Ionis announces presentation of positive Phase 2b data for chronic hepatitis B treatment at the EASL International Liver Congress™

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- *Interim analysis of B-Clear clinical study of bepirovirsen demonstrated end-of-treatment virologic response (VR) in patients with chronic hepatitis B*
- *Phase 3 clinical study evaluating bepirovirsen as a monotherapy is anticipated to start in the first half of 2023*
- *GSK to explore potential combination treatments to further reduce the global burden of chronic hepatitis B*

CARLSBAD, Calif., June 25, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), today announced that GSK presented positive results from an interim analysis of the Phase 2b B-Clear clinical study of bepirovirsen (formerly IONIS-HBV_{Rx}), an investigational antisense medicine for the treatment of patients with chronic hepatitis B virus (CHB).

The data were presented in an oral late-breaker session at the European Association for the Study of the Liver's (EASL) International Liver Congress™ 2022 in London, UK. The final results from the study will be submitted for presentation at a scientific congress later this year, and for publication in a peer-reviewed journal.

"Chronic hepatitis B represents a significant healthcare challenge for which there is particular need for new treatments that provide a longer-lasting solution. Data from the Phase 2b B-Clear study demonstrated the potential of bepirovirsen to provide rapid reductions in hepatitis B surface antigen in both patients not on nucleoside analogue treatment and those on stable NA therapy. These findings, together with results of previous clinical studies, support GSK's plan to initiate a Phase 3 clinical study evaluating bepirovirsen," said Sanjay Bhanot, M.D., Ph.D., senior vice president, chief medical officer and metabolic and liver franchise leader at Ionis.

In the study, 28% of patients on standard of care, which is stable nucleoside/nucleotide analogue (NA), and 29% of patients not on NA treatment, experienced a virologic response (VR) on 300 mg of bepirovirsen weekly, following 24 weeks of treatment. Virologic response is defined as serum/plasma levels of hepatitis B virus (HBV) DNA and hepatitis B surface antigens (HBsAg) below the lower limit of quantification. Up to 68% of patients on NA therapy and up to 65% of patients not on NA achieved HBsAg <100 IU/mL at the end of treatment.

End-of-treatment virologic responses were observed in patients with high or low baseline HBsAg levels, who were hepatitis B e-antigen (HBeAg) negative or positive, and who were receiving NA treatment or not, indicating that bepirovirsen has the potential to treat broad segments of the CHB population. Durability of the responses is being assessed.

Treatment-related serious adverse events (SAEs) were observed in <1% of patients receiving NA treatment and 1% of patients who were not on NA. SAEs were reported in 3% and 4% of patients receiving NA treatment and those who were not on NA, respectively. There were no clinically meaningful differences in adverse events across treatment arms in either trial.

Chronic hepatitis B infection is caused by HBV and is a major global health concern, affecting nearly 300 million people worldwide.[i,ii]

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 must be taken for life. Bepirovirsen is uniquely designed to reduce HBV replication and suppress HBsAg which could potentially lead to functional cure, largely defined as sustained, undetectable levels of hepatitis B virus DNA and HBsAg in the blood with or without generating protective antibodies after a finite course of treatment.

GSK is also exploring combinations of bepirovirsen and other therapeutic modalities in the following trials. Combination treatments could increase functional cure rates in more patients, thereby further reducing the global disease burden of CHB. Trials include:

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

About the B-Clear Phase 2b trial

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 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 1 of 4 treatment arms within each cohort, with treatment administered weekly with or without loading doses (LD) on days 4 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.

In both cohorts, virologic responses were observed at the end of treatment:

- For those patients receiving NA treatment (n=227), 24 weeks treatment of 300 mg bepirovirsen weekly resulted in HBsAg < LLOQ and HBV DNA < LLOQ in 28% of patients at end of treatment.
- For patients not on NA (n=230), 24 weeks treatment of 300 mg bepirovirsen weekly resulted in HBsAg < LLOQ and HBV DNA < LLOQ in 29% of patients at end of treatment.
- The durability of these responses is being assessed.

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 (formerly IONIS-HBV$_{Rx}$), also known as GSK3228836, is an investigational antisense medicine Ionis designed to reduce the production of viral proteins associated with hepatitis B virus (HBV) infection and replication, including hepatitis B surface antigen, which is present in both acute and chronic infections and is associated with a poor prognosis in patients with chronic HBV infection. GSK licensed bepirovirsen from Ionis 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 Dec. 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.

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

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