Ionis and Akcea announce that Pfizer has initiated a Phase 2b clinical study of vupanorsen (AKCEA-ANGPTL3-LRx)

November 3, 2020

CARLSBAD, Calif. and BOSTON, Nov. 3, 2020 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) and its wholly owned subsidiary Akcea Therapeutics, Inc., today announced that Pfizer Inc. (NYSE: PFE) has initiated a Phase 2b study of vupanorsen (AKCEA-ANGPTL3-L_{Rx}) in statin-treated patients with elevated non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TGs). The study, **T**a**r**geting ANGPTL3 with an a**n**ti**s**ense ol**i**gonucleotide in **a**dul**t**s with dyslipid**e**mia (TRANSLATE-TIMI 70), will evaluate various doses of vupanorsen to inform potential future development.

In the Phase 2a study, vupanorsen met the primary endpoint of significant reductions in TG levels and multiple secondary endpoints compared to placebo, with a favorable safety and tolerability profile.

"Results from the Phase 2a study recently presented at the ESC Congress and published in the European Heart Journal, showed that antisense-mediated reduction of ANGPTL3 has the potential to address unmet needs in patients with atherosclerotic cardiovascular diseases, and adds to the growing body of evidence supporting our LICA antisense technology," said Sam Tsimikas, vice president of global cardiovascular development at Ionis. "We look forward to seeing Pfizer advance the Phase 2b study and report results on this clinical program."

The first patient has been treated in the multicenter, double-blind, placebo-controlled, dose-ranging Phase 2b study. TRANSLATE-TIMI 70 has an estimated total enrollment of 260 participants (≥ 40 years old) with elevated non-HDL-C (≥ 100 mg/dL) and triglycerides (150-500 mg/dL) who are receiving a stable dose of a statin. The study will explore different doses and dose regimens versus placebo, with patients receiving either 80 mg, 120 mg or 160 mg every 4 weeks, or 60 mg, 80 mg, 120 mg or 160 mg every two weeks via subcutaneous injection. The study (NCT04516291) will assess the efficacy, safety, tolerability and pharmacokinetics of vupanorsen, and the primary endpoint is percent change from baseline in non-HDL-C at week 24.

In November 2019, Akcea and Ionis announced the closing of a worldwide exclusive licensing agreement with Pfizer for vupanorsen. Pfizer is responsible for all development and regulatory activities and costs for vupanorsen beyond those associated with the Phase 2a study. Under the terms of the licensing agreement, the initiation of the Phase 2b study triggered a milestone payment of $75 million from Pfizer.

ABOUT VUPANORSEN
Vupanorsen is an investigational antisense therapy being developed for potential indications in cardiovascular risk reduction and severe hypertriglyceridemia. Vupanorsen is designed to reduce the production of angiopoietin-like 3 (ANGPTL3) protein, a key regulator of triglyceride and cholesterol metabolism, in the liver. This antisense therapy was developed using Ionis' advanced **LI**gand **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 TG, and a decreased risk of diabetes and cardiovascular disease.[1] In a Phase 1 study, subjects treated with vupanorsen achieved robust, dose-dependent reductions in ANGPTL3, TG, LDL-C, non-HDL-C and total cholesterol with a favorable safety and tolerability profile.[2] In a Phase 2a study, vupanorsen met the primary endpoint of significant reductions in TG levels and multiple secondary endpoints compared to placebo, with a favorable safety and tolerability profile.

Vupanorsen was discovered by Ionis and has been co-developed by Akcea and Ionis. 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 the Phase 2a study.

About Ionis Pharmaceuticals
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 all patients, 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 or follow us on twitter @ionispharma.

ABOUT AKCEA THERAPEUTICS
Akcea Therapeutics, Inc. is a wholly owned subsidiary of Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in RNA therapeutics. Akcea commercializes TEGSEDI® (inotersen) and WAYLIVRA® (volanesorsen), and with Ionis, is advancing a mature pipeline of novel medicines discovered by Ionis and 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. For more information about Akcea, please visit www.akceatx.com.

FORWARD-LOOKING STATEMENT
This press release includes forward-looking statements regarding Ionis' business, financial guidance and the therapeutic and commercial potential of vupanorsen (AKCEA-ANGPTL3-L_{Rx}) and Ionis' technologies and products in development, including the business of Akcea Therapeutics, Inc., Ionis' wholly owned subsidiary. Any statement describing Ionis' 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, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. 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 Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2019, and the most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available from the Company.

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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