Akcea and Ionis Announce Submission of Marketing Authorization Application for Volanesorsen to the European Medicines Agency

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CAMBRIDGE, Mass. and CARLSBAD, Calif., July 27, 2017 /PRNewswire/ -- Akcea Therapeutics, Inc. (NASDAQ: AKCA) and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that a marketing authorization application (MAA) has been submitted to the European Medicines Agency (EMA) for volanesorsen for the treatment of patients with familial chylomicronemia syndrome (FCS). Volanesorsen, a product of Ionis' proprietary antisense technology, was discovered by Ionis and co-developed by Ionis and Akcea and, if approved, will be commercialized by Akcea.

"The submission of the volanesorsen MAA to the EMA represents a critical milestone for Akcea. This filing brings us one step closer to our goal of providing physicians and patients with a treatment for a disease with multiple, severe, daily and chronic manifestations," said Paula Soteropoulos, president and chief executive officer of Akcea. "We have had productive communications with regulatory agencies in the EU, the U.S., and Canada, and are on track to also complete regulatory submissions in the U.S. and Canada in September. Further, Akcea is building the organization and infrastructure to commercialize volanesorsen globally."

FCS is a severe, rare disorder characterized by extremely high levels of triglycerides and the risk of recurrent, potentially fatal pancreatitis. People with FCS are unable to effectively metabolize large, triglyceride-rich lipid particles called chylomicrons due to a deficiency in lipoprotein lipase, an enzyme that helps to break down triglycerides. There is no effective therapy available.

"Patients with FCS need new therapies that can meaningfully lower their severely elevated triglycerides. Because of their very high triglycerides, these patients suffer from daily and chronic symptoms and are at significantly increased risk for morbidity and mortality, primarily due to recurrent attacks of pancreatitis," said Dr. Marcello Arca, Head of the Lipid and Atherosclerosis Unit of the University Hospital Policlinico Umberto I. "Based on the positive results from the Phase 3 program with volanesorsen, I'm encouraged that for the first time, these patients may have a new therapy that can help them achieve the triglyceride reductions they need to lessen the burden of their disease and decrease their risk for pancreatitis."

"Akcea has shown great commitment in supporting patients and working to find a treatment for this debilitating condition. Their work means that the European FCS community of patients, families, and physicians are one step closer to having an effective treatment that will make the life-long struggle of living with the burden of FCS much more manageable. It is great to be working with a supportive partner like Akcea, and we also appreciate the perseverance of our community in the quest to find an effective treatment," said Jill Prawer, Founder and Chair, LPLD Foundation.

ABOUT THE VOLANESORSEN CLINICAL PROGRAM

The submission of volanesorsen for the treatment of FCS is based on data from the Phase 3 APPROACH and COMPASS studies. The pivotal APPROACH study, a one-year, randomized, placebo-controlled study in 66 patients with FCS (average baseline triglycerides of 2,209 mg/dL, or 25.0 mmol/L), 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 (19.3 mmol/L) mean absolute triglyceride reduction in volanesorsen-treated patients. This compared to an 18% increase for placebo, or a -94% treatment effect. Further, 50% of treated patients achieved triglyceride levels below 500 mg/dL (5.6 mmol/L), a recognized threshold for enhanced pancreatitis risk. In addition, in the APPROACH study, treatment with volanesorsen was associated with a statistically significant reduced rate of on-study pancreatitis attacks in the group of patients who had a higher incidence of pre-study pancreatitis and reduced abdominal pain in patients reporting pain as a prominent pre-treatment symptom.

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 on-study pancreatitis attacks.

The most common adverse event in the studies was injection site reactions, which were mostly mild. Platelet count reductions 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 reductions, two of which were severe; four patients discontinued due to other nonserious adverse events.

Akcea and Ionis continue to conduct the BROADEN study, a Phase 3 clinical trial in patients with FPL, which continues to enroll, with topline data expected in 2019. Akcea plans to file for marketing authorization for volanesorsen to treat FPL in 2019 if the data from the BROADEN study are positive. The U.S. and EU regulatory agencies have granted Orphan Drug Designation to volanesorsen for the treatment of patients with FCS. Volanesorsen has also received Orphan Drug Designation in the EU for the treatment of FPL.

ABOUT VOLANESORSEN, FCS AND FPL

Volanesorsen, a product of Ionis' proprietary antisense technology, is in development for two rare metabolic disorders: FCS and familial partial lipodystrophy (FPL). Volanesorsen is designed to reduce the production of ApoC-III, a protein produced in the liver that plays a central role in the regulation of plasma triglycerides and may also affect other metabolic parameters.

FCS is a severe, rare disorder characterized by extremely high levels of triglycerides and the risk of recurrent, potentially fatal pancreatitis. People with FCS are unable to effectively metabolize large, triglyceride-rich lipid particles called chylomicrons due to a deficiency in lipoprotein lipase, an enzyme that helps to break down triglycerides. There is no effective therapy available. Additional information on FCS is available at www.fcsfocus.com and

through the FCS Foundation at http://www.livingwithfcs.org and the LPLD Alliance at www.lpldalliance.org.

FPL is a severe, rare genetic metabolic disorder characterized by an inability of the body to store fat in normal locations. This results in high levels of triglycerides in the bloodstream, abnormal fat distribution around and within organs, such as the liver and heart, and a range of metabolic abnormalities, including severe insulin resistance. People with FPL are at increased risk of acute pancreatitis in addition to other long-term, progressive manifestations, such as premature cardiomyopathy, atherosclerosis, and liver disease. Additional information on FPL is available through Lipodystrophy United at www.lipodystrophyunited.org.

ABOUT AKCEA THERAPEUTICS

Akcea Therapeutics, an affiliate of Ionis Pharmaceuticals, Inc., is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. Akcea is advancing a mature pipeline of four novel drugs with the potential to treat multiple diseases, including volanesorsen, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}. All four drugs were discovered and co-developed by Ionis, a leader in antisense therapeutics, based on Ionis' proprietary antisense technology. The most advanced drug in its pipeline, volanesorsen, is under regulatory review in the EU 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. Akcea is building the infrastructure to commercialize its drugs globally with a focus on lipid specialists as the primary call point. Akcea is located in Cambridge, Massachusetts. Additional information about Akcea is available at www.akceatx.com.

ABOUT IONIS PHARMACEUTICALS

Ionis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Ionis has created a large pipeline of first-in-class or best-in-class drugs, with over three dozen drugs in development. SPINRAZA® (nusinersen) has been approved in the U.S., Europe, Japan and Canada for the treatment of spinal muscular atrophy (SMA). Biogen is responsible for commercializing SPINRAZA. Drugs that have successfully completed Phase 3 studies include inotersen (IONIS-TTRRx), an antisense drug Ionis is developing with GSK to treat patients with TTR amyloidosis, and volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy. Akcea, an affiliate of Ionis, is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. If approved, volanesorsen will be commercialized through Ionis' affiliate, Akcea. Both inotersen and volanesorsen are progressing toward regulatory filings for marketing authorization. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

AKCEA FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the business of Akcea Therapeutics, Inc., and the therapeutic and commercial potential of volanesorsen and other products in development. Any statement describing Akcea's 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. Akcea's 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 Akcea's forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Akcea. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Akcea's programs are described in additional detail in its final prospectus for its initial public offering, which is on file with the SEC.

IONIS FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the business of Ionis Pharmaceuticals, Inc. and the therapeutic and commercial potential of volanesorsen and other products in development. Any statement describing Ionis' 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. Ionis' 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 Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2016, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Akcea," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals or Akcea Therapeutics.

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