Promising new data for Ionis' antisense medicine targeting PCSK9 presented at American Heart Association (AHA) Scientific Sessions 2020

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- Single doses resulted in potent, dose-dependent PCSK9 reductions of up to >90%, demonstrating best-in-class potential for the treatment of patients with high cholesterol at risk of cardiovascular disease

CARLSBAD, Calif., Nov. 13, 2020 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that new data for ION449, an investigational antisense medicine designed to reduce plasma levels of proprotein convertase subtilisin/kexin type 9, or PCSK9, were presented today at the American Heart Association (AHA) Scientific Sessions. PCSK9 is integrally involved in the regulation of LDL-cholesterol (LDL-C). 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.

ION449, also known as AZD8233 for subcutaneous administration and AZD6615 for oral administration, is being developed as part of a collaboration between Ionis and the biopharmaceutical company AstraZeneca. ION449 incorporates Ionis' advanced Generation 2.5 and **LI**gand **C**onjugated **A**ntisense, or LICA, technology. In a Phase 1 study, single subcutaneous doses of ION449 demonstrated dose-dependent reductions in circulating plasma PCSK9 protein and LDL-C levels of up to >90 percent and up to ~70 percent, respectively, in humans with a baseline LDL-C between 100 and 190 mg/dL.[1] Doses of 4, 12, 20, 30, 60, 90 and 120 mg were evaluated. The single 90 mg dose was the minimum dose required to achieve maximum reduction in PCSK9 and LDL-C. ION449 was observed to be safe and well tolerated at all dose levels.

In addition, the feasibility of oral administration of ION449 was established in three *in vivo* studies:

- A study in rats demonstrated liver bioavailability of 5 percent with ION449 following intrajejunal administration, mimicking oral administration of tablets not feasible in rodents.
- A study in dogs demonstrated liver bioavailability of 7 percent following ION449 oral tablet administration for 28 days.
- A study in healthy monkeys found repeated oral administration of ION449 tablets for 14 days resulted in LDL-cholesterol reductions of 45–50 percent.

An oral formulation of ION449 is currently being evaluated in a Phase 1 study in healthy volunteers.

"Even with existing treatments, cardiovascular disease remains the leading cause of death worldwide, affecting tens of millions of people. Additional treatments are clearly needed for patients still at risk. The data from these studies are very encouraging and demonstrate the best-in-class potential of ION449 for lowering LDL-C via PCSK9 reduction for the treatment of patients with high cholesterol who are at risk of cardiovascular disease," said Brett P. Monia, Ph.D., chief executive officer at Ionis.

The full poster presentations, "Single Dose Safety, Pharmacokinetics, and Pharmacodynamics of a Potent PCSK9 Synthesis Inhibitor, AZD8233, in Subjects With Elevated LDL Cholesterol" (Poster #MP515) and "An Oral Antisense Oligonucleotide for PCSK9 Inhibition in Humans" (Poster #P244) are available to view on the AHA Scientific Sessions website.

Ionis' collaboration with AstraZeneca focuses on leveraging Ionis' pioneering antisense technology to discover and develop antisense therapies and AstraZeneca's expertise in drug development and commercialization. In addition to cardiovascular programs, the companies are also collaborating to discover and develop antisense drugs to treat cancer, metabolic and other diseases.

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 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 and 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 ION449 (AZD8233 or AZD6615), 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 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.

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

[1] Clinical study (NCT03593785), sponsored by AstraZeneca.

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Ionis Pharmaceuticals Investor Contact: D. Wade Walke, Ph.D., Vice President, Investor Relations, 760-603-2741 or Ionis Pharmaceuticals Media Contact: Roslyn Patterson, Vice President, Corporate Communications, 760-603-4679