Ionis announces positive data from GSK's Phase 2b clinical study of bepirovirsen

November 8, 2022

- *GSK plans to advance bepirovirsen into Phase 3 development program in 1H 2023*

CARLSBAD, Calif., Nov. 8, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that GSK presented positive end of study data from the Phase 2b B-Clear study of bepirovirsen (formerly IONIS-HBV$_{Rx}$), an investigational antisense oligonucleotide treatment for patients with chronic hepatitis B virus (CHB). The results showed that treatment with bepirovirsen resulted in sustained clearance of hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA for 24 weeks after end of bepirovirsen treatment in people with CHB. The study results were presented at the American Association for the Study of Liver Diseases' (AASLD) The Liver Meeting® in Washington, DC.

"Ionis is pleased with the results of the Phase 2b B-Clear study and to see bepirovirsen advance to Phase 3 clinical studies for the potential to offer a first-in-class therapy for people with CHB, including the possibility of functional cures. With these clinically meaningful results, we believe bepirovirsen has the potential to provide significant benefit to the millions of people with this chronic disease," said Richard S. Geary, Ph.D., executive vice president, drug development at Ionis.

The results from the B-Clear Phase 2b study provide initial evidence that bepirovirsen, as monotherapy or in combination with nucleoside/nucleotide analogue (NAs), can deliver sustained reductions in HBsAg and HBV viral DNA in specific patient groups. The full results from the study are now available in *The New England Journal of Medicine.*

In treatment arm 1 of the study, 9% of patients on NA treatment and 10% of patients not on NA treatment achieved the primary outcome of HBsAg levels below the Lower Limit of Quantification (LLOQ) and HBV DNA levels below the LLOQ, respectively. This is defined as a sustained response and was observed for 24 weeks post last dose. In the study, sustained response rates were higher in subjects with low baseline HBsAg (< 1000 IU/mL) than in those with high baseline HBsAg (>1000 IU/mL). Patients with low baseline hepatitis B surface antigen levels responded best to treatment with bepirovirsen with 16% and 25% of patients achieving the primary outcome in treatment arm 1 of the on NA and not on NA cohort, respectively.

Currently, nucleoside/nucleotide analogues are the recommended first-line therapy for patients with chronic HBV because they can inhibit viral replication. However, they cannot clear the virus and are generally taken for life. Bepirovirsen is uniquely designed to reduce HBV replication and suppress HBsAg and stimulate innate immunity which could potentially lead to functional cure. Functional cure is largely defined as sustained, undetectable levels of HBV DNA and HBsAg in the blood with or without generating protective antibodies after a finite course of treatment. Functional cure occurs when the virus is not eliminated from the body but is at low levels that are undetectable in blood and can be controlled by the immune system without medication.

GSK is exploring sequential treatment trials of bepirovirsen with other therapeutic modalities, with the aim of increasing functional cure rate in more patients and reducing the overall burden of CHB. These include:

- Phase 2b study of bepirovirsen in sequential combination with pegylated interferon (PegIFN) treatment
- Phase 2 study of bepirovirsen in sequential combination with GSK's chronic hepatitis B targeted immunotherapy

About the B-Clear Phase 2b study

The B-Clear Phase 2b study is investigating the efficacy and safety of 12- or 24-weeks treatment with bepirovirsen in people living with CHB on stable NA treatment or not on NA treatment at study start. The primary endpoints are the proportion of patients achieving HBsAg levels below the Lower Limit of Quantification (LLOQ), and HBV DNA levels below the LLOQ sustained for 24 weeks without rescue medication after end of treatment with bepirovirsen.

The study consists of two parallel cohorts, one for patients receiving NA treatment and the other for patients who were not on NA. Patients from each arm were randomized to one of four treatment arms within each cohort, with treatment administered weekly with or without loading doses (LD) on days four and 11:

- Bepirovirsen 300 mg with LD for 24 weeks;
- Bepirovirsen 300 mg with LD for 12 weeks then 150 mg for 12 weeks;
- Bepirovirsen 300 mg with LD for 12 weeks then placebo for 12 weeks;
- Placebo with LD for 12 weeks then bepirovirsen 300 mg without LD for 12 weeks.

About Hepatitis B virus infection

Hepatitis B virus infection is a serious health problem that can lead to significant and potentially fatal health conditions, including cirrhosis, liver failure and liver cancer. Chronic hepatitis B infection is caused by the hepatitis B virus and is a major global health concern, affecting nearly 300 million people worldwide.[i,ii] Chronic HBV infection is one of the most common persistent viral infections in the world. Currently available therapies, although effective in reducing circulating HBV DNA in the blood, do not efficiently inhibit HBV antigen production and secretion.

About Bepirovirsen

Bepirovirsen is an investigational antisense oligonucleotide (ASO) designed to specifically recognize the RNA that the hepatitis B virus uses to replicate itself in the infected liver cells (hepatocytes) and make the viral antigens (proteins) which facilitate chronicity of the disease by helping to avoid clearance by the immune system. The ASO recruits the liver's own enzymes to eliminate the RNA by digesting it to an active form. The subsequent reduction in the levels of the RNA results in a decrease in both the virus and the production of viral antigen (HBsAg) by the hepatocytes, which can be measured by a drop in the HBV DNA and antigen levels in the circulating blood.

Bepirovirsen (formerly IONIS-HBV$_{Rx}$), also known as GSK3228836, was discovered, and jointly developed with GSK. GSK licensed bepirovirsen from Ionis in August 2019 under a collaborative development and licensing agreement.

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 cardiovascular and neurological 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, bepirovirsen 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 December 31, 2021, and the most recent Form 10-Q quarterly filing, which is on file with the Securities and Exchange Commission. 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.

i Trepo C, et al. Hepatitis B virus infection. Lancet. 2014 Dec 6; 384(9959): 2053-63. https://doi.org/10.1016/S0140-6736(14)60220-8

i[i] World Health Organization, https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

View original content to download multimedia:https://www.prnewswire.com/news-releases/ionis-announces-positive-data-from-gsks-phase-2b-clinical-study-of-bepirovirsen-301671811.html

SOURCE Ionis Pharmaceuticals, Inc.

Ionis Investor, 760-603-2331; Ionis Media, 760-603-4679