

Positive Phase 2 Clinical Data of Vupanorsen (AKCEA-ANGPTL3-L(Rx)) Presented at ESC Congress 2020

August 29, 2020

Results from Phase 2 study demonstrate patients receiving vupanorsen experienced significant, dose-dependent reductions in triglyceride levels, ANGPTL3 and additional lipid parameters compared to placebo

Favorable safety and tolerability profile demonstrated for LICA platform-based therapy

Results from the Phase 2 study to be published in the European Heart Journal

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 from the Phase 2 clinical trial of vupanorsen (AKCEA-ANGPTL3-L_{Rx}) in an online Late Breaking Clinical Trial Session at the ESC Congress 2020, the annual meeting for the European Society of Cardiology.



Vupanorsen is an investigational antisense therapy being developed to treat patients with certain cardiovascular diseases. In the Phase 2 study, vupanorsen met the primary endpoint of significant reductions in triglyceride (TG) levels and multiple secondary endpoints compared to placebo, with a favorable safety and tolerability profile.

"We are very encouraged by the demonstrated efficacy, safety and tolerability profile of vupanorsen," said Damien McDevitt, Ph.D., chief executive officer at Akcea. "There are millions of patients worldwide living with dyslipidemia that puts them at risk of cardiovascular events. By reducing ANGPTL3, vupanorsen has the potential to reduce the risk of cardiovascular events caused by dyslipidemia in many of these patients, thereby addressing a major area of continued unmet medical need. We look forward to working with Pfizer as they continue to advance this important clinical development program."

Vupanorsen was developed using Ionis' proprietary Ligand Conjugated Antisense (LICA) technology platform to reduce the production of angiotensin-like 3 (ANGPTL3) protein from the liver, a key regulator of triglyceride and cholesterol metabolism.

The goal of the randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study was to assess the safety and efficacy of vupanorsen. A total of 105 patients with hypertriglyceridemia (fasting plasma TG levels >150 mg/dL), type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) were randomized to three dosing cohorts in a 3:1 ratio (vupanorsen: placebo) within each cohort and treated for six months. The dosing cohorts explored different doses and dose regimens vs placebo, with patients receiving either 40 mg or 80 mg every four weeks or 20 mg every week. Participants received either vupanorsen or placebo via subcutaneous injection. Results from the Phase 2 study show:

- Statistically significant dose-dependent reductions in fasting TGs at all dose levels, with the highest mean reduction of 53% at the dose of 80 mg every four weeks (44% mean reduction compared to placebo, $P < 0.0001$)
- Statistically significant dose-dependent reductions compared to placebo in ANGPTL3 (62%), very low-density lipoprotein (VLDL) cholesterol (38%), total cholesterol (19%), and non-high-density lipoprotein (non-HDL) cholesterol (18%) (numbers indicate mean reductions achieved with the 80 mg every four week dose)
- No effect on glycemic parameters and no decrease in hepatic steatosis
- No significant reductions in low-density lipoprotein cholesterol (LDL-C) levels compared to placebo in this patient population, which did not have high baseline LDL-C levels
- A favorable tolerability and safety profile. The most common treatment-emergent adverse events were injection site reactions, which were mostly mild.

"Antisense-mediated reduction of ANGPTL3 has the potential to address significant unmet needs in patients with cardiovascular diseases," said Daniel Gaudet, M.D., professor of medicine, Department of Medicine, University of Montreal. "Results from the Phase 2 study bring essential insights about this investigational therapy that may help guide disease management strategies and clinical research moving forward."

"Clinical data from the Phase 2 study show an impressive and meaningful reduction in triglyceride levels and ANGPTL3, and add to the growing body of evidence supporting our LICA antisense technology for large indications, such as cardiovascular disease," said Brett P. Monia, Ph.D., chief executive officer at Ionis. "We believe vupanorsen has the potential to bring much-needed benefit to this patient population."

In November 2019, Akcea and Ionis announced the closing of a worldwide exclusive licensing agreement with Pfizer Inc. for vupanorsen. Pfizer is responsible for all development and regulatory activities and costs beyond those associated with this Phase 2 study. Pfizer plans to further evaluate vupanorsen in a Phase 2b study among statin-treated patients with elevated non-HDL-C and high triglyceride levels, in order to identify the optimal dose to maximize target engagement and lipid lowering. The Phase 2b study is expected to initiate in 2H 2020.

ABOUT VUPANORSEN (AKCEA-ANGPTL3-L_{Rx})

AKCEA-ANGPTL3-L_{Rx} (vupanorsen) is an investigational antisense therapy being developed to treat patients with certain cardiovascular diseases. This antisense medicine is designed to reduce the production of angiopoietin-like 3 (ANGPTL3) protein, a key regulator of triglyceride and cholesterol metabolism, in the liver. AKCEA-ANGPTL3-L_{Rx} was developed using Ionis' advanced **L**Igand **C**onjugated **A**ntisense (LICA) technology platform. The potential therapeutic benefits of ANGPTL3 reduction are supported by the discovery that people with a genetic deficiency in ANGPTL3 have reduced levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides, and a decreased risk of diabetes and cardiovascular disease.¹ In a previous Phase 1 study, subjects treated with AKCEA-ANGPTL3-L_{Rx} achieved robust, dose-dependent reductions in ANGPTL3, triglycerides, LDL-C, non-HDL-C and total cholesterol with a positive safety and tolerability profile.² AKCEA-ANGPTL3-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-ANGPTL3-L_{Rx}. Any statement describing Akcea's or Ionis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of AKCEA-ANGPTL3-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.

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References

1. JAMA Cardiol. 2018 Oct 1;3(10):957-966.
2. N Engl J Med. 2017 Jul 20;377(3):222-232.



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Akcea Investor Contact: Matt Roache, Director, Investor Relations, (617)-841-9535, mroache@akceatx.com; Akcea Media Contact: Angelyn Lowe, VP, Corporate Communications & Investor Relations, 442-287-0470, alowe@akceatx.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