Positive Phase 2 Clinical Data of AKCEA-APOCIII-L(Rx) Presented at ESC Congress 2020

August 29, 2020

Results in late-breaking presentation show patients with hypertriglyceridemia experienced dose-dependent reductions in triglyceride levels, apoC-III, and significant reductions in atherogenic lipoproteins

Favorable safety and tolerability profile

BOSTON and CARLSBAD, Calif., Aug. 29, 2020 /PRNewswire/ -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), a majority-owned affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), presented data today from the Phase 2 study of AKCEA-APOCIII-L_{Rx} in an online Late Breaking Clinical Trial Session at the ESC Congress 2020, the annual meeting of the European Society of Cardiology.

Results showed that AKCEA-APOCIII-L_{Rx} met primary and key secondary endpoints with significant reductions in triglyceride (TG) and apoC-III levels, and a favorable safety and tolerability profile in the treatment of patients with hypertriglyceridemia who have established cardiovascular disease (CVD) or are at risk for CVD.

"Hypertriglyceridemia and high levels of apoC-III are associated with increased residual risk for cardiovascular events, even in patients receiving appropriate lipid-lowering therapies. These results demonstrate that AKCEA-APOCIII-L_{Rx} can substantially reduce TG and apoC-III levels, and thus has the potential to fulfill an unmet need in this patient population," said Jean-Claude Tardif, M.D., director of the Research Center at the Montreal Heart Institute and professor of Medicine at University of Montreal.

AKCEA-APOCIII-L_{Rx} is designed using Ionis' proprietary **Li**gand **C**onjugated **A**ntisense (LICA) technology platform to inhibit production of apolipoprotein C-III (apoC-III), a protein produced in the liver that plays a central role in the regulation of serum triglycerides. Epidemiological studies show that apoC-III levels may help predict risk of CVD.

"We are encouraged by the results from our Phase 2 study, in which treatment with AKCEA-APOCIII-L_{Rx} significantly reduced triglycerides and other atherogenic lipoproteins in patients with hypertriglyceridemia and a history of CVD, or a high risk for CVD," said William Andrews, M.D., FACP, chief medical officer at Akcea. "We look forward to further assessing AKCEA-APOCIII-L_{Rx} in other severe diseases associated with high triglyceride levels, including familial chylomicronemia syndrome (FCS), for which we plan to initiate a Phase 3 trial later this year."

The Phase 2 study was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study designed to evaluate the safety, tolerability and efficacy of AKCEA-APOCIII-L_{Rx} in patients with hypertriglyceridemia and a clinical diagnosis of CVD or who are at high risk of CVD. The study was also designed to identify the optimal dose and dose regimen to lower TG, apoC-III and other lipid and lipoprotein levels for subsequent Phase 3 studies. The study involved 114 patients randomized to four cohorts and in a 4:1 ratio (treatment: placebo) within each cohort. AKCEA-APOCIII-L_{Rx} or placebo was administered via subcutaneous injection for at least six months, with some patients treated up to a year. Weekly, bi-weekly, and monthly dosing regimens were explored with total monthly doses ranging from 10 mg to 50 mg. Data from the Phase 2 study show:

- Statistically significant dose-dependent reductions in fasting TGs compared to placebo at all dose levels with a 62% reduction at the highest dose (50 mg every four weeks), and with 91% of patients achieving TG levels of < 150 mg/dL (≤1.7 mmol/L) at this dose at six months
- Significant reductions in apoC-III (up to 74%) and atherogenic lipoproteins including very low-density lipoprotein (VLDL) cholesterol (60%), non-high-density lipoprotein (non-HDL) cholesterol (24%), and apolipoprotein B, or apoB (16%)
- High-density lipoprotein (HDL) cholesterol levels increased by up to 42%
- AKCEA-APOCIII-L_{Rx} demonstrated a favorable tolerability and safety profile with mild treatment-emergent adverse events at the injection site being the most frequent

"These data further demonstrate the tremendous value that our LICA antisense platform brings to patients suffering from a broad range of diseases," said Brett P. Monia, Ph.D., chief executive officer at Ionis. "We look forward to advancing AKCEA-APOCIII-L_{Rx} into Phase 3 development to address patient populations with high triglyceride levels".

ABOUT AKCEA-APOCIII-L_{Rx}

AKCEA-APOCIII-L_{Rx} is an investigational antisense medicine designed to reduce the production of apolipoprotein C-III, or apoC-III. ApoC-III is a protein produced in the liver that plays a central role in the regulation of serum triglycerides. Genetically reduced levels of apoC-III are correlated to lower levels of triglycerides and lower risk of cardiovascular disease whereas elevated levels of apoC-III correlate with high triglyceride levels that have been associated with multiple metabolic abnormalities, such as insulin resistance and/or metabolic syndrome as well as elevated cardiovascular

event risk. AKCEA-APOCIII-L_{Rx} was developed using Ionis' advanced **LI**gand **C**onjugated **A**ntisense (LICA) technology platform. AKCEA-APOCIII-L_{Rx} will be entering Phase 3 development for patients with FCS, with plans to evaluate AKCEA-APOCIII-L_{Rx} in patients with other hypertriglyceridemia disorders. AKCEA-APOCIII-L_{Rx} was discovered by Ionis and has been co-developed by Akcea and Ionis.

ABOUT AKCEA THERAPEUTICS

Akcea Therapeutics, Inc., a majority-owned affiliate of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with serious and rare diseases. Akcea is commercializing TEGSEDI® (inotersen) and WAYLIVRA® (volanesorsen), as well as advancing a mature pipeline of novel medicines, including AKCEA-APO(a)-L_{Rx}, vupanorsen (AKCEA-ANGPTL3-L_{Rx}), AKCEA-APOCIII-L_{Rx}, and AKCEA-TTR-L_{Rx}, with the potential to treat multiple diseases. All six drugs were discovered by Ionis, a leader in antisense therapeutics, and are based on Ionis' proprietary antisense technology. TEGSEDI is approved in the U.S., E.U., Canada and Brazil, and WAYLIVRA is approved in the E.U. Akcea is headquartered in Boston and is building the infrastructure to commercialize its medicines globally. Additional information about Akcea is available at www.akceatx.com and you can follow us on Twitter at @akceatx.

ABOUT IONIS PHARMACEUTICALS, INC.

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology that can treat diseases where no other therapeutic approaches have proven effective. Our drug discovery platform has served as a springboard for actionable promise and realized hope for patients with unmet needs. We created the first and only approved treatment for children and adults with spinal muscular atrophy as well as the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 novel medicines designed to potentially treat a broad range of disease, including neurological, cardio-renal, metabolic, infectious, and pulmonary diseases. To learn more about Ionis visit www.ionispharma.com and follow us on Twitter @ionispharma.

AKCEA AND IONIS FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the business of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc. and the therapeutic and commercial potential of AKCEA-APOCIII-L_{Rx}. Any statement describing Akcea's or Ionis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of AKCEA-APOCIII-L_{Rx} or other of Akcea's or Ionis' drugs in development 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 and 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 Akcea's and Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Akcea and Ionis. In particular, we caution you that our forward-looking statements are subject to the ongoing and developing circumstances related to the COVID-19 pandemic, which may have a material adverse effect on our business, operations and future financial results. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Akcea's and Ionis' programs are described in additional detail in Akcea's and Ionis' quarterly reports on Form 10-Q and annual reports on Form 10-K, which are on file with the SEC. Copies of these and other documents are available from each company.

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.

View original content to download multimedia:http://www.prnewswire.com/news-releases/positive-phase-2-clinical-data-of-akcea-apociii-lrx-presented-at-esc-congress-2020-301120533.html

SOURCE Akcea Therapeutics, Inc.; Ionis Pharmaceuticals, Inc.

Akcea Investor Contact, Matt Roache, Director, Investor Relations, (617)-841-9535, mroache@akceatx.com; Akcea Media Contact, Lynn Granito, Berry & Company, T: 212 253-8881, lgranito@berrypr.com; Ionis Investor Contact, D. Wade Walke, Ph.D., Vice President, Investor Relations, 760-603-2741, wwalke@ionisph.com; Ionis Media Contact, Roslyn Patterson, Vice President, Corporate Communications, 760-603-2681, rpatterson@ionisph.com