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SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): **March 27, 2017**

IONIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	(IRS Employer Identification No.)

2855 Gazelle Court
Carlsbad, CA 92010
(Address of Principal Executive Offices and Zip Code)

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

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01 Other Events.

On March 27, 2017 Ionis Pharmaceuticals, Inc's subsidiary, Akcea Therapeutics, Inc., filed a registration statement on Form S-1 with the U.S. Securities and Exchange Commission relating to a proposed initial public offering of Akcea's common stock. The registration statement contains, among other things, a description of Akcea's business. Ionis is filing the following information with the Securities and Exchange Commission for the purpose of updating certain aspects of its publicly disclosed descriptions of its Akcea Therapeutics, Inc. business to include portions of the description contained therein.

In this report, "Akcea Therapeutics," "Akcea," "Company," "we," "us" and "our" refer to Akcea Therapeutics, Inc., unless the context requires otherwise.

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_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}, 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_{Rx} and AKCEA-APOCIII-L_{Rx}. 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 will retain $60.0 million and will pay $15.0 million to Ionis as a sublicense fee. After we complete Phase 2 development of each of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, 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 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_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx} 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.

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_{Rx} and AKCEA-APOCIII-L_{Rx} 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 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_{Rx} 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_{Rx} and AKCEA-APOCIII-L_{Rx}, 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.

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 in our pipeline to commercialization***. Our pipeline of antisense drugs currently contains four 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. 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 disorder company.

- ***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_{Rx} and AKCEA-APOCIII-L_{Rx}, 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 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.

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_{Rx} and AKCEA-APOCIII-L_{Rx}, if and when approved.

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_{Rx} and AKCEA-APOCIII-L_{Rx} 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 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.

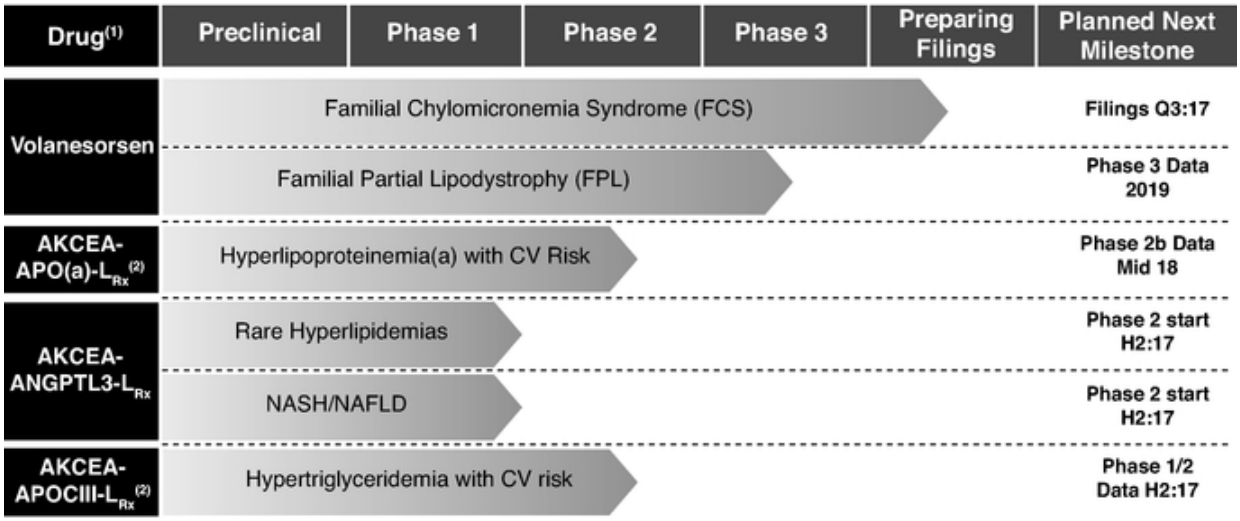
Clinical Pipeline

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:



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

- Volanesorsen also has been known as IONIS-APOCIII$_{Rx}$, ISIS-APOCIII$_{Rx}$ and ISIS 304801.
- AKCEA-APO(a)-L$_{Rx}$ also has been known as IONIS-APO(a)-L$_{Rx}$, ISIS-APO(a)-L$_{Rx}$ and ISIS 681257.
- AKCEA-ANGPTL3-L$_{Rx}$ also has been known as IONIS-ANGPTL3-L$_{Rx}$, ISIS-ANGPTL3-L$_{Rx}$ and ISIS 703802.
- AKCEA-APOCIII-L$_{Rx}$ also has been known as IONIS-APOCIII-L$_{Rx}$, ISIS-APOCIII-L$_{Rx}$ and ISIS 678354.

(2) We have initiated a strategic collaboration with Novartis for AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$.

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

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 ($p=0.01$). 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 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.

AKCEA-APO(a)-L_{Rx}

We are developing AKCEA-APO(a)-L_{Rx} for patients who are at significant risk of CVD because of their elevated levels of Lp(a). AKCEA-APO(a)-L_{Rx} 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_{Rx} 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_{Rx} 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_{Rx}. With multiple doses of AKCEA-APO(a)-L_{Rx}, 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_{Rx} 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_{Rx} 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-APO(a)-L_{Rx} worldwide. We plan to co-commercialize AKCEA-APO(a)-L_{Rx} with Novartis in selected markets 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 high Lp(a) levels.

AKCEA-ANGPTL3-L$_{Rx}$

We are developing AKCEA-ANGPTL3-L$_{Rx}$ 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$_{Rx}$ 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$_{Rx}$ 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$_{Rx}$ 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$_{Rx}$ was reported to be well tolerated. The most common adverse events in the AKCEA-ANGPTL3-L$_{Rx}$ 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$_{Rx}$ 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$_{Rx}$ 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$_{Rx}$ 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$_{Rx}$ include other rare hyperlipidemias and lipodystrophies.

AKCEA-APOCIII-L$_{Rx}$

We are developing AKCEA-APOCIII-L$_{Rx}$ 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$_{Rx}$ 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$_{Rx}$ 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_{Rx} 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_{Rx} worldwide. We plan to co-commercialize AKCEA-APOCIII-L_{Rx} with Novartis in selected markets 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.

FORWARD-LOOKING STATEMENT

This report includes forward-looking statements regarding the business of Ionis Pharmaceuticals, Inc. and Akcea Therapeutics, Inc., a subsidiary of Ionis Pharmaceuticals, and the therapeutic and commercial potential of volanesorsen and other products in development. Any statement describing the companies' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. The companies' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although the companies' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by the companies. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning the companies' programs are described in additional detail in Ionis Pharmaceuticals, Inc.'s annual report on Form 10-K for the year ended December 31, 2016, which is on file with the SEC. Copies of this and other documents are available from Ionis.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

IONIS PHARMACEUTICALS, INC.

Dated: March 27, 2017

By: /s/ B. LYNNE PARSHALL

B. LYNNE PARSHALL
Chief Operating Officer

QuickLinks

Item 8.01 Other Events.

SIGNATURE