

Ionis announces AstraZeneca's initiation of the Phase 2b clinical study of its antisense medicine targeting PCSK9 to lower LDL-cholesterol

November 30, 2020

Phase 1 results for ION449 (AZD8233) demonstrate best-in-class potential, showing potent, dose-dependent PCSK9 reductions of >90% with favorable safety profile

CARLSBAD, Calif., Nov. 30, 2020 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced that the biopharmaceutical company AstraZeneca has initiated a Phase 2b clinical trial of ION449 (AZD8233), an investigational antisense medicine designed to reduce blood cholesterol levels in patients with dyslipidemia by targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), an important regulator of low-density lipoprotein cholesterol (LDL-C). PCSK9 is an enzyme that controls the number of LDL receptors on the surface of cells. People with genetic variations that reduce PCSK9 function have lower LDL-C levels in the blood and a lower risk for major cardiovascular events. ION449 is a Ligand Conjugated Antisense (LICA) medicine being developed by AstraZeneca as part of a collaboration between Ionis and AstraZeneca.

The Phase 2b, randomized, double-blind, placebo-controlled trial will enroll approximately 108 participants, aged 18-75, who have LDL-C levels between 70 and 190 mg/dL and are receiving moderate- or high-intensity statin therapy as defined by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on blood cholesterol management. The primary objective is to assess the effect of different doses of ION449 on LDL-C compared to placebo at Week 12 in patients taking baseline statin therapy. The study will evaluate three dose levels of ION449 versus placebo, all administered once a month by subcutaneous injection. Safety and tolerability will be evaluated along with a number of secondary endpoints. Learn more about the trial at: <https://clinicaltrials.gov/ct2/show/NCT04641299>.

In a Phase 1 study reported at the American Heart Association (AHA) Scientific Sessions on November 13, single subcutaneous doses of ION449 (AZD8233) demonstrated dose-dependent mean reductions in circulating plasma PCSK9 and LDL-C levels of >90 percent and up to 70 percent, respectively, in subjects who had a baseline LDL-C between 100 and 190 mg/dL without concomitant statin therapy.¹ Doses up to 120 mg were evaluated. ION449 was observed to be safe and well-tolerated at all dose levels.

"Results from the Phase 1 study showed that ION449 potently reduces PCSK9 and LDL cholesterol. ION449 demonstrated best-in-class potential for PCSK9 inhibition and LDL-C reduction, supporting larger clinical trials that are now underway to further evaluate efficacy and safety," said Sotirios "Sam" Tsimikas, M.D., senior vice president, clinical development and cardiovascular franchise leader at Ionis. "The growing evidence supporting Ionis' advanced LICA technology in cardiovascular disease holds promise for more effective approaches to lower LDL-C and to address cardiovascular disease, the leading cause of death worldwide."

Dr. Tsimikas will provide an update on Ionis' cardiovascular programs during Ionis' Virtual Investor Day, Dec. 7, 2020, beginning at 12 p.m. EST.

Ionis earned a milestone payment of \$20 million from AstraZeneca for the Phase 2b clinical trial initiation of ION449. Ionis and AstraZeneca are collaborating on potential treatments for kidney disease, cardiometabolic disease and cancer.

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), 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.

Ionis Pharmaceuticals is a trademark of Ionis Pharmaceuticals, Inc.

¹ Clinical study (NCT03593785), sponsored by AstraZeneca.

[2b-clinical-study-of-its-antisense-medicine-targeting-pcsk9-to-lower-ldl-cholesterol-301181930.html](https://www.ionispharm.com/~/media/Investor-Relations/2018/03/20180301-2b-clinical-study-of-its-antisense-medicine-targeting-pcsk9-to-lower-ldl-cholesterol-301181930.html)

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