Ionis announces positive results from Phase 2 study of ION224, an investigational medicine demonstrating clinical efficacy in the treatment of NASH/MASH

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- Significant improvement in steatohepatitis with ≥2 point improvement in NAS score without worsening fibrosis, the primary endpoint of the study
- Achieved key secondary endpoint of MASH resolution without worsening of fibrosis
- More ION224 treated patients had an improvement of ≥1 stage fibrosis compared to placebo
- ION224 was safe and well-tolerated in this study with once-monthly subcutaneous dosing

CARLSBAD, Calif., March 13, 2024 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) announced positive results from a Phase 2 study of ION224, an investigational DGAT2 antisense inhibitor in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), previously referred to as nonalcoholic steatohepatitis (NASH). The study met its primary endpoint at both doses (120 mg and 90 mg), achieving liver histologic improvement, and also met the important secondary endpoint of MASH resolution.

Key highlights from the 160-patient study at 51 weeks included:

- ION224 achieved statistically significant liver histologic improvement as measured by at least a 2-point reduction in NAFLD Activity Score (NAS)* ($p<0.001$ (120 mg) and $p=0.015$ (90 mg)).
- Subgroup analysis indicated that significant improvements in the primary endpoint were observed in patients with both F2 and F3 (advanced) fibrosis.
- ION224 achieved statistically significant MASH resolution without worsening of fibrosis, as measured by biopsy ($p=0.039$).
- 44% of patients treated with 120 mg achieved ≥50% relative reduction in liver steatosis as measured by MRI-PDFF compared to 3% for placebo.
- 32% of patients treated with 120 mg achieved a ≥1 stage improvement in fibrosis without worsening steatohepatitis as measured by biopsy compared to 12.5% for placebo.
- ION224 was safe and well-tolerated in the study.

"This Phase 2 trial of ION224 is the first to demonstrate clinical evidence that the reduction of hepatic fat after DGAT2 inhibition correlates with improvements in MASH histological endpoints," said Rohit Loomba, MD, MHSc, professor of medicine and chief, division of gastroenterology and hepatology, University of California San Diego; founding director, MASLD Research Center, University of California San Diego. "I believe ION224 offers a unique precision medicine opportunity with an approach that is potentially complementary to others in development for MASH, and I look forward to continued evaluation of this important investigational medicine."

MASH is the more severe form of metabolic dysfunction-associated steatotic liver disease (MASLD) and can lead to liver fibrosis, cirrhosis and liver-related death. ION224 is an investigational **LI**gand-**C**onjugated **A**ntisense (LICA) medicine designed to reduce the production of diacylglycerol acyltransferase 2 (DGAT2) to treat patients with MASH.

"Reducing the production of DGAT2 enzyme decreases the overproduction of triglycerides that contribute to excess liver fat, which can result in liver damage and inflammation. We are encouraged by these ION224 data, showing that a monthly subcutaneous medicine targeting DGAT2 has the potential to improve MASH and prevent its progression to more severe stages, including advanced liver fibrosis and cirrhosis," said Sanjay Bhanot, MD, PhD, senior vice president and chief medical officer at Ionis. "The inhibition of DGAT2 represents a novel approach for MASH, a progressive disease in need of better treatment options. We look forward to sharing the full results from this study at an upcoming medical conference and discussing next steps to advance this potentially promising therapy for patients."

In this study, ION224 was safe and well-tolerated in MASH participants. Those in the ION224 study arms did not experience any worsening of hepatic or renal function or gastrointestinal side effects, and there was a lower rate of early termination compared to placebo. Additionally, there were no on-study deaths or treatment-related serious adverse events.

The adaptive Phase 2, two-part, multi-center, randomized, double-blind, placebo-controlled study was designed to assess the efficacy, safety and pharmacokinetics of multiple doses of ION224 when administered subcutaneously once-monthly in adults with MASH. The study enrolled 160 patients to receive ION224 or placebo over a period of 49 weeks. In Part 1, 93 patients were randomized 1:1:1 to the three dose cohorts (60, 90, and 120 mg) and within each dose cohort, randomized 3:1 to receive ION224 or placebo. In Part 2, an additional 67 patients were randomized 1:1 to two selected dose cohorts (90 and 120 mg) and then in a 2:1 ratio to receive either ION224 or placebo within each cohort. The study was powered for the primary endpoint, which was the percentage of patients who achieved MASH histologic improvement, defined as achieving at least a 2-point reduction in NAS with at least 1-point improvement in hepatocellular ballooning or lobular inflammation, and without worsening of fibrosis at end of the treatment period.

About ION224
ION224 is an investigational **LI**gand-**C**onjugated **A**ntisense (LICA) medicine designed to reduce the production of diacylglycerol acyltransferase 2 (DGAT2) to treat patients with MASH. DGAT2 is an enzyme that catalyzes the final step in triglyceride synthesis in the liver. Reducing the production of DGAT2 should therefore decrease triglyceride synthesis in the liver. Additionally, there is evidence of an increase in both fatty acid oxidation and oxidative gene expression associated with antisense inhibition of DGAT2. ION224 offers a unique approach, which is potentially complementary to other therapies currently in clinical development.

About Metabolic dysfunction-associated steatohepatitis (MASH)
MASH is the more severe form of metabolic dysfunction-associated fatty liver disease (MASLD). It is related to the epidemic of obesity, pre-diabetes and diabetes. Unlike liver disease caused by alcohol consumption, MASH is the result of an accumulation of fat in the liver, which can lead to inflammation and cirrhosis, an advanced scarring of the liver that prevents the liver from functioning normally. About 20% of MASH patients are reported to develop cirrhosis, which is associated with increased risk of liver-related and overall mortality.[i] MASH is the fastest growing indication for liver transplantation in the U.S. and Europe.[ii]

In 2023, several multinational liver societies made the recommendation to update NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD) and to update non-alcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatohepatitis (MASH). Ionis has adopted the use of MASH to describe this Phase 2 trial. ION224-CS2 is registered on clinicaltrials.gov as a study in patients with non-alcoholic steatohepatitis (NASH) and was registered before the recommended update.

About Ionis Pharmaceuticals, Inc.
For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has five marketed medicines and a leading pipeline in neurology, cardiology, and other areas of high patient need. As the pioneer in RNA-targeted medicines, Ionis continues to drive innovation in RNA therapies in addition to advancing new approaches in gene editing. A deep understanding of disease biology and industry-leading technology propels our work, coupled with a passion and urgency to deliver life-changing advances for patients. To learn more about Ionis, visit Ionispharma.com and follow us on X (Twitter) and LinkedIn.

Forward-looking Statements
This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of ION224, additional medicines and technologies. 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 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. 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, 2023, which is on file with the SEC. Copies of this and other documents are available at www.ionispharma.com.

***** Nonalcoholic Fatty Liver Disease Activity Score (NAS) with at least 1-point improvement in hepatocellular ballooning or lobular inflammation, and without worsening in fibrosis stage.

[i]Le MH, et al. Clin Mol Hepatology 2022;28:841–850.
[ii]Estes C, et al. Hepatology. 2018;67(1):123-133.

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