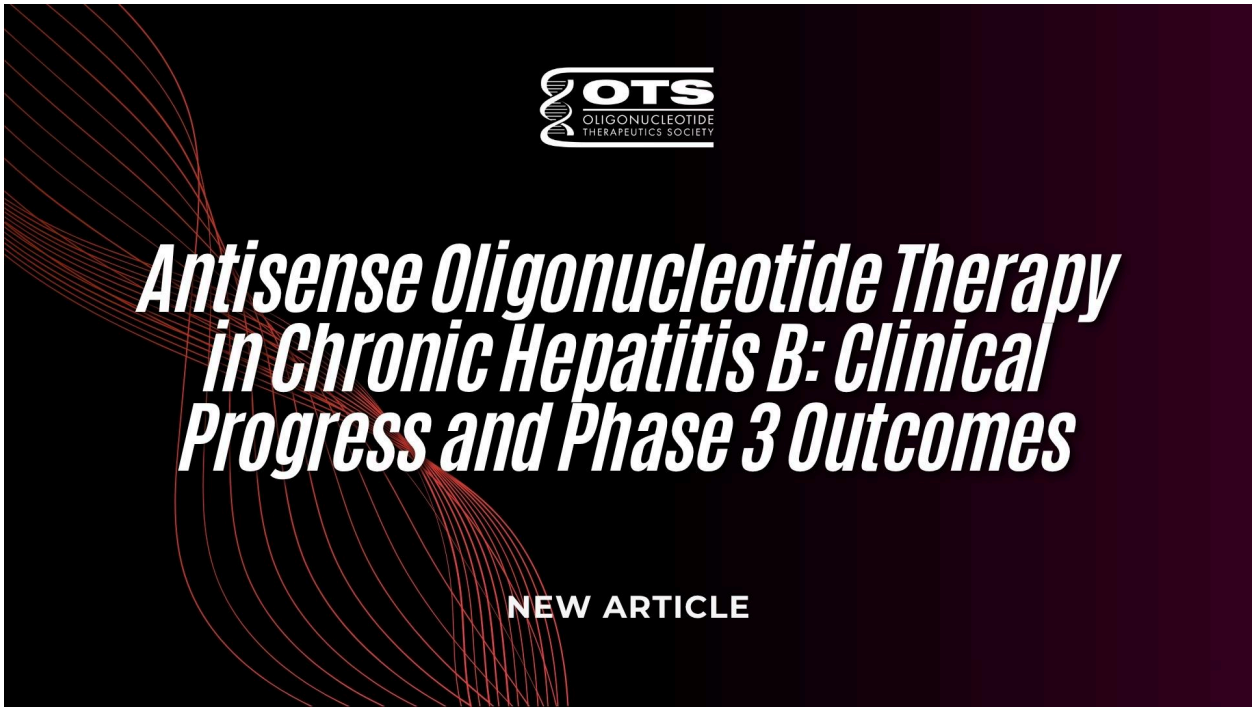
**Antisense Oligonucleotide Therapy in Chronic Hepatitis B: Clinical Progress and Phase 3 Outcomes**




When Sheree was 26, she kept wondering why she was always so tired. Though she was a mom and a nurse working multiple double shifts, she was still young and knew she shouldn't be this fatigued. Then the nausea and abdominal pain began. Soon, the only things she could tolerate were burnt toast, oatmeal, and water. When she woke up in the hospital's isolation ward — a room where no one could come in without protective gowns and gloves — she was diagnosed with chronic hepatitis B and resulting liver damage.

When a person is first infected with the virus, it is called an acute infection, which most healthy adults can get rid of without any complications. However, if the virus persists for more than six months, the diagnosis changes to chronic hepatitis. Sheree's thoughts quickly went to her son and husband. What if she had unwittingly passed it to them? Fortunately, tests showed they were uninfected. Sheree assumed she had contracted the virus at work from exposure to infected blood or body fluids from a jaundiced patient she had cared for.

Like Sheree, more than 250 million people worldwide live with hepatitis B, the leading cause of liver cancer, yet most are unaware this silent killer may be within them. Hepatitis B often moves stealthily, with few or no symptoms, and requires lifelong medication to suppress it, which rarely clears the virus completely. However, recent results published in the New England Journal of Medicine suggest that researchers may have found a therapy that does much more than suppress the virus, providing a finite treatment with a functional cure (1).

**Hepatitis B: The Silent Killer**

Hepatitis refers to inflammation of the liver, which can result from heavy alcohol use, toxins, and autoimmune diseases, but is primarily caused by five main viruses (A, B, C, D, and E), with hepatitis B being the most common and contagious. The virus can be transmitted through blood and bodily fluids such as semen, vaginal fluids, and amniotic fluid, and it can survive on surfaces outside the body for up to a week. Casual daily contact, such as sneezing, coughing, or sharing a meal, will not transmit the virus, but it can be contracted by sharing toothbrushes, nail clippers, or razors, exposure to infected needles, or through sexual contact. Acute hepatitis B is often asymptomatic or produces mild symptoms such as stomach pain, fatigue, fever, joint pain, and loss of appetite.

Hepatitis B is especially harmful for babies and can be passed from mother to baby during childbirth. These infections become chronic in about 90% of babies and 50% of children ages 1-5, compared with 5-10% of older children, teens, and adults.

Chronic hepatitis B is a lifelong condition that leads to T-cell exhaustion, impaired B-cell responses, and quiet liver damage over many years. Those with chronic hepatitis B have a higher risk of developing a serious liver disease or liver cancer. The liver performs dozens of vital functions, including processing nutrients, filtering toxins, producing bile and clotting factors, and storing vitamins, minerals, and sugar. A malfunctioning liver can disrupt metabolism, immune function, digestion, and detoxification.

Although Sheree eventually returned to work, she faced relapses and frequent hospital stays because of fatigue and abdominal pain linked to the virus. Over the years, she continued to suffer debilitating fatigue, pain, and relapses, prompting her to learn as much as she could about the virus.

Four years after her diagnosis, Sheree became pregnant with twins. Fortunately, Sheree's babies were immunized within 12 hours of birth, which prevented transmission.

"There are days when I think, 'why do I have to go through this?'" she said. "But most of the time, I try not to dwell on it. These are the cards that I've been dealt, and I have to play my best hand with them."

Many people with acute hepatitis B will have no symptoms, as Sheree's family discovered after her younger brother was diagnosed with hepatitis B and died suddenly of liver cancer a few weeks later. After his death, several immediate and extended family members were tested and found to be positive for the virus.

Since sharing her story with the Hepatitis B Foundation, Sheree has died from chronic liver disease. Over one million people die annually from the virus and its complications — liver scarring, failure, and cancer — making it the leading carcinogen after tobacco.

Scientists are searching for a cure — likely a combination of drugs that inhibit viral replication, reduce viral protein production, and boost the immune system to eliminate the virus. Bepirovirsen, developed jointly by GSK and Ionis Pharmaceuticals, is the first agent to demonstrate functional-cure rates of this magnitude in Phase 3 trials.

**Bepirovirsen Trial: treatment at a new level**

Bepirovirsen is an antisense oligonucleotide (ASO) that targets all HBV transcripts, aiming to reduce viral proteins and enable a functional cure. It recognizes the viral RNA used for replication and antigen production in infected hepatocytes and recruits cellular enzymes to degrade it. The result is reduced viral proteins — notably HBsAg — decreased HBV DNA replication and circulating viral load, and a lowering of HBsAg thought to help reverse immune exhaustion, allowing the immune system to regain control.

Clinical and preclinical data show that bepirovirsen elicits an innate immune response, as evidenced by increased production of inflammatory cytokines and enhanced killing of infected hepatocytes. The combination of direct RNA knockdown plus immune restoration supports the potential for a functional cure, which is rare with the standard treatment, nucleotide analogue therapy (NA), alone.

In the Phase 3 study, two replicate, double-blind trials enrolled 1,838 adults with noncirrhotic chronic HBV infection. Participants were randomly assigned to receive either a 300 mg subcutaneous weekly injection of bepirovirsen or placebo for 24 weeks, in addition to their regular nucleotide analogue (NA) therapy. The trials were conducted across 29 countries (1).

Researchers defined a functional cure as sustained viral control for more than six months without medication. This result surpasses the current standard of care, where functional cure rates are approximately 3% after 8 to 10 years of therapy. Eligible patients in the trial discontinued NA therapy at 48 weeks (1).

At 72 weeks, the number of patients achieving a functional cure was significantly higher in the bepirovirsen group than in the placebo group in both trials: 20% versus 0% (1), a meaningful advance compared to the prior standard of 1-3%. Participants who started the study with the lowest levels of hepatitis B surface antigen (HBsAg ≤ 1,000 IU/mL) achieved a higher functional cure rate of 26%, suggesting greater efficacy in people whose infection was already more controlled (1). While patients with a low baseline level of HBsAg represent a substantial group, many diagnosed patients have levels exceeding this number.

Experts noted that the results reinforce that new treatments will only change lives if people are diagnosed early, regularly monitored, and connected to care. However, the results will give a boost to many infected patients who do not believe a cure is possible and are living with long-term oral antiviral therapy and the continued stigma of carrying hepatitis B, said Seng Gee Lim, study co-author and director of hepatology at the National University Health System, Singapore.

“We’ve not had a treatment come close to this level of cure,” he said. “I think my patients will be extremely delighted to have this treatment available.”

While the results are encouraging, there are limitations. The benefit was concentrated among those with a lower baseline surface antigen (HBsAg) level, and the trials excluded patients with cirrhosis, HIV coinfection, or severe HBV, so the results cannot be generalized to those groups. Additionally, the primary endpoint was assessed at week 72, and a longer follow-up period is

needed to confirm that viral protein levels remain low and that the HBV DNA suppression is sustained long-term. While the drug was generally well-tolerated, a pooled analysis at 72 weeks showed that adverse events were reported in 91% of patients receiving bepirovirsen and 73% receiving placebo. Serious adverse events occurred in 7% and 4% of patients, respectively (1). Grade 3 or higher adverse events — severe or medically significant side effects — occurred in 16% of the bepirovirsen group versus 3% of the placebo group (1).

**The Fight Against Hepatitis B: Other Therapeutics, Vaccines, and Access Concerns**

The hepatitis B vaccine, introduced in 1981, provides nearly complete protection and has reduced new cases by more than 90% in multiple countries. However, communities in sub-Saharan Africa and the western Pacific have both the highest infection rates and the lowest vaccination coverage due to limited resources and infrastructure. Although tools to control the virus exist, they are often unavailable where they are needed most.

While prophylactic vaccines prevent Hepatitis B infection, therapeutic vaccines are designed for those already chronically infected and aim to restore or enhance HBV-specific immune responses to achieve a functional cure. Bepirovirsen is the most advanced therapy with positive Phase 3 data, but other therapies are in development. AusperBio is also an ASO that has shown meaningful results in smaller studies but is still in early stages. Several siRNA therapies, including Elebsiran, Imdusiran, JNJ-3989, and Xalnesiran, are also currently under study. Several other candidates are in trials, including BRII-179, a recombinant virus-like particle (VLP) vaccine in Phase 2; NASVAC is a nasally administered drug containing the recombinant hepatitis B core and surface antigens, with Phase 3 data showing durable virological suppression post-treatment; TherVacB, a heterologous protein prime/MVA boost therapeutic hepatitis B vaccine which targets multiple HBV antigens; VTP-300, an immunotherapeutic candidate consisting of an initial dose using the ChAdOx vector and a secondary dose(s) using the MVA vector, in its Phase 2 trial; and others.

While the trial results for bepirovirsen are encouraging, its affordability and accessibility for the large number of patients in resource-poor areas remain unclear. Experts emphasize the immediate priority: find people living with hepatitis B, connect them with culturally safe care, and support them before liver disease or liver cancer develops.

**The future of Hepatitis B treatment**

Bepirovirsen represents a clinically meaningful step in the effort to cure chronic hepatitis B. Phase 3 trial results suggest that, when added to standard therapy, it can produce functional cure rates far beyond current treatment benchmarks, especially in patients whose disease is already better controlled. Still, important questions remain about long-term durability, safety, and access — particularly for the populations most affected by hepatitis B and least likely to receive timely care. Defeating hepatitis B will likely require combination therapy, as well as earlier diagnosis, stronger prevention, and more equitable access to care.

As of August 2026, the current standard treatment for chronic hepatitis B remains unchanged, and bepirovirsen remains investigational in the US, available through clinical trials or special

access programs. Most patients with chronic hepatitis B continue on daily NA therapy, coupled with regular monitoring of liver function, viral load, and liver health. While these medicines effectively suppress the virus and lower the risks of liver damage and cancer, they seldom result in a functional cure on their own.

Bepirovirsen has received Breakthrough Therapy, Fast Track, and Priority Review designations from the US FDA (NDA is currently under Priority Review), reflecting its potential to substantially improve outcomes for patients with Chronic Hepatitis B. It has also received regulatory recognition in China (decision pending) and was just approved in Japan, “as a functional cure for chronic hepatitis B (CHB) virus infection in adult patients who have received at least 6 months of prior nucleos(t)ide analogue therapy and meet pre-defined viral markers.” The Prescription Drug User Fee Act (PDUFA) goal date for FDA review is set for October 26, 2026.

**References:**
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