Ionis announces positive data for ETESIAN Phase 2b study of antisense medicine targeting PCSK9 at 2022 American College of Cardiology Scientific Session

April 4, 2022

- *ETESIAN Phase 2b study of ION449 (AZD8233) met its primary and secondary endpoints; ION449 was generally well tolerated*
- *ION449 demonstrated potential best-in-class efficacy profile for a self-administered subcutaneous monthly dose regimen*
- *Study findings warrant further clinical development of ION449 for patients with hypercholesterolemia at high cardiovascular risk*

CARLSBAD, Calif., April 4, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), the leader in antisense therapeutics, and its partner, AstraZeneca, today announced positive data from the ETESIAN Phase 2b study of ION449 (AZD8233), an investigational antisense medicine designed to reduce blood cholesterol levels in patients with hypercholesterolemia by targeting proprotein convertase subtilisin/kexin type 9 (PCSK9). These data were presented at the American College of Cardiology's 71st Annual Scientific Session & Expo.

The ETESIAN Phase 2b study's objective was to assess the efficacy, safety and tolerability of ION449 in patients with high-risk hypercholesterolemia. The study met its primary endpoint in reducing serum LDL-C levels by up to 79%. Both the 50mg and 90mg doses reached statistically significant and clinically meaningful reductions in LDL-C levels from baseline of 73% (95% confidence interval [CI]: 77%, 68%) and 79% (95% CI: 83%, 76%), respectively, versus 2% (95% CI: 17%, -15%) for placebo. The reductions in LDL-C were maintained until week 14 (6 weeks after the last dose).

The trial also met the secondary endpoints, including significantly reducing PCSK9 levels by up to 94%. The 50mg and 90mg doses achieved reductions in PCSK9 levels of 89% (95% CI: 91%, 86%) and 94% (95% CI: 95%, 92%), respectively, versus 5% (95% CI: 23%, -18%) for placebo. The sustained reductions in PCSK9 levels were maintained until week 14 (6 weeks after last dose). Reducing PCSK9 levels leads to lower LDL-C levels in the bloodstream, which is known to reduce the risk of developing coronary heart disease.

ION449 was generally well tolerated during the 12-week treatment period and the 12-week follow up period in the study.

"The positive results of the ETESIAN study, along with the clinical studies to date, reinforces our confidence that ION449 (AZD8233) is a potential new treatment option that may be able to change the current standard of care for patients affected by hypercholesterolemia who have cardiovascular disease," said Brett P. Monia, Ph.D., Ionis' chief executive officer.

"Today, we are pleased to announce that ETESIAN Phase 2b for ION449 (AZD8233) demonstrated a clear dose-response for both PCSK9 and LDL-C levels. The results underscore ION449's (AZD8233) potential best-in-class efficacy profile and support further development of ION449 (AZD8233) as a next-generation PCSK9 inhibitor that is self-administered monthly," said Mene Pangalos, executive vice president and president, BioPharmaceuticals R&D at AstraZeneca.

ION449 is being developed by AstraZeneca as part of a collaboration between Ionis and AstraZeneca.

About ION449

ION449 (AZD8233) dosed once monthly via subcutaneous administration, is an investigational medicine that uses Ionis' advanced **LI**gand-**C**onjugated **A**ntisense (LICA) technology platform. It is designed to reduce plasma levels of proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is integrally involved in the regulation of LDL-cholesterol. Genetic studies have shown that individuals with life-long reduction of LDL-C due to reduced function of PCSK9 have substantially reduced risk of cardiovascular disease. Pharmacological inhibition of PCSK9 substantially lowers LDL-C. ION449 is designed to reduce the liver production of PCSK9 and lower the plasma level of LDL-C and thus reduce the risk of cardiovascular disease.

Elevated levels of LDL-C are a key risk factor in the development of cardiovascular disease, including heart attack, stroke and peripheral arterial disease. Higher levels of LDL-C in the blood are directly related to greater risk of vascular disease, while reduction of LDL-C leads to a significant decrease in risk. Despite the presence of several lipid-lowering agents, many patients are unable to achieve recommended LDL-C levels and remain at increased risk for cardiovascular disease. The development of additional, highly potent LDL-C lowering drugs can address this persistent unmet need.

About ETESIAN

ETESIAN is a randomized, double-blind, placebo-controlled, dose-ranging Phase 2b study in patients with hypercholesterolemia. The primary objective was to assess the effect of different doses of ION449 (AZD8233) on LDL-C compared to placebo at Week 12 in patients on statin therapy. Secondary endpoints included change in PCSK9 levels and the assessment of safety and tolerability of ION449.

The study had 119 participants, aged 18-75, who had LDL-C levels between 70 and 190mg/dL and were receiving moderate or high-intensity statin therapy.

Three dose levels of ION449 were evaluated (15mg, 50mg, 90mg), given monthly by sub-cutaneous injection over the 12-week dosing period. All active arms demonstrated reductions in LDL-C and PCSK9 levels at week 12 compared to placebo.

The percent changes from baseline to week 12 in LDL-C at the 15mg, 50mg and 90mg monthly dose were –39% (95% confidence interval [CI] –48%, –29%), –73% (95% CI: –77%, –68%), –79% (95% CI: –83%, –76%), respectively. The percent changes from baseline to week 12 in PCSK9 levels at the 15mg, 50mg and 90mg monthly dose were –58% (95% CI, –66%, –48%), –89% (95% CI: –91%, –86%), –94% (95% CI: –95%, –92%), respectively. ION449 was generally well-tolerated. The adverse events (AEs) were similar between the 15mg, 50mg and placebo groups. Most AEs were mild to moderate including transient, moderate treatment-emergent elevations in liver enzyme levels in the 90mg group.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing 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 a leading, fully integrated biotechnology company.

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

Ionis' Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of Ionis' technologies, ION449 and other 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 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 Dec. 31, 2021, which is 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.

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Ionis Investor Contact: 760-603-2331, Ionis Media Contact: 760-603-4679