ENANTA Pharmaceuticals

Hepatitis B Virus (HBV)

About Hepatitis B Virus

Hepatitis B virus, or HBV, can cause potentially life-threatening liver infection. The virus is transmitted through contact with the blood or other bodily fluids of an infected person.

It is estimated that approximately 250 million people worldwide are chronically infected, and 15-25% of patients with chronic HBV infection develop chronic liver disease, including cirrhosis, liver cancer, or liver decompensation. It is also estimated that more than 885,000 people worldwide died in 2015 due to complications of HBV. Estimates for the total number of persons chronically infected with HBV in the U.S. vary but generally range between 0.5 million and 2.0 million. Combining U.S., Japan, and major EU populations, estimates of HBV prevalence can be as high as 4.8 million.

Current approaches to treatment include interferon therapy and/or inhibitors of HBV reverse transcriptase. Treatment with interferon offers poor cure rates and is accompanied by serious side effects. Reverse transcriptase inhibitors can be very effective at suppressing the virus but rarely result in full eradication of the virus from the liver. New treatments that can provide functional cures to chronically infected patients are urgently needed.

Scientific Background

HBV is a partially double-stranded DNA virus with a complex life cycle. There are multiple mechanisms associated with HBV replication that could potentially be targeted with new drugs, and combination approaches may ultimately provide the most effective therapy for HBV. Some of the many mechanisms under study for HBV include the following:

- **HBsAg** inhibition- The surface antigen of HBV is the main envelope protein of the virus and critical to ongoing infection. The inhibition of HBsAg is associated with a functional cure of HBV characterized by no inflammation, normal liver enzymes and normal liver biopsy.

- **Core protein inhibition**- The hepatitis B core protein plays a critical role in viral replication, intracellular trafficking, and maintenance of chronic infections. Core inhibitors, also known as capsid assembly modulators or core protein allosteric modulators, are a novel class of replication inhibitors that have been shown to act at multiple steps in the HBV lifecycle.

- **RNA destabilization –**Disruption of HBV RNA transcripts can lead to destabilization of the RNA, resulting in decreased HBV proteins, including HBsAg.

- **RNA silencing of gene expression** - Silencing the expression of HBV RNA may be possible by using small interfering RNA's(siRNA's). This mechanism has the potential to significantly reduce HBV RNA, HBV DNA, and HBV protein levels.

- **Modulation of the human immune system** - Immunomodulators can augment the immune response to counteract HBV's ability to evade the natural host immune mechanisms that normally would respond to and clear a viral infection Interferon is an example of an immunomodulator and has been used for the treatment of HBV for decades. However, with interferon a functional cure is only seen in a small percentage of patients and the treatment is generally not well tolerated.

- **Other mechanisms -** Additional mechanisms include entry inhibitors that interfere with the initial binding of HBV to hepatocytes, preventing new infection from occurring; and inhibitors of covalently-closed circular DNA, or cccDNA, the template for HBV replication.

EDP-514, Enanta's Core Inhibitor for HBV

Enanta is initially focusing on new core inhibitors that it expects to have an impact on capsid assembly and possibly interfere with other viral replication processes.

This approach is supported by early clinical validation with the core inhibitors NVR 3-778 from Novira, JNJ-56136379 from Janssen, and ABI-H0731 from Assembly, demonstrating clinical reduction of viral DNA and RNA in chronic HBV patients in short-term Phase 1b or Phase 2 clinical studies.

Enanta's strong preclinical data further support exploration of this mechanism. In July 2019, Enanta initiated a Phase 1 clinical study of EDP-514, its lead core inhibitor candidate. You can read about the study here.