Akcea and Ionis Announce Positive Results from Pivotal Study of Volanesorsen in Patients with Familial Chylomicronemia Syndrome (FCS)

77% Mean Triglyceride Reduction in Patients with FCS

Reductions in Pancreatitis Events and Abdominal Pain

Webcast to Discuss Results March 6, 2017 at 8:30 am ET

Carlsbad, Calif. and Cambridge, Mass., March 6, 2017 /PRNewswire/ -- Akcea Therapeutics, a wholly owned subsidiary of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced that the pivotal Phase 3 APPROACH study of volanesorsen met its primary endpoint of reducing triglyceride levels in patients with familial chylomicronemia syndrome (FCS).

APPROACH is a randomized, double-blind, placebo-controlled, 52-week Phase 3 study in 66 patients with FCS, a rare disease affecting approximately 3,000 to 5,000 patients worldwide. The average incoming triglyceride level of patients in the study was 2,209 mg/dL. Patients treated with volanesorsen experienced robust reductions in triglycerides and related benefits as follows:

- 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 3 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 observed was sustained over the 52-week treatment period.
- 50% of the treated patients who entered the study with triglycerides ≥750 mg/dL achieved triglyceride levels less than 500 mg/dL after 3 months of treatment. By comparison, none of the placebo-treated patients achieved this level ($p<0.003$).
- Volanesorsen-treated patients with the highest documented frequency of pancreatitis attacks suffered no attacks during the 52-week treatment period ($p=0.02$).
- A reduction in abdominal pain was observed in volanesorsen-treated patients compared to placebo-treated patients.

"We are excited about the strong profile of volanesorsen in not only robustly reducing triglycerides, but also providing additional important patient benefits. FCS is a life-threatening, rare disease with multiple severe daily and chronic manifestations. We believe the efficacy and safety data from volanesorsen studies demonstrate a favorable risk-benefit profile for patients with FCS," said Paula Soteropoulos, president and chief executive officer, Akcea Therapeutics.

The APPROACH study will support the regulatory submission for FCS of volanesorsen. Additional data from the study will be presented at an upcoming medical meeting.

"People with FCS have inherited mutations that inhibit the activity of lipoprotein lipase, the enzyme required to break down triglycerides carried by chylomicrons. The results from this study provide encouraging data

about triglyceride reduction in patients with FCS treated with volanesorsen, and are consistent with data from other clinical trials with the drug. Since there are currently very few effective treatment options for FCS patients, I am encouraged that, if approved, volanesorsen could offer FCS patients an option to achieve the therapeutic benefit they need," said Daniel Gaudet, M.D. Ph.D., head of the Clinical Lipidology and Rare Lipid Disorders Unit, Community Gene Medicine Center, Department of Medicine, Université de Montreal.

The APPROACH results were consistent with findings from both the Phase 3 COMPASS study as well as the Phase 2 program for volanesorsen. In the COMPASS study, the five FCS patients treated for three months with volanesorsen experienced a 73% average decrease in triglycerides, which represented a mean absolute reduction of 1,511 mg/dL. In the Phase 2 program, which was the subject of two separate publications in the *New England Journal of Medicine*, the three FCS patients profiled in one publication had an average triglyceride reduction after three months of treatment with volanesorsen of 69% or a mean absolute reduction of 1,298 mg/dL.

"The success of APPROACH represents an important milestone towards our first regulatory submissions for volanesorsen in the U.S., Europe and Canada in 2017," said Dr. Louis O'Dea, chief medical officer, Akcea Therapeutics. "We seek to bring this new treatment as expeditiously as possible to FCS patients who have a high unmet need with potentially life-threatening consequences."

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. The most common adverse event in the volanesorsen-treated group of patients was injection site reactions (ISRs), which were mostly mild. Five volanesorsen-treated patients discontinued due to ISRs. Declines in platelet counts associated with decreases in triglycerides were observed in many patients. These were generally well managed with dose adjustment. Five volanesorsen-treated patients discontinued due to declines in platelets. No patients discontinued in the last six months of the study after platelet monitoring was fully implemented. In the volanesorsen Phase 3 program, there were infrequent serious platelet events (grade 4 thrombocytopenia) in three volanesorsen-treated patients, which resolved without incident following cessation of dosing. In the entire volanesorsen clinical program 232 individuals have been treated with volanesorsen, including 66 FCS patients, some for more than two years.

WEBCAST INFORMATION

Interested parties may listen to the call by dialing 877-443-5662 or access the webcast at www.ionispharma.com. A webcast replay will be available for a limited time at the same address.

ABOUT VOLANESORSEN, FCS and FPL

Volanesorsen is an antisense drug 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 genetic disorder characterized by extremely high levels of triglycerides and the risk of recurrent, potentially fatal pancreatitis. People with FCS are unable to effectively clear large, triglyceride-rich lipid particles called chylomicrons due to a deficiency of 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.

For more information about this clinical trial program for volanesorsen, please visit www.apociii.com.

ABOUT VOLANESORSEN CLINICAL PROGRAM

The volanesorsen clinical program is focused on generating data to support registration in two severe, rare, genetic diseases, FCS and FPL. The program is supported by Phase 1 and Phase 2 studies that explored volanesorsen doses across both healthy volunteers and a number of patient populations, including patients with hypertriglyceridemia, Type 2 diabetes, and FCS. In these studies, volanesorsen resulted in dose-dependent, consistent and sustained reductions in plasma ApoC-III and in triglyceride levels, both as a single agent and as an add-on to fibrates. Akcea and Ionis have now successfully completed two Phase 3 studies, APPROACH and COMPASS, which support planned regulatory filings for the treatment of FCS. Patients with FCS who have completed or meet the study criteria for the APPROACH study can enroll in an open-label extension study. Akcea and Ionis are also currently conducting, BROADEN, a Phase 3 study in patients with FPL.

ABOUT AKCEA THERAPEUTICS

Akcea Therapeutics is a development and commercialization company focused on transforming the lives of patients with serious cardiometabolic lipid disorders. Akcea has a robust portfolio of development-stage drugs covering multiple targets and diseases using advanced RNA-targeted antisense therapeutics. Akcea's most advanced drug, volanesorsen, is being developed to address two severe, rare, genetically defined lipid disorders, FCS and FPL. Based on positive results in the Phase 3 program, Akcea is preparing regulatory dossiers for volanesorsen for the treatment of FCS and conducting a Phase 3 study evaluating volanesorsen in patients with FPL. Akcea's drug pipeline includes three additional novel antisense drugs designed to address a number of lipid risk factors, including ApoC-III, triglycerides, Lp(a), and LDL-cholesterol. Akcea is continuing to assemble the global infrastructure to develop and commercialize the drugs in its pipeline. Akcea is a wholly owned subsidiary of Ionis Pharmaceuticals, Inc. and is located in Cambridge, Massachusetts. Additional information about Akcea is available at www.akceatx.com.

ABOUT IONIS PHARMACEUTICALS, INC.

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 and/or best-in-class drugs, with over a dozen drugs in mid- to late-stage development. Drugs currently in Phase 3 development include volanesorsen, a drug Ionis is developing and, if approved, plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with FCS and FPL; IONIS-TTR$_{Rx}$, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and SPINRAZA™ (nusinersen), a drug Ionis is developing with Biogen to treat infants and children with spinal muscular atrophy. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

FORWARD-LOOKING STATEMENT

This press release 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 at www.ionispharma.com.

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

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