Ionis announces that Pfizer reports topline results from Phase 2b clinical study of vupanorsen

November 24, 2021

- Study met its primary endpoint, achieving statistically significant reduction in non-high density lipoprotein cholesterol (non-HDL-C) compared to placebo at all doses tested

- Key secondary endpoints were met including statistically significant reductions in triglycerides and angiopoietin-like-3 (ANGPTL3) at all doses tested

- Pfizer is continuing to review the findings to determine next steps regarding future development

CARLSBAD, Calif., Nov. 24, 2021 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced that Pfizer has provided an update on the Phase 2b study of vupanorsen, formerly IONIS-ANGPTL3-L_{Rx}. Vupanorsen is an investigational antisense therapy being developed for indications in cardiovascular (CV) risk reduction and severe hypertriglyceridemia (SHTG). In the dose-ranging study in subjects with elevated non-HDL-C and triglycerides (TG), the study met its primary endpoint, achieving a statistically significant reduction in non-HDL-C at all doses tested at 24 weeks, compared to placebo. In addition, subjects treated with vupanorsen achieved statistically significant reductions in TG and ANGPTL3 at all dose levels at 24 weeks, compared to placebo.

"We were pleased to see statistically significant reductions in the primary endpoint, non-HDL-cholesterol, and in the secondary endpoint of triglycerides at all doses tested. The topline results of the Phase 2b study also showed that vupanorsen dose-dependently lowered its target, angiopoietin-like 3. Pfizer is continuing to review the findings to determine next steps regarding future development. We look forward to the full data set being presented at a medical meeting next year," said Sotirios "Sam" Tsimikas, M.D., vice president of global cardiovascular development and cardiovascular franchise lead at Ionis.

The most common adverse events were injection site reactions, which occurred most often in the highest vupanorsen dose group. The most common laboratory abnormalities were increases in liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and were seen primarily at the higher doses. There were no Hy's Law cases in vupanorsen-treated subjects, and no meaningful changes in bilirubin. Certain doses of vupanorsen were associated with increases from baseline in hepatic fat fraction, measured by magnetic resonance imaging proton density fat fraction at Week 24, compared to placebo. No subject had a confirmed platelet count abnormality or a confirmed reduction in the estimated glomerular filtration rate. There were no serious adverse events (SAEs) related to treatment. The incidence of SAEs was similar between active and placebo groups.

The global multicenter, double-blind, placebo-controlled, dose-ranging Phase 2b study **Ta****R**geting **A**NGPTL3 with an a**N**ti**S**ense o**L**igonucleotide in **A**dul**T**s with dyslipid**E**mia (TRANSLATE-TIMI 70) enrolled 286 participants (≥ 40 years old) with dyslipidemia, defined in this study as participants with elevated non-HDL-C (≥ 100 mg/dL) and TG (150-500 mg/dL), who are receiving a stable dose of a statin. Participants received 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 was designed to assess the efficacy, safety, tolerability and pharmacokinetics of vupanorsen, and the primary endpoint was percent change from baseline in non-HDL-C at week 24.

About vupanorsen

Vupanorsen is an investigational antisense therapy discovered by Ionis and being developed by Pfizer for potential indications in CV risk reduction and SHTG. Vupanorsen is designed to reduce the production of 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. The potential therapeutic benefits of ANGPTL3 reduction are supported by the discovery that people with a genetic deficiency in ANGPTL3 have reduced levels of LDL-C and TG, and a decreased risk of diabetes and CV disease.[i] 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.[ii] 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.[iii]

In November 2019, Pfizer licensed vupanorsen from Ionis in a worldwide exclusive agreement.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing the standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a premier late-stage pipeline highlighted by industry leading neurological and cardiometabolic franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming one of the most successful biotechnology companies.

To learn more about Ionis visit www.ionispharma.com or follow us on Twitter @ionispharma.

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' business, and the therapeutic and commercial potential of vupanorsen and Ionis' technologies and products in development. 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 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, 2020, 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.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Ionis Pharmaceuticals ™ is a trademark of Ionis Pharmaceuticals, Inc.

References

[i] *JAMA Cardiol.* 2018 Oct 1;3(10):957-966.
[ii] *N Engl J Med.* 2017 Jul 20;377(3):222-232.
[iii] Eur Heart J. 2020 Oct 21;41(40):3936-3945.

View original content to download multimedia:https://www.prnewswire.com/news-releases/ionis-announces-that-pfizer-reports-topline-results-from-phase-2b-clinical-study-of-vupanorsen-301431363.html

SOURCE Ionis Pharmaceuticals, Inc.

Ionis Pharmaceuticals Investor Contact: 760-603-2741; Ionis Pharmaceuticals Media Contact: 760-603-4679