



Akcea and Ionis report positive topline Phase 2 results of AKCEA-APOCIII-L Rx

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Favorable safety and tolerability were demonstrated in hypertriglyceridemia patients in the study
Primary and key secondary endpoints were met with significant reduction in apoC-III and triglyceride levels
More than 90% of patients achieved serum triglycerides ≤ 150 mg/dL at the highest monthly dose

BOSTON and CARLSBAD, Calif., Jan. 22, 2020 /PRNewswire/ -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), a majority-owned affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced positive topline results from the Phase 2 study of AKCEA-APOCIII-L_{Rx} in the treatment of patients with hypertriglyceridemia who are at risk for or have established cardiovascular disease (CVD). The study met the primary endpoint of significant triglyceride lowering and multiple secondary endpoints with a favorable safety and tolerability profile.



The objective of the Phase 2 study was to evaluate the safety and efficacy of different doses and dosing frequencies of AKCEA-APOCIII-L_{Rx}. The multicenter, randomized, double-blind, placebo-controlled, dose-ranging study included 114 patients with a clinical diagnosis of CVD or who are at high risk of CVD. Participants were administered AKCEA-APOCIII-L_{Rx} or placebo via subcutaneous injection for at least six months with some patients being treated up to a year. Weekly, bi-weekly, and monthly dosing was explored in four cohorts with doses ranging from 10 mg to 50 mg of total monthly dose. Observations from the AKCEA-APOCIII-L_{Rx} study included:

- Statistically significant dose-dependent reductions in fasting triglycerides compared to placebo at all dose levels
 - At the highest once monthly dose of 50 mg, more than 90% of patients achieved serum triglycerides of ≤ 150 mg/dL, compared to less than 5% of patients in the placebo group; mean triglyceride levels of patients at baseline was 285 mg/dL
- Significant reductions in multiple additional risk factors, including apoC-III, very low-density lipoprotein (VLDL-C) and remnant cholesterol, compared to placebo
- Statistically significant increases in high-density lipoprotein cholesterol (HDL-C) compared to placebo at all dose levels
- Treatment-emergent adverse events (TEAEs) were comparable between active and placebo groups. The most common adverse event was injection site reactions (ISRs). ISRs were mostly mild, infrequent and primarily occurred in the weekly dose group. In the highest monthly dose group, the occurrence of ISRs was similar to the placebo group
- There were no safety signals, including those related to platelet counts, liver function or renal function
- Approximately 85% of patients completed treatment and the rate of treatment discontinuation was comparable between the active and placebo groups

"We are very encouraged that patients achieved a significant reduction in apoC-III and triglyceride levels in this study, with the majority reaching triglyceride levels below the recognized threshold for cardiovascular risk. These data further validate the consistent efficacy and safety profile that we have seen across Ionis' LICA technology platform," said Louis O'Dea, M.D., chief medical officer at Akcea Therapeutics. "Based on the positive results from this study, we plan to rapidly pursue development of AKCEA-APOCIII-L_{Rx} for familial chylomicronemia syndrome or FCS. Because we were able to achieve substantial triglyceride lowering with this investigational medicine, we are also considering developing it for other rare and common diseases associated with elevated triglycerides. We are very grateful to the patients, families and physicians who participated in this study and are excited about the potential to bring this much needed therapy to patients."

AKCEA-APOCIII-L_{Rx} was discovered by Ionis and has been co-developed by Akcea and Ionis. It is an antisense drug developed using Ionis' proprietary **L**igand **C**onjugated **A**ntisense (LICA) technology platform and is designed 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.

ABOUT AKCEA-APOCIII-L_{Rx}

AKCEA-APOCIII-L_{Rx} is a ligand conjugated antisense (LICA) drug 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} is in Phase 2 development for hypertriglyceridemia and established cardiovascular disease. Akcea and Ionis intend to pursue development in familial chylomicronemia syndrome, or FCS, and are considering pursuing development in additional indications.

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 drugs 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 drugs, including AKCEA-APO(a)-L_{Rx}, 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. WAYLIVRA is approved in the E.U. and is currently in Phase 3 clinical development for the treatment of people with familial partial lipodystrophy, or FPL. Akcea is building the infrastructure to commercialize its drugs globally. Akcea is a global company headquartered in Boston, Massachusetts. 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, cardiovascular, 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. 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.

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