LBP-043

First evidence of elimination and inactivation of cccDNA in liver biopsies collected from patients with chronic hepatitis B treated with PBGENE-HBV

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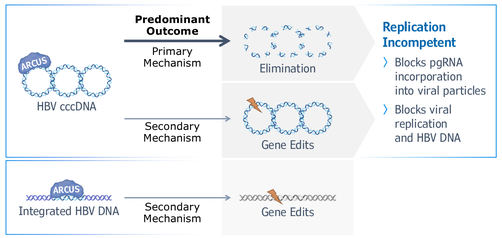
Introduction

Targeting the Root Cause of Chronic Hepatitis B

- cccDNA is the only source of new infectious particles and the therapeutic target to cure hepatitis B
- PBGENE-HBV is an LNP-encapsulated ARCUS mRNA that encodes an ARCUS nuclease. Once taken up into hepatocytes, the mRNA is translated to an ARCUS protein that cuts a highly conserved target sequence in cccDNA and integrated HBV DNA (IntDNA)
- Cleavage of the target site leads to cccDNA elimination as a primary mechanism or inactivation of cccDNA and IntDNA through editing as a secondary mechanism, leading to a reduction of all viral products (pgRNA, HBsAg, and HBV DNA) and inhibition of viral replication in preclinical models[1-3]

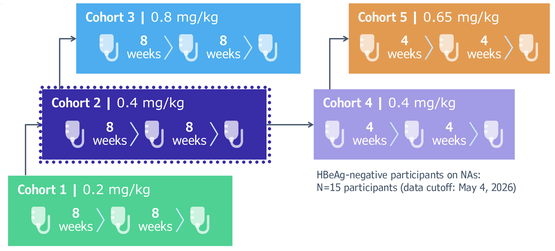


Methods

ELIMINATE-B is an ongoing, multicenter, multinational, phase 1 first-in-human trial designed to evaluate the safety, pharmacokinetics, and antiviral activity of PBGENE-HBV, a first-in-class gene editor for cHBV infection. Part 1 of ELIMINATE-B evaluates multiple ascending doses, dose intervals, and number of administrations in participants with cHBV.[4]

Part 1: Multiple Ascending Dose Escalation

Finite Treatment: Participants received up to 3 dose administrations



HBeAg-negative participants on NAs:
N=15 participants (data cutoff: May 4, 2026)

Primary Endpoint

Frequency and Severity of DLTs

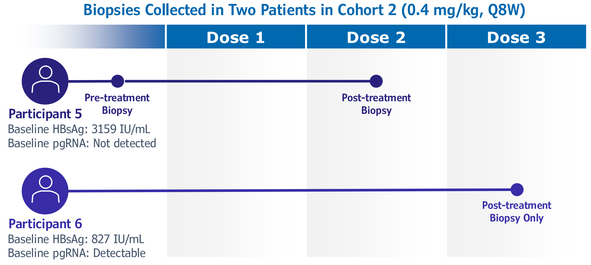
A DLT is any clinically significant, organ-specific, treatment-emergent adverse event ≥grade 3 that does not decrease to ≤grade 2 within 7 days and is related to study medication. DLT period: 28 days post–dose administration.

Secondary Endpoints

- Frequency and severity of AEs
- Changes in clinical laboratory data
- PK parameters of PBGENE-HBV
- Antiviral activity of PBGENE-HBV
  - pgRNA levels over time (Roche cobas)
  - HBsAg levels over time (Roche cobas)

Biopsy Analyses

Biopsies Collected in Two Patients in Cohort 2 (0.4 mg/kg, Q8W)

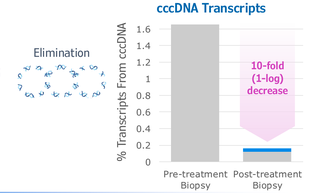


- Confirm PBGENE-HBV target engagement and activity, supporting a deeper understanding of the therapy's mechanism of action, efficacy, and safety profile
- Optional in part 1, timing determined on a case-by-case basis
  - **Participant 5:** Pre-treatment biopsy and post-treatment biopsy after second dose administration
  - **Participant 6:** Post-treatment biopsy after third dose administration
- RNA Transcript Sequencing
  - Quantitate levels of cccDNA transcripts pre- and post-treatment
  - Quantitate edits in remaining cccDNA transcripts comparing 2 and 3 dose administrations

Results

Primary Mechanism of Action: PBGENE-HBV Eliminates cccDNA

Participant 5
Biopsy after 2 doses



10-fold (1-log) decrease in cccDNA-derived RNA transcripts after only 2 dose administrations

Durable 51% decline in HBsAg 9 months after initial treatment
AEs included transient infusion-related reactions expected with LNPs and no SAEs or DLTs[4]

Participant 6
Biopsy after 3 doses

		Pre-treatment	Post-treatment
pgRNA	In Blood	Detectable	Not detected
	In Biopsy	N/A	Not detected

Pre-treatment biopsy not available (N/A); however, pgRNA was detectable in blood at baseline; became undetectable after treatment, supporting elimination and inactivation of cccDNA

Undetectable pgRNA in both blood and liver after 3 dose administrations

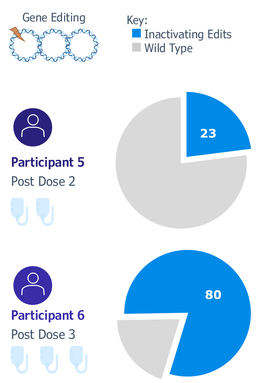
Further supporting pgRNA as a valuable blood biomarker to indicate PBGENE-HBV activity on cccDNA in the liver

Durable 34% decline in HBsAg 9 months after initial treatment
AEs included transient infusion-related reactions expected with LNPs and no SAEs or DLTs[4]

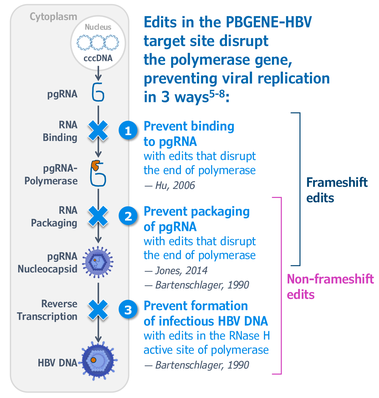
HBsAg Consistent with Elimination of cccDNA

- 100% (15/15) of participants demonstrate substantial maximal HBsAg declines (28-94%), indicating broad activity of PBGENE-HBV consistent with the elimination of cccDNA and inactivation of IntDNA in biopsy data
- HBsAg is produced from both cccDNA and IntDNA. In HBeAg-negative patients, HBsAg is primarily produced from IntDNA, limiting the clinical utility of HBsAg as a direct biomarker for cccDNA antiviral activity

Secondary Mechanism of Action: PBGENE-HBV Inactivating Edits on cccDNA Render the Virus Replication Incompetent



Editing of cccDNA reached 80% after 3 administrations, suggesting additional administrations drive cumulative editing and permanent inactivation of the remaining cccDNA not eliminated via primary mechanism

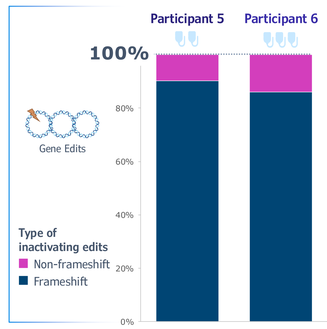


Edits in the PBGENE-HBV target site disrupt the polymerase gene, preventing viral replication in 3 ways[5-8]:

1. **Prevent binding to pgRNA** with edits that disrupt the end of polymerase — *Hu, 2006*
2. **Prevent packaging of pgRNA** with edits that disrupt the end of polymerase — *Jones, 2014* — *Bartenschlager, 1990*
3. **Prevent formation of infectious HBV DNA** with edits in the RNase H active site of polymerase — *Bartenschlager, 1990*

Frameshift edits

Non-frameshift edits



RNA sequencing from biopsies shows viral editing creates consistent outcomes that render the virus replication incompetent 100% of the time

Primary and secondary mechanism drive loss of pgRNA in blood

pgRNA was detectable at baseline in 6 of 14* participants

All undetectable after treatment with PBGENE-HBV (n=6)

50% after 1 dose

50% after 2 doses

100% of participants (n=14) are currently undetectable

Undetectable pgRNA is associated with higher cure rates off NA therapy[9]

*Evaluable participants defined as those who have 28 days of data from initial dose

Loss of pgRNA
across 4 dosing cohorts provides multiple paths for expansion of the ELIMINATE-B trial

Conclusions

- Biopsy data demonstrate direct targeting of cccDNA preventing viral replication via both PBGENE-HBV's primary and secondary mechanisms
- pgRNA is the specific blood biomarker for assessing the potent cccDNA activity of PBGENE-HBV
- Loss of detectable pgRNA and durable HBsAg declines are consistent with the elimination and inactivation of cccDNA
- These data support increased probability of cure after treatment with PBGENE-HBV and warrant ongoing clinical evaluation

Abbreviations: AE, adverse event; cccDNA, covalently closed circular DNA; cHBV, chronic hepatitis B virus; DLT, dose-limiting toxicity; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IntDNA, integrated HBV DNA; LNP, lipid nanoparticle; mRNA, messenger RNA; NA, nucleoside analog; pgRNA, pregenomic RNA; PK, pharmacokinetics; Q8W, every 8 weeks; SAE, serious adverse event.

References: 1. Harrison EB, et al. Preclinical efficacy and safety of ARCUS-POL nucleases for chronic hepatitis B: a potentially curative strategy. Presented at: Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 10-14, 2023; Boston, MA. 5040-C. **2.** Harrison EB, et al. Preclinical safety data for PBGENE-HBV gene editing program supports advancement to clinical trials as a potentially curative treatment for chronic hepatitis B. Presented at: European Association for the Study of the Liver (EASL): June 5-8, 2024; Milan, Italy. LBP-022. **3.** Van Cott A, et al. PBGENE-HBV: definitive preclinical toxicokinetic and toxicology data enables advancement to clinical trials for a potentially curative gene editing treatment for chronic hepatitis B. Presented at: Global Hepatitis Summit (GHS); March 18-21, 2025; Los Angeles, CA. 30267. **4.** Yuen MF, et al. PBGENE-HBV, a first-in-class gene editing therapy for chronic hepatitis B, demonstrates safety and antiviral activity in early cohorts. Presented at: Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 7-11, 2025; Washington, DC. 5017. **5.** Hu J, et al. Hepatitis B virus reverse transcriptase and ε RNA sequences required for specific interaction in vitro. *J Virol*. 2006;80(5):2141-2150. **6.** Jones SA, et al. Comparative analysis of hepatitis B virus polymerase sequences required for viral RNA binding, RNA packaging, and protein priming. *J Virol*. 2014;88(3):1564-1572. **7.** Bartenschlager R, et al. The P gene product of hepatitis B virus is required as a structural component for genomic RNA encapsidation. *J Virol*. 1990;64(11):5324-5332. **8.** Chen Y, et al. Selected mutations of the duck hepatitis B virus P gene RNase H domain affect both RNA packaging and priming of minus-strand DNA synthesis. *J Virol*. 1994;68(8):5232-5238. **9.** Terrault N, et al. Hepatitis B virus RNA as a biomarker for safe antiviral discontinuation: a prospective study of nucleos(t)ide analogue withdrawal. *J Infect Dis*. 2025;231:1290-1298.

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