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Bepirovirsen: The first antisense oligonucleotide approved to achieve a functional cure for chronic hepatitis B

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SUMMARY: Chronic hepatitis B (CHB) remains a major global health burden despite the availability of potent nucleos(t)ide analogue (NA) therapy. Although NAs effectively suppress hepatitis B virus (HBV) DNA replication and reduce the risks of cirrhosis and hepatocellular carcinoma, they have limited effects on covalently closed circular DNA and hepatitis B surface antigen (HBsAg) production, and most patients require prolonged treatment. Bepirovirsen is an antisense oligonucleotide that targets conserved HBV RNA sequences, promotes RNase H1-mediated RNA degradation, and reduces viral antigen expression and replication. In August 2026, Japan approved bepirovirsen (Hibsago) for selected adults with chronic HBV infection receiving NA therapy, representing its first global regulatory approval. Approval was supported by the phase III B-Well 1 and B-Well 2 trials, in which a functional cure after treatment withdrawal was achieved in 20% and 19% of bepirovirsen-treated patients, respectively, versus 0% with a placebo. Response rates were higher among patients with lower baseline HBsAg levels. The overall safety profile was acceptable; however, elevated alanine aminotransferase levels were observed in 6% of bepirovirsen-treated participants. Ongoing studies will further define long-term durability, broader applicability, and optimal treatment strategies.

Keywords: HBV, bepirovirsen, antisense oligonucleotide, HBsAg, functional cure

Chronic hepatitis B (CHB) is a chronic inflammatory liver disease caused by persistent infection with hepatitis B virus (HBV). Clinically, persistent positivity for hepatitis B surface antigen (HBsAg) for ≥ 6 months is a key criterion for determining if a chronic HBV infection is present. Ongoing viral replication, together with host immune-mediated liver injury, drives the progression of hepatic fibrosis, and a proportion of patients eventually develop cirrhosis, hepatic decompensation, or liver cancer (*1,2*). According to data from the World Health Organization, approximately 240 million people worldwide were living with chronic hepatitis B in 2024, with an estimated 900,000 new infections occurring annually (*3*). HBV infection was responsible for approximately 1.1 million deaths in 2024, predominantly from cirrhosis and HCC (*3*). Geographically, the Western Pacific and African regions bear the greatest burden of HBV infection worldwide (*3*). In China, the fourth national seroepidemiological survey showed that the prevalence of HBsAg among individuals age 1–69 was 5.86% in 2020, which corresponds to approximately 75 million people with chronic HBV infection nationwide and which represents a persistent, substantial disease burden (*4*).

For patients with CHB who are eligible for antiviral therapy, potent nucleos(t)ide analogues (NAs) with a high barrier to resistance are the preferred treatment and remain the cornerstone of long-term antiviral therapy (*1*). First-line NAs include entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide fumarate (*1*). These agents effectively suppress HBV DNA replication and substantially reduce the risks of cirrhosis and HCC. However, NAs primarily inhibit viral reverse transcription and have little effect on covalently closed circular DNA (cccDNA) persisting in the hepatocyte nucleus. They also do not eliminate viral antigen production from integrated HBV DNA. Consequently, their effect on HBsAg levels is limited, with an annual HBsAg clearance rate of only approximately 1% during treatment (*5*). HBsAg loss remains the most desirable endpoint for discontinuing treatment, so sustained suppression of HBV DNA alone is not generally sufficient to safely discontinue therapy. Most patients therefore require long term or even lifelong treatment. There is still an urgent need for new therapeutic approaches that can reduce viral antigen levels within a finite treatment course, restore immune control, and increase the likelihood of a functional cure.

Bepirovirsen is an antisense oligonucleotide originally discovered by Ionis Pharmaceuticals and subsequently licensed to GSK for clinical development. On August 24, 2026, the Japanese Ministry of Health, Labour and Welfare approved bepirovirsen under the trade name Hibsago for adults with chronic HBV infection who had received NA therapy for ≥ 6 months and who had baseline HBsAg levels ≤ 3,000 IU/mL and HBV DNA levels < 90 IU/mL, representing the first regulatory approval of the drug worldwide (*6,7*). Bepirovirsen binds to a conserved sequence shared by multiple HBV messenger RNAs and pregenomic RNA, thereby recruiting RNase H1 to cleave and degrade the target RNAs (*8*). This mechanism simultaneously reduces viral protein expression and the generation of templates required for viral replication, leading to a reduction in levels of HBsAg, HBeAg, and HBV DNA (*8*). In addition, changes in proteins associated with innate immune responses have been observed during treatment, suggesting that bepirovirsen may also have immunomodulatory effects, potentially through Toll-like receptor 8 activation (*9,10*). Unlike NAs, which act mainly by inhibiting reverse transcription, bepirovirsen directly reduces viral RNA and antigen production. The clinical regimen consists of 24 weeks of subcutaneous bepirovirsen administered in combination with ongoing NA therapy, and it seeks to achieve a functional cure after withdrawal of all antiviral treatment. Importantly, a functional cure does not imply a sterilizing cure, as residual cccDNA may persist in hepatocytes.

Bepirovirsen's approval was substantiated by two identically designed global phase III trials, B-Well 1 and B-Well 2 (NCT05630807 and NCT05630820) (*11*). Together, the two studies enrolled more than 1,800 adults without cirrhosis from 29 countries who were receiving stable NA therapy and who had baseline HBsAg levels of > 100 to 3,000 IU/mL. Participants were randomly assigned in a 2:1 ratio to receive subcutaneous bepirovirsen at a dose of 300 mg once weekly for 24 weeks or a placebo (*11*). At week 48, NA therapy was discontinued for participants who met prespecified criteria. The primary endpoint, assessed at week 72, was a functional cure, defined as HBsAg loss together with sustained HBV DNA below the lower limit of quantification for at least 24 weeks after discontinuation of all treatment. The primary endpoint was achieved in 20% of participants in the bepirovirsen group versus 0% in the placebo group in B-Well 1 (127/650 *vs* 0/328), and in 19% of participants in the bepirovirsen group versus 0% in the placebo group in B-Well 2 (106/570 *vs* 0/286) (*11*). Among the participants with baseline HBsAg levels ≤ 1,000 IU/mL, the pooled functional cure rate increased to 26% (*11*). During the treatment period, adverse events occurred in 91% of participants in the bepirovirsen group versus 73% in the placebo group, serious adverse events occurred in 7% of participants in the bepirovirsen group versus 4% in the placebo group, and grade ≥ 3 adverse events occurred in 16% of participants in the bepirovirsen group versus 3% of participants in the placebo group (*11*). The most common grade ≥ 3 event was an increase in alanine aminotransferase levels, which occurred in 6% of bepirovirsen-treated participants (*11*). Several limitations should be considered when interpreting these findings. The trials enrolled only adults without cirrhosis in whom virological suppression had already been achieved and who had relatively low HBsAg levels, and the off-treatment observation period was limited to 24 weeks (*12*). The studies therefore do not establish the long-term risk of virological or clinical relapse, the extent of cccDNA clearance, or whether treatment translates into a reduction in cirrhosis, HCC, or mortality. Moreover, a functional cure was not achieved in approximately 80% of treated patients, and heterogeneity in treatment response and safety concerns such as elevated liver enzymes warrant further investigation.

Currently, multiple follow-up studies are underway to further strengthen the clinical evidence for bepirovirsen. B-Sure (NCT04954859) is evaluating the long-term durability of treatment response (*13*), B-Focus (NCT06497504) is assessing bepirovirsen in individuals with HIV/HBV coinfection (*14*), and B-United (NCT06537414) is investigating a sequential treatment strategy in which daplusiran/tomligisiran is followed by bepirovirsen (*15*). These studies may help define the patient populations most likely to benefit, optimize combination or sequential treatment strategies, and clarify the feasibility of sustained treatment-free disease control. In summary, bepirovirsen has demonstrated clinically meaningful efficacy with an overall manageable safety profile in carefully selected populations under controlled trial conditions. Its effectiveness in broader patient populations, long-term safety, and impact on clinically meaningful outcomes still need to be established through post-marketing and real-world studies.

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