

## Akcea and Ionis Announce Positive Results from COMPASS Phase 3 Study of Volanesorsen

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### **71% Mean Triglyceride Reduction in Patients with Severe Hypertriglyceridemia 73% Mean Triglyceride Reduction in Patients with FCS**

CARLSBAD, Calif. and CAMBRIDGE, Mass., Dec. 19, 2016 /PRNewswire/ -- Akcea Therapeutics, a wholly-owned subsidiary of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced that the Phase 3 COMPASS study met its primary endpoint. COMPASS is a randomized, double-blind, placebo-controlled, 26-week Phase 3 study evaluating volanesorsen in 113 patients with severe hypertriglyceridemia. The average incoming triglyceride level of patients in the study was 1,261 mg/dl. Patients treated with volanesorsen experienced clinically meaningful benefits on triglycerides 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 71.2% 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 sustained through the end of the 26 week treatment period.
- In a subset of seven patients with familial chylomicronemia syndrome (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 sustained through the end of the 26-week treatment period.
- In addition, 82% of patients treated with volanesorsen, including three of the FCS patients, achieved triglyceride levels less than 500 mg/dl after 13 weeks of treatment, compared to 14% of placebo-treated patients ( $p<0.0001$ ).

The COMPASS study is an important component of the planned regulatory filings for volanesorsen, an antisense drug designed to decrease triglyceride levels by directly targeting apolipoprotein C-III (ApoC-III), being developed for the treatment of patients with FCS and familial partial lipodystrophy (FPL), two rare metabolic disorders. Ionis and Akcea management plan to discuss the results from this study at an upcoming Ionis pipeline update call on January 5, 2017, and also to present additional data from the study at an upcoming medical meeting.

"Current therapies are inadequate for patients with extremely high triglycerides, most specifically those with FCS, leaving them at risk for significant morbidity and mortality, including pancreatitis," said Daniel Gaudet, M.D., associate professor of medicine and director of the Community Genomic Medicine Center, Department of Medicine, Université de Montréal and scientific director and strategic development officer of BioBank, Genome Quebec's Technological Centers. "People with FCS have particular challenges because in addition to having triglyceride levels that can be 10 to 20 times normal values, the currently available triglyceride-lowering drugs are usually ineffective. The data from studies in patients with FCS treated with volanesorsen, including those from the COMPASS study, show that for the first time these patients can achieve the triglyceride reductions needed to potentially improve their health."

COMPASS results were consistent with findings from the Phase 2 program for volanesorsen, which were published twice in the *New England Journal of Medicine*. In the three FCS patients profiled in one publication, the incoming average triglyceride number was 1,844 mg/dl, and the average triglyceride reduction after three months of dosing with volanesorsen was 1,298 mg/dl. In the COMPASS study, the average incoming triglyceride level of the five FCS patients treated with volanesorsen was 2,134 mg/dl, and the average triglyceride reduction was 1,511 mg/dl after three months of dosing.

"The findings in COMPASS reinforce the efficacy and safety of volanesorsen observed in Phase 2 studies across multiple patient populations, including FCS," said Dr. Louis O'Dea, chief medical officer for Akcea. "No drug available today has demonstrated the magnitude of the triglyceride reductions observed with volanesorsen. These results confirm the potential value of targeting ApoC-III to lower triglycerides in patients who have high unmet need with potentially life-threatening consequences."

The most common adverse event in the volanesorsen-treated group of patients was injection site reactions (ISRs), which were mostly mild. In this study with patients who are largely asymptomatic and, unlike FCS patients, do not need to manage the daily burden and symptoms of their disease, 13% of treated patients discontinued due to ISRs and 7% of treated patients discontinued treatment for other non-serious adverse events. There were no deaths in the study. None of the FCS patients in the study discontinued. In addition, there were no serious platelet events in the study. There was one potentially related SAE on the drug-treated arm. This was a report of serum sickness that occurred two weeks after the last study dose and resolved without treatment, and after thorough investigation the sponsor determined that the case was not likely caused by the drug.

Including COMPASS, four global trials form the Phase 3 program for volanesorsen. Akcea plans to have top-line data from the pivotal APPROACH study in patients with FCS in the first quarter of 2017. Akcea plans to have data from the pivotal BROADEN study in patients with FPL in 2019.

Patients with FCS who have completed or meet the study criteria for the APPROACH and COMPASS studies can enroll in an open-label extension (APPROACH OLE) study. Patients in the BROADEN study are also eligible to roll over into an open-label extension study upon completing dosing in the pivotal study.

"The success of COMPASS represents an important milestone towards our planned regulatory filings for volanesorsen in the U.S., Europe and Canada in 2017," said Paula Soteropoulos, president and chief executive officer of Akcea Therapeutics. "As we complete this and other ongoing preparatory regulatory and pre-commercial activities, we are gratified to see clinical data that support this therapy's potential to help the patients who have shared with us the severe challenges and fear with which they live, and the life-changing benefit a new therapy could potentially represent."

#### **ABOUT VOLANESORSEN, FCS and FPL**

Volanesorsen is an antisense drug in development for two rare metabolic disorders: FCS and 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 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 cure available for FCS, and risk of morbidity and mortality persists despite current standards of care. Additional information on FCS is available at [www.fcsfocus.com](http://www.fcsfocus.com) and through the FCS Foundation at <http://www.livingwithfcs.org> and the LPLD Alliance at [www.lpldalliance.org](http://www.lpldalliance.org).

FPL is a rare, underdiagnosed 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 long-term, progressive consequences, such as premature cardiomyopathy, atherosclerosis, and liver disease. Additional information on FPL is available through Lipodystrophy United at [www.lipodystrophyunited.org](http://www.lipodystrophyunited.org).

For more information about this clinical trial program for volanesorsen, please visit [www.apociii.com](http://www.apociii.com).

#### **ABOUT AKCEA THERAPEUTICS**

Akcea Therapeutics is a development and commercialization company focused on transforming the lives of patients with serious cardiometabolic lipid disorders. Established as a wholly-owned subsidiary of Ionis Pharmaceuticals, Inc., Akcea has a robust portfolio of development-stage drugs covering multiple targets and diseases using advanced RNA-targeted antisense therapeutics. Akcea's drug pipeline includes novel antisense drugs designed to address a number of lipid risk factors, including LDL-cholesterol, ApoC-III, triglycerides and Lp(a). Akcea's most advanced program, volanesorsen, is in Phase 3 development to treat patients with FCS and patients with FPL, two ultra-orphan lipid disorders that are characterized by extremely high triglycerides and ApoC-III. Akcea is located in Cambridge, Massachusetts. Additional information about Akcea is available at [www.akceatx.com](http://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<sub>RX</sub>, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and SPINRAZA<sup>TM</sup> (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](http://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, 2015, 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 at [www.ionispharma.com](http://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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To view the original version on PR Newswire, visit: <http://www.prnewswire.com/news-releases/akcea-and-ionis-announce-positive-results-from-compass-phase-3-study-of-volanesorsen-300380863.html>

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