartis and began recognizing revenue. Given that Akcea recently entered into the Novartis collaboration agreement, the Company is currently determining the adoption method and the effects the adoption will have on its consolidated financial statements and disclosures.

In January 2016, the FASB issued amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires the Company to measure and record equity investments at fair value, except those accounted for under the equity method of accounting that have a readily determinable fair value, and for the Company to recognize the changes in fair value in its net income (loss), instead of recognizing unrealized gains and losses through accumulated other comprehensive income, as the Company currently does under the existing guidance. The amended guidance also changes several disclosure requirements for financial instruments, including the methods and significant assumptions the Company uses to estimate fair value. The guidance is effective for annual and interim periods, beginning after December 15, 2017. The Company will adopt this guidance on January 1, 2018 and it will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. The Company is currently determining the effects the adoption will have on its consolidated financial statements and disclosures.

In February 2016, the FASB issued amended accounting guidance related to lease accounting, which requires Akcea to record all leases with a term longer than one year on its balance sheet. When it records leases on its balance sheet under the new guidance, the Company will record a liability with a value equal to the present value of payments it will make over the life of the lease and an asset representing the underlying leased asset. The new accounting guidance requires the Company to determine if its leases are operating or financing leases, similar to current accounting guidance. The Company will record expense for operating type leases on a straight-line basis as an operating expense and it will record expense for finance type leases as interest expense. The new lease standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted. The Company must adopt the new standard on a modified retrospective basis, which requires it to reflect its leases on its consolidated balance sheet for the earliest comparative period presented. The Company is currently assessing the timing of adoption as well as the effects it will have on its consolidated financial statements and disclosures.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**1. Organization and Significant Accounting Policies (Continued)**

In March 2016, the FASB issued amended guidance to simplify certain aspects of share-based payment accounting. Under the amended guidance, Akcea will recognize excess tax benefits and tax deficiencies as income tax expense or benefit in its consolidated statement of operations on a prospective basis. As Akcea has a valuation allowance, this change will impact the Company's net operating loss carryforward and the valuation allowance disclosures. Additionally, the Company will classify excess tax benefits as an operating activity and classify amounts the Company withholds in shares for the payment of employee taxes as a financing activity on the consolidated statement of cash flows for each period presented. Lastly, the amended guidance allows the Company to account for forfeitures when they occur or continue to estimate them. Akcea will continue to estimate its forfeitures. The amended share-based payment standard is effective for annual and interim periods beginning after December 15, 2016, with early adoption permitted in any interim or annual period. The Company adopted this guidance on January 1, 2017. The amended guidance did not impact its financial results.

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

**2. Investments**

As of March 31, 2017, Akcea primarily invested its excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's or Fitch, respectively. Akcea has established guidelines relative to diversification and maturities that maintain safety and liquidity. The Company periodically reviews and modifies these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

As of March 31, 2017, all of the securities held by Akcea have a contractual maturity of one year or less and all of the Company's available-for-sale securities were available to the Company for use in its current operations and are classified as current assets.

As of December 31, 2016, Akcea was only invested in money market funds.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**2. Investments (Continued)**

The following is a summary of Akcea's investments at December 31, 2015 (in thousands):

	Cost	Gross Unrealized		Estimated Fair Value
		Gains	Losses	
Available-for-sale securities(1):				
Corporate debt securities . . . . .	\$16,266	\$ 1	\$(27)	\$16,240
Total securities with a maturity of one year or less . . . . .	16,266	1	(27)	16,240
Corporate debt securities . . . . .	12,730	1	(43)	12,688
Debt securities issued by U.S. government agencies . . . . .	6,000	—	(7)	5,993
Total securities with a maturity of more than one year . . . . .	18,730	1	(50)	18,681
Total available-for-sale securities . . . . .	<u>\$34,996</u>	<u>\$ 2</u>	<u>\$(77)</u>	<u>\$34,921</u>

(1) Akcea's available-for-sale securities are held at amortized cost.

The following is a summary of Akcea's investments at March 31, 2017 (in thousands):

	Cost	Gross Unrealized		Estimated Fair Value
		Gains	Losses	
Available-for-sale securities(1):				
Corporate debt securities . . . . .	\$47,412	\$3	\$(31)	\$47,384
Total available-for-sale securities . . . . .	<u>\$47,412</u>	<u>\$3</u>	<u>\$(31)</u>	<u>\$47,384</u>

(1) Akcea's available-for-sale securities are held at amortized cost.

Investments the Company considers to be temporarily impaired at March 31, 2017 were as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment		More than 12 months of temporary impairment		Total temporary impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities . . . . .	15	\$37,178	\$(27)	\$3,999	\$(4)	\$41,177	\$(31)
Total temporarily impaired securities . . . . .	<u>15</u>	<u>\$37,178</u>	<u>\$(27)</u>	<u>\$3,999</u>	<u>\$(4)</u>	<u>\$41,177</u>	<u>\$(31)</u>

The Company believes that the decline in value of these securities is temporary and for its investments is primarily related to the change in market interest rates since purchase. The Company believes it is more likely than not that it will be able to hold the Company's debt securities to maturity. Therefore, the Company anticipates a full recovery of its debt securities' amortized cost basis at maturity.



**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**3. Development, Commercialization and License Agreement and Services Agreement with Ionis**

Akcea entered into a development, commercialization and license agreement and a services agreement in December 2015 with Ionis. The following section summarizes these related party agreements with Ionis.

***Development, Commercialization and License Agreement***

Akcea's development, commercialization and license agreement, or the license agreement, with Ionis granted exclusive rights to the Company to develop and commercialize volanesorsen, AKCEA-APO(a)-L<sub>Rx</sub>, AKCEA-APOCIII-L<sub>Rx</sub>, and AKCEA-ANGPTL3-L<sub>Rx</sub>, which are collectively referred to as the Lipid Drugs. As a part of the grant to Akcea from Ionis, Ionis has granted an exclusive license to certain patents to develop and commercialize products containing the Lipid Drugs. Ionis also granted the Company a non-exclusive license to the Ionis antisense platform technology for Akcea to develop and commercialize products containing the Lipid Drugs. Ionis also granted Akcea non-exclusive rights under its manufacturing technology to manufacture the Lipid Drugs in the Company's own facility, or at a contract manufacturer. As a part of this agreement both companies agreed not to work with any other parties to develop or commercialize other drugs that are designed to inhibit any of the Lipid Drug targets so long as Akcea is developing or commercializing the Lipid Drugs.

Akcea and Ionis share development responsibilities for the Lipid Drugs. The Company pays Ionis for the research and development expenses it incurs on Akcea's behalf, which include both external and internal expenses. External research and development expenses include costs for contract research organizations, or CROs, costs to conduct nonclinical and clinical studies on Akcea's drugs, costs to acquire and evaluate clinical study data such as investigator grants, patient screening fees and laboratory work, and fees paid to consultants. Internal research and development expenses include costs for the work that Ionis' research and development employees perform for the Company. Ionis charges Akcea a full-time equivalent rate that covers personnel-related expenses, including salaries and benefits, plus an allocation of facility-related expenses, including rent, utilities, insurance and property taxes, for those development employees who work either directly or indirectly on the development of Akcea's drugs. In accordance with the license agreement, the Company began paying Ionis for external research and development expenses on January 1, 2015 and began paying Ionis for internal research and development expenses on January 1, 2016. All Ionis provided research and development expenses shown in Akcea's financial statements for 2014 and all internal research and development expenses for 2015 were treated as a capital contribution from Ionis. The Company also pays Ionis for the active pharmaceutical ingredient, or API, and drug product it uses in the Company's nonclinical and clinical studies for all of its drugs. Ionis manufactures the API for Akcea and charges it a price per gram consistent with the price Ionis charges its pharmaceutical partners, which includes the cost for direct materials, direct labor and overhead required to manufacture the API. If Akcea needs the API filled in vials for its clinical studies, Ionis will contract with a third party to perform this work and Ionis will charge Akcea for the resulting cost. Akcea began paying Ionis for API that commenced manufacturing during 2015 in accordance with the license agreement. All Ionis-manufactured API that began the manufacturing process prior to 2015 was treated as a capital contribution from Ionis.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**3. Development, Commercialization and License Agreement and Services Agreement with Ionis (Continued)**

As Akcea commercializes each of the Lipid Drugs, it will pay Ionis royalties from the mid-teens to the mid-twenty percent range on sales related to the Lipid Drugs that it sells. If Akcea sells a Lipid Drug for a Rare Disease Indication (defined in the agreement as less than 500,000 patients worldwide or an indication that required a Phase 3 program of less than 1,000 patients and less than 2 years of treatment), it will pay a higher royalty rate to Ionis than if the Company sells a Lipid Drug for a Broad Disease Patient Population (defined in the agreement as more than 500,000 patients worldwide or an indication that required a Phase 3 program of 1,000 or more patients and 2 or more years of treatment). Other than with respect to the drugs licensed to Novartis under the collaboration agreement, if Akcea's annual sales reach \$500.0 million, \$1.0 billion and \$2.0 billion, the Company will be obligated to pay Ionis sales milestones in the amount of \$50.0 million for each sales milestone reached by each Lipid Drug. If and when triggered, Akcea will pay Ionis each of these sales milestones over the subsequent 12 quarters in equal payments.

Akcea may terminate this agreement if Ionis is in material breach of the agreement. Ionis may terminate this agreement if Akcea is in material breach of the agreement. In each circumstance the party that is in breach will have an opportunity to cure the breach prior to the other party terminating this agreement.

In the first quarter of 2017, the Company entered into letter agreements with Ionis to reflect the agreed upon payment terms with respect to the upfront option payment that the Company received from Novartis and to allocate the premium that Novartis paid for Ionis' common stock in connection with the strategic collaboration. For additional detail regarding the strategic collaboration with Novartis see note 7, *Strategic Collaboration with Novartis*.

***Services Agreement***

Under the services agreement, Ionis provides Akcea certain services, including, without limitation, general and administrative support services and development support services. Ionis has allocated a certain percentage of personnel to perform the services that it provides to the Company based on its good faith estimate of the required services. Akcea pays Ionis for these allocated costs, which reflect the Ionis full-time equivalent, or FTE, rate for the applicable personnel, plus out-of-pocket expenses such as occupancy costs associated with the FTEs allocated to providing Akcea these services. Akcea does not pay a mark-up or profit on the external or internal expenses Ionis bills to it. In accordance with the services agreement, Akcea began paying Ionis for these services on January 1, 2015. All Ionis-provided general and administrative service expenses shown in the Company's financial statements for 2014 were treated as a capital contribution from Ionis. Ionis invoices Akcea quarterly for all amounts due under the services agreement and payments are due within 30 days of the receipt of an invoice.

In addition, as long as Ionis continues to consolidate Akcea's financials, Akcea will comply with Ionis' policies and procedures and internal controls. As long as Akcea is consolidated into Ionis' financial statements under U.S. GAAP, Akcea will continue to obtain the following services from Ionis:

- investor relations services,
- human resources and personnel services,

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**3. Development, Commercialization and License Agreement and Services Agreement with Ionis (Continued)**

- risk management and insurance services,
- tax related services,
- corporate record keeping services,
- financial and accounting services,
- credit services, and
- COO/CFO/CBO oversight.

However, if Akcea wanted to provide for its own human resources and personnel services, and doing so would not negatively impact Ionis' internal controls and procedures for financial reporting, Akcea can negotiate in good faith with Ionis for a reduced scope of services related to human resources and personnel services. When Ionis determines it should no longer consolidate Akcea's financials, Akcea may mutually agree with Ionis in writing to extend the term in six month increments.

Following the completion of the IPO, Akcea can establish its own benefits programs or can continue to use Ionis' benefits, however, the Company must provide Ionis a minimum advance notice to opt-out of using Ionis' benefits.

As of December 31, 2015 and 2016 and March 31, 2017, Akcea owed Ionis \$9.2 million, \$24.4 million and \$15.0 million, respectively.

The following table summarizes the amounts included in Akcea's operating expenses that were generated by transactions with Ionis for the following periods (in thousands):

	Years Ended December 31,			Three Months Ended March 31,	
	2014	2015	2016	2016	2017
Services performed by Ionis . . . . .	\$ 7,254	\$ 7,162	\$ 8,599	\$ 2,052	\$ 2,957
Active pharmaceutical ingredient manufactured by Ionis . . . . .	4,941	5,620	12,648	—	3,083
Sublicensing expenses . . . . .	—	—	—	—	48,394
Out-of-pocket expenses paid by Ionis . . . . .	17,709	40,771	42,367	9,852	8,868
Total expenses generated by transactions with Ionis . . . . .	<u>29,904</u>	<u>53,553</u>	<u>63,614</u>	<u>11,904</u>	<u>63,302</u>
Payable balance to Ionis at the beginning of the period . . . . .	—	—	\$ 9,198	9,198	24,355
Prepaid amounts to Ionis . . . . .	—	—	—	—	3,005
Less: amounts contributed by Ionis in the form of capital . . . . .	(31,602)	(8,689)	—	—	—
Less: total amounts paid to Ionis during the period . . . . .	—	(35,666)	(48,457)	—	(42,268)
Less: non-cash sublicensing expenses . . . . .	—	—	—	—	(33,394)
Plus: exclusive license granted to Akcea (recorded on a carryover basis) . . . . .	1,698	—	—	—	—
Total amount payable to Ionis at period end . . . . .	<u>\$ —</u>	<u>\$ 9,198</u>	<u>\$ 24,355</u>	<u>\$ 21,102</u>	<u>\$ 15,000</u>

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**4. Line of Credit Agreement with Ionis**

In January 2017, Akcea entered into a line of credit agreement with Ionis for up to \$150.0 million. The Company has drawn \$91.0 million as of March 31, 2017. The Company used a portion of its proceeds from its line of credit drawdowns to pay \$24.4 million to Ionis to satisfy its outstanding intercompany payable as of December 31, 2016 and to pay \$18.0 million to Ionis for the estimated intercompany expenses Akcea expected to incur for the first quarter of 2017. Any amounts the Company borrows under the line of credit bear interest at an annual interest rate of 4%, compounded monthly. At any time prior to an IPO, Ionis has the right to require the Company to convert the outstanding balance into Series A convertible preferred stock at a conversion price per share of \$18.80. The outstanding principal and accrued interest under the line of credit will convert into shares of Akcea common stock in connection with the closing of the IPO at the IPO price per share. If the total amount outstanding on the line of credit is not converted prior to January 2019, all amounts will be due to Ionis at that date payable in cash. At March 31, 2017, the outstanding balance on the line of credit including principal and interest with Ionis was \$91.5 million and for the three months ended, March 31, 2017 interest expense was \$541,000.

**5. Stockholders' Equity (Deficit)**

***Series A Convertible Preferred Stock***

In December 2015, Akcea issued and sold to Ionis an aggregate of 28,880,540 shares of Series A convertible preferred stock for a total purchase price of \$100.0 million plus the grant of the rights and licenses it received under the development, commercialization and license agreement with Ionis. The \$100.0 million of proceeds received is recorded in Series A convertible preferred stock on the Company's consolidated balance sheet.

Akcea has 28,880,540 shares of Series A convertible preferred stock authorized, issued and outstanding as of December 31, 2015, December 31, 2016 and March 31, 2017, of which all is currently held by Ionis.

*Conversion*

Shares of the Company's Series A convertible preferred stock are convertible 1:1 into common stock, subject to certain adjustments for reorganizations, reclassifications, stock splits, stock dividends and dilutive issuances, at the election of the holder thereof. In addition, all shares of Series A convertible preferred stock will automatically convert into common stock upon (i) the affirmative election of the holders of 67% of the outstanding shares of Series A convertible preferred stock or (ii) immediately prior to the closing of a firm commitment underwritten public offering of the Company's common stock (a) at a share price of not less than two times the original issue price of the Series A convertible preferred stock and (b) resulting in gross proceeds to the Company of no less than \$50.0 million.

*Dividends*

Each share of Series A convertible preferred stock is entitled to receive a cumulative dividend in preference to any dividend on shares of common stock at the rate of six percent of the original issue price of \$18.80 per share. Dividends began accruing on January 1, 2015 and compound on an annual basis. These dividends only become payable when declared by the Company's board of directors or upon the liquidation, dissolution, sale of all or substantially all of Akcea's assets, change of control or winding-up of the Company.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**5. Stockholders' Equity (Deficit) (Continued)**

The following table shows dividends accrued for each period presented (in thousands):

	Year Ended December 31,		Three Months Ended March 31,	
	2015	2016	2016	2017
Dividends accrued on Series A convertible preferred stock . . . .	\$32,590	\$34,545	\$8,636	\$9,155

As of December 31, 2015 and 2016 and March 31, 2017, accumulated accrued dividends were \$32.6 million, \$67.1 million and \$76.3 million, respectively. As long as Series A convertible preferred stock is outstanding, Akcea is not permitted to pay, set-aside, or declare any dividend on common stock unless all accrued dividends with respect to outstanding Series A convertible preferred stock have been paid, except in certain limited circumstances. From inception of the Company through December 31, 2015 and 2016 and March 31, 2017, no dividends have been declared or paid and therefore no dividends have been recorded in the consolidated financial statements.

*Voting Rights*

Series A convertible preferred stockholders are entitled to general voting rights equal to the amount in which their shares could be converted to common stock. Additionally, as long as at least 2,896,281 shares of Series A convertible preferred stock are outstanding, a majority vote of these stockholders will be required for various corporate and capitalization activities. Series A convertible preferred stockholders are entitled to elect two-thirds of the members of the Company's board of directors.

*Liquidation*

Upon liquidation, before any distribution is made to common stockholders, holders of Series A convertible preferred stock are entitled to be paid out of the assets legally available for distribution equal to the original issue price plus any accrued dividends that are unpaid. Each holder of shares of Series A convertible preferred stock is entitled to receive the greater of (i) the liquidation preference amount and (ii) the amount such holder would have received if such holder's Series A convertible preferred stock had been converted to common stock. After distributions or payments to holders of Series A convertible preferred stock are paid in full, the remaining assets available for distribution, if any, will be distributed to the holders of common stock on a pro rata basis.

The holders of Series A convertible preferred stock are entitled to receive rights, preferences and privileges no less favorable than those attributable to any other class or series of equity securities issued by the Company prior to December 2018.

*Redemption*

The Series A convertible preferred stock is not redeemable.

**Common Stock**

At December 31, 2015 and 2016 and March 31, 2017, Akcea had 100,000,000 shares of common stock authorized, of which none was issued or outstanding. Common stockholders are entitled to elect one-third of the members of Akcea's board of directors. As of March 31, 2017, total shares of common stock reserved for future issuance were 1,276,923.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**5. Stockholders' Equity (Deficit) (Continued)**

**Stock Plans**

*2015 Equity Incentive Plan*

In December 2015, Akcea's board of directors and stockholders adopted and approved the Company's 2015 Equity Incentive Plan, or the 2015 Plan. As of March 31, 2017, the aggregate number of shares of common stock that may be issued pursuant to stock awards under the 2015 Plan was 6,340,508 shares. Additionally, the 2015 Plan provides that no more than 12,681,017 shares may be issued under the 2015 Plan pursuant to the exercise of incentive stock options, or ISOs, within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended. The 2015 Plan also provides for the grant of nonstatutory stock options, or NSOs, stock appreciation rights, restricted stock awards, and restricted stock unit awards. At March 31, 2017, options with respect to a total of 5,063,585 shares of common stock were outstanding, of which 1,895,855 were exercisable, and 1,276,923 shares were available for future grant under the 2015 Plan.

**Stock Option Activity**

The following table summarizes the stock option activity (in thousands, except per share and contractual life data) for the 2015 Plan:

	Number of Shares	Weighted Average Exercise Price Per Share (\$)	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (\$)
Outstanding at December 31, 2015 . . . . .	2,905	6.48	—	—
Granted . . . . .	2,159	6.48	—	—
Cancelled/forfeited/expired . . . . .	—	—	—	—
Outstanding at December 31, 2016 . . . . .	5,064	6.48	9.11	—
Exercisable at December 31, 2016 . . . . .	1,306	6.48	8.96	—
Outstanding at March 31, 2017 . . . . .	5,064	6.48	8.86	28,980
Exercisable at March 31, 2017 . . . . .	1,896	6.48	8.75	10,850

The weighted average estimated fair values of options granted under the 2015 Plan were \$4.01 and \$4.13 for the years ended December 31, 2015 and 2016, respectively. Akcea did not grant any options during the first quarter of 2017.



**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**5. Stockholders' Equity (Deficit) (Continued)**

The following table summarizes the stock option activity (in thousands, except per share and contractual life data) for options granted to Akcea employees under the Ionis 2011 Equity Incentive Plan:

	Number of Shares	Weighted Average Exercise Price Per Share (\$)	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (\$)
Outstanding at December 31, 2015	383	62.61	—	—
Granted	418	47.90	—	—
Cancelled/ forfeited/ expired	—	—	—	—
Outstanding at December 31, 2016	801	54.92	5.72	2,203
Exercisable at December 31, 2016	159	63.14	5.22	—
Granted	367	46.99	—	—
Cancelled/forfeited/expired	—	—	—	—
Outstanding at March 31, 2017	1,168	52.43	5.88	661
Exercisable at March 31, 2017	270	59.65	5.24	38

The weighted average estimated fair values of options to purchase Ionis common stock granted to Akcea employees were \$27.99, \$23.02 and \$25.05 for the years ended December 31, 2015 and 2016 and the three months ended March 31, 2017, respectively.

As of March 31, 2017, total unrecognized compensation cost related to non-vested stock-based compensation plans was \$16.5 million. Akcea will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. The Company expects to recognize this cost over a weighted average period of 1.5 years.

**Stock-Based Compensation Expense and Valuation Information**

The following table summarizes stock-based compensation expense (in thousands), which was allocated as follows:

	Year Ended December 31,		Three Months Ended March 31,	
	2015	2016	2016	2017
Research and development expenses	\$ 827	\$ 4,576	\$ 835	\$1,600
General and administrative expenses	5,669	5,573	2,354	1,580
Total	<u>\$6,496</u>	<u>\$10,149</u>	<u>\$3,189</u>	<u>\$3,180</u>

The Company measures stock-based compensation expense for equity-classified stock option awards based on the estimated fair value of the award on the date of grant. The Company recognizes the value of the portion of the award that it ultimately expects to vest as stock-based compensation expense over the requisite service period in its statements of operations. The

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**5. Stockholders' Equity (Deficit) (Continued)**

Company reduces stock-based compensation expense for estimated forfeitures at the time of grant and revises in subsequent periods if actual forfeitures differ from those estimates.

Prior to December 2015, Ionis granted the Company's employees options to purchase shares of Ionis' common stock, or Ionis options. In December 2015, the Company granted its employees holding Ionis options additional options to purchase shares of Akcea common stock, or Akcea options. Subject to service based vesting requirements, the Ionis options only become exercisable if (1) the Company is not acquired or if it does not complete a qualified financing transaction, such as an IPO, by June 30, 2017 and (2) the employee forfeits his or her Akcea equity. Upon the consummation of any such transaction, the Company's employees would forfeit their rights to the Ionis options that they hold such that under no circumstances would an employee be able to exercise both Ionis options and Akcea options.

The Company determined the stock-based compensation expense for the Ionis options at the date of grant and recognized compensation expense over the vesting period of the Ionis options. In December 2015, the Company accounted for the issuance of the Akcea options as a modification to the original grant of the Ionis options because the grant of the Ionis options and Akcea options essentially represented a single stock award as the exercisability provisions of the Ionis options and Akcea options grants were interrelated and mutually exclusive. The total compensation expense measured on the modification date was the sum of the grant date fair value of the Ionis options plus any incremental compensation cost resulting from the grant of the Akcea options.

In 2016, the Company began concurrently granting Ionis options and Akcea options to its employees. Because the exercisability provisions of the awards are interrelated and mutually exclusive as described above, the fair values of the Ionis options and the Akcea options were determined on the date of grant and the option with the greater fair value is recognized over the vesting period of the awards.

The Company and Ionis value stock option awards using the Black-Scholes option pricing model.

In valuing options for Ionis common stock, Ionis made a number of assumptions, including the risk-free interest rate, expected dividend yield, expected volatility, expected term, rate of forfeiture and fair value of common stock. Ionis considered the following factors in applying these assumptions:

*Risk-Free Interest Rate.* Ionis bases the risk-free interest rate assumption on the yields of U.S. Treasury securities with maturities that correspond to the term of the award.

*Expected Dividend Yield.* Ionis bases the dividend yield assumption on its history and expectation of dividend payouts. Ionis has not paid dividends in the past and it does not expect to pay dividends for the foreseeable future.

*Expected Volatility.* Ionis uses an average of the historical stock price volatility of Ionis' stock. It computed the historical stock volatility based on the expected term of the awards.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**5. Stockholders' Equity (Deficit) (Continued)**

*Expected Term.* The expected term of stock options Ionis has granted represents the period of time that it expects them to be outstanding. Ionis estimated the expected term of options Ionis has granted based on actual and projected exercise patterns.

*Rate of Forfeiture.* Ionis estimates forfeitures at the time of grant and revises, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Ionis estimates forfeitures based on historical experience. Ionis' historical forfeiture estimates have not been materially different from its actual forfeitures.

*Fair Value of Common Stock.* Ionis uses the market closing price for its common stock on the date of grant as reported on Nasdaq to determine the fair value of Ionis' common stock on the date of grant.

For the years ended December 31, 2015 and 2016 and the three months ended March 31, 2016 and 2017, Ionis used the following weighted-average assumptions in its Black-Scholes calculations for stock options granted under the Ionis 2011 Equity Incentive Plan:

	Year Ended December 31,		Three Months Ended March 31,	
	2015	2016	2016	2017
Risk-free interest rate . . . . .	1.5%	1.5%	1.5%	1.8%
Dividend yield . . . . .	0.0%	0.0%	0.0%	0.0%
Volatility . . . . .	54.1%	59.4%	57.9%	66.3%
Expected life . . . . .	4.5 years	4.5 years	4.5 years	4.5 years

In valuing Akcea options, the Company made a number of assumptions, including the risk-free interest rate, expected dividend yield, expected volatility, expected term, rate of forfeitures and fair value of common stock. The Company considered the following factors in applying these assumptions:

*Risk-Free Interest Rate.* Akcea determines the risk-free interest rate assumption based on the yields of U.S. Treasury securities with maturities that correspond to the term of the award.

*Expected Dividend Yield.* Akcea assumes a dividend yield of zero as it has not paid dividends in the past and does not expect to pay dividends on its common stock for the foreseeable future.

*Expected Volatility.* Akcea does not have sufficient history to estimate the volatility of its common stock. Akcea calculates expected volatility based on reported data from selected publicly traded peer companies for which historical information is available. Akcea plans to continue to use a peer group to calculate its volatility until the historical volatility of its common stock is sufficient to measure expected volatility for future option grants.

*Expected Term.* The expected term estimates represent the period of time that Akcea expects the options to be outstanding. As Akcea does not have historical information, it uses the simplified method for estimating the expected term. Under the simplified method the Company calculates the expected term as the average time-to-vesting and the contractual life of the options. As Akcea gains additional historical information, it will transition to calculating its expected term based on its exercise patterns.

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**5. Stockholders' Equity (Deficit) (Continued)**

*Rate of Forfeiture.* Akcea estimates forfeitures based on Ionis' historical rates of forfeiture as Akcea does not have similar historical information for itself. Akcea and Ionis are engaged in similar businesses and Akcea believes this is a good estimate of expected forfeitures. As Akcea gains additional historical information, it will transition to using its historical forfeiture rate.

*Fair Value of Common Stock.* As the Company's common stock has not historically been publicly traded, its board of directors estimated the fair value of its common stock considering, among other things, contemporaneous valuations of its common stock prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants 2013 Practice Aid, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*.

For the years ended December 31, 2015 and 2016 and the three months ended March 31, 2016, Akcea used the following weighted-average assumptions in its Black-Scholes calculations for stock option grants under its 2015 Plan:

	Year Ended December 31,		Three Months Ended
	2015	2016	March 31, 2016
Risk-free interest rate . . . . .	2.0%	1.6%	1.6%
Dividend yield . . . . .	0.0%	0.0%	0.0%
Volatility . . . . .	67.9%	71.4%	68.9%
Expected life . . . . .	6.08 years	6.08 years	6.08 years
Fair value of common stock . . . . .	\$6.48	\$6.48	\$6.48

Akcea did not grant any options during the three months ended March 31, 2017.

**6. Income Taxes**

There is no provision for income taxes because Akcea has historically incurred operating losses and it maintains a full valuation allowance against its net deferred tax assets.

The reconciliation between Akcea's effective tax rate on loss from continuing operations and the statutory U.S. tax rate is as follows (in thousands):

	Years Ended December 31,					
	2014		2015		2016	
Pre-tax loss . . . . .	\$(30,023)		\$(61,422)		\$(83,217)	
Statutory rate . . . . .	(10,508)	35.0%	(21,498)	35.0%	(29,126)	35.0%
State income tax net of federal benefit . . . . .	(1,561)	5.2%	(3,194)	5.2%	(4,099)	4.9%
Net change in valuation allowance . . . . .	12,845	(42.8)%	30,857	(50.2)%	43,438	(52.1)%
Tax credits . . . . .	(785)	2.6%	(6,187)	10.0%	(11,007)	13.2%
Nondeductible items and other . . . . .	9	0.0%	22	0.0%	794	(1.0)%
Effective rate . . . . .	\$ —	0.0%	\$ —	0.0%	\$ —	0.0%

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**6. Income Taxes (Continued)**

Significant components of the Company's deferred tax assets and liabilities as of December 31, 2015 and 2016 were as follows (in thousands):

	Years Ended December 31,	
	2015	2016
Deferred Tax Assets:		
Net operating loss carryovers . . . . .	\$ 29,700	\$ 48,813
Tax credits . . . . .	10,545	30,057
Stock-based compensation . . . . .	2,607	6,620
Other . . . . .	501	1,251
Total deferred tax assets . . . . .	\$ 43,353	\$ 86,741
Deferred Tax Liabilities:		
Intangible assets . . . . .	(302)	(281)
Total deferred tax liabilities . . . . .	\$ (302)	\$ (281)
Valuation allowance . . . . .	(43,051)	(86,460)
Net deferred tax assets and liabilities . . . . .	\$ —	\$ —

The Company files its tax returns on a consolidated or combined basis with Ionis. For purposes of its financial statements, the Company has calculated its income tax amounts, including net operating losses and credit carryforwards, using a separate return methodology and has presented these amounts as if it were a separate taxpayer from Ionis in each jurisdiction for each period the Company has presented. The Company has not determined the amount of tax attributes, including net operating losses and tax credit carryovers, which it would retain if it were to deconsolidate for tax purposes from Ionis. An analysis will be performed at a future date, if necessary.

Akcea has net deferred tax assets consisting primarily of net operating loss carryforwards, or NOLs, and research and development tax credit carryforwards. At December 31, 2016, the Company had federal and state tax net operating loss carryforwards on a separate basis of approximately \$121.9 million and \$118.1 million, respectively. The Company's federal and state loss carryforwards will begin to expire in 2034 and 2030, respectively, unless previously utilized. At December 31, 2016, the Company had federal research and development tax credit carryforwards of approximately \$33.4 million that will begin to expire in 2034 unless previously utilized.

Akcea can offset taxable income in future periods with its deferred tax assets, including its net operating loss and tax credit carryforwards. As the likelihood of future profitability is not assured, the Company established a valuation allowance against its net deferred tax assets as of December 31, 2015 and 2016. In the future, if Akcea determines that it is able to realize a portion or all of these deferred tax assets, it will record an adjustment to increase their recorded value and a corresponding adjustment to increase income or additional paid in capital, as appropriate, in that same period.

Akcea recognizes excess tax benefits associated with stock-based compensation to stockholders' equity (deficit) only when realized. When assessing whether excess tax benefits

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**6. Income Taxes (Continued)**

relating to stock-based compensation have been realized, the Company follows the with-and-without approach excluding any indirect effects of the excess tax deductions. Under this approach, excess tax benefits related to stock-based compensation are not deemed to be realized until after the utilization of all other tax benefits available to the Company. During the year ended December 31, 2016, the Company did not realize any excess tax benefits.

In March 2016, the FASB issued amended guidance to simplify certain aspects of share-based payment accounting which affects how the Company accounts for unrecognized tax benefits. The Company adopted this amended guidance on January 1, 2017. As of December 31, 2016, the Company did not have any excess tax benefits for which a benefit could not previously be recognized. Therefore, the adoption of this guidance did not affect the Company's accumulated loss.

The Company analyzes filing positions in all of the federal and state jurisdictions where it is required to file income tax returns, and all open tax years in these jurisdictions to determine if the Company has any uncertain tax positions on any income tax returns. The Company recognizes the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. Akcea does not recognize a tax benefit if the position has a less than 50 percent likelihood of being sustained upon examination.

The following table summarizes Akcea's gross unrecognized tax benefits (in thousands):

	Year Ended December 31,	
	2015	2016
Beginning balance of unrecognized tax benefits . . . . .	\$ 138	\$1,766
Increase for current period tax positions . . . . .	1,628	3,246
Ending balance of unrecognized tax benefits . . . . .	<u>\$1,766</u>	<u>\$5,012</u>

Due to the Company's valuation allowance, none of the unrecognized tax benefits at December 31, 2016 would impact Akcea's effective tax rate, if recognized.

The Company does not foresee any material changes to its gross unrecognized tax benefits within the next twelve months. The Company recognizes interest and/or penalties related to income tax matters in income tax expense. The Company did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2016.

The Company is subject to taxation in the United States and various state jurisdictions. Tax years for 2014 and forward are subject to examination by the U.S. federal and state tax authorities.

**7. Strategic Collaboration with Novartis**

In January 2017, the Company initiated a strategic collaboration with Novartis for the development and commercialization of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. Under the Novartis collaboration, Novartis has an exclusive option to develop and commercialize these drugs. The Company is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and providing API for each drug. If Novartis exercises an option for one of



**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**7. Strategic Collaboration with Novartis (Continued)**

these drugs, Novartis will be responsible, at its expense, to use commercially reasonable efforts to develop and commercialize that drug. The Company received \$75.0 million in an upfront payment in the first quarter of 2017, of which the Company will retain \$60.0 million and will pay Ionis \$15.0 million as a sublicense fee under its license agreement with Ionis.

If Novartis exercises its option for a drug, Novartis will pay the Company a license fee equal to \$150.0 million for each drug licensed by Novartis. In addition, for AKCEA-APO(a)-L<sub>Rx</sub>, the Company is eligible to receive up to \$600.0 million in substantive milestone payments, 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 \$285.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L<sub>Rx</sub>, the Company is eligible to receive up to \$530.0 million in substantive milestone payments, including \$25.0 million for the achievement of a development milestone, up to \$240.0 million for the achievement of regulatory milestones and up to \$265.0 million for the achievement of commercialization milestones. Akcea plans to co-commercialize any licensed drug commercialized by Novartis in selected markets, under terms and conditions that it plans to negotiate with Novartis in the future. The Company will earn the next milestone payment of \$25.0 million under this collaboration if Novartis advances the Phase 3 study for either drug. The Company is also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-L<sub>Rx</sub> and AKCEA-APOCIII-L<sub>Rx</sub>. Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. The Company will pay 50% of these license fees, milestone payments and royalties to Ionis as a sublicense fee.

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

- Novartis may terminate the agreement as a whole or with respect to any drug at any time by providing written notice to us;
- Either the Company or Novartis may terminate the agreement with respect to any drug by providing written notice to the other party in good faith that the Company or Novartis has determined that the continued development or commercialization of the drug presents safety concerns that pose an unacceptable risk or threat of harm in humans or would violate any applicable law, ethical principles, or principles of scientific integrity;
- Either the Company or Novartis may terminate the agreement for a drug by providing written notice to the other party upon the other party's uncured failure to perform a material obligation related to the drug under the agreement, or the entire agreement if the other party becomes insolvent; and
- The Company may terminate the agreement if Novartis disputes or assists a third party to dispute the validity of any of the Company's or Ionis' patents.

Additionally, in January 2017, Akcea and Ionis entered into a SPA with Novartis. Under the SPA, Novartis has agreed to purchase up to \$50.0 million of Akcea's common stock in a separate private placement concurrent with the completion of Akcea's initial public offering at a price per

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**7. Strategic Collaboration with Novartis (Continued)**

share equal to the initial public offering price; provided that the gross proceeds from the offering, exclusive of the concurrent private placement, equal or exceed \$100.0 million. If the gross proceeds from the offering do not equal or exceed \$100.0 million, Novartis is not required to complete such concurrent private placement in any amount. Further, in no event will Novartis purchase more than 30% of the aggregate number of shares to be sold in the offering and the concurrent private placement. The sale of shares in the concurrent private placement will not be registered under the Securities Act of 1933, as amended. The closing of Akcea's initial public offering is not conditioned upon the closing of such concurrent private placement. The shares of common stock purchased in the concurrent private placement will not be subject to any underwriting discounts or commission.

During the three months ended March 31, 2017, the Company earned revenue of \$9.6 million from its relationship with Novartis, representing 100% of its revenue. The Company's consolidated balance sheet at March 31, 2017 included deferred revenue of \$98.8 million related to its relationship with Novartis.

**8. Employment Benefits**

Akcea's employees participate in Ionis' employee 401(k) salary deferral plan, which covers all Ionis employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit (\$18,000 and \$24,000 in 2016 for employees under 50 years old and employees 50 years old or over, respectively). Akcea made approximately \$28,000 and \$211,000 in matching contributions for the years ended December 31, 2015 and 2016.

**9. Subsequent Events**

In preparing the Company's condensed consolidated financial statements, Akcea evaluated events through May 9, 2017, which is the date that the condensed consolidated financial statements were available to be issued. After the original issuance of the Company's condensed consolidated financial statements, Akcea evaluated subsequent events through June 20, 2017.

In May 2017, the Company's board of directors approved an amendment to the Company's certificate of incorporation to (1) effect a reverse stock split on outstanding shares of the Company's common stock and preferred stock on a one-for-2.555 basis, (2) decrease the authorized shares of the Company's preferred stock to 40,000,000 and (3) modify the threshold for automatic conversion of the Company's preferred stock into shares of the Company's common stock in connection with an initial public offering to eliminate the price per share threshold and only require that the Company raise at least \$50.0 million in gross proceeds (collectively, the "Charter Amendment"). The par values of the common stock and preferred stock were not adjusted as a result of the reverse stock split. The amendment to the Company's certificate of incorporation was approved by the Company's stockholder and became effective upon the filing with the State of Delaware in June 2017. All issued and outstanding common stock and preferred stock and related share and per share amounts contained in these consolidated financial statements have been retroactively adjusted to reflect the reverse stock split for all periods presented.

In May 2017 and June 2017, the Company's board of directors and stockholder, respectively, approved an amendment to the Company's 2015 Equity Incentive Plan in order to, among other

**Akcea Therapeutics, Inc.**  
**Consolidated Notes to Financial Statements (Continued)**

**9. Subsequent Events (Continued)**

things, increase the number of shares of common stock reserved for issuance thereunder to 8,500,000 shares of common stock.

In May 2017 and June 2017, the Company's board of directors and stockholder, respectively, approved the Company's 2017 Employee Stock Purchase Plan, to be effective upon the completion of the Company's initial public offering, and the reservation for issuance thereunder of 500,000 shares of common stock.

In May 2017, the Company borrowed \$15.0 million under its line of credit with Ionis, which when combined with the Company's prior borrowings, total \$106.0 million as of June 20, 2017.

In May 2017, the Company formed Akcea Therapeutics Canada, Inc. as a wholly-owned subsidiary.

In June 2017, the Company issued options to certain employees and members of the Company's Board of Directors to purchase up to 1,678,661 shares of the Company's common stock under the 2015 Plan at an exercise price of \$12.21 per share. These common stock options vest over four years and expire 10 years following the date of grant.

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**15,625,000 Shares**



**Common stock**

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**PROSPECTUS**

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*Joint Book-running Managers*

**Cowen**

**Stifel**

**Wells Fargo Securities**

*Lead Manager*

**BMO Capital Markets**

July 13, 2017

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