AASLD 2025 Publication Number: 5017

PBGENE-HBV, a First-in-class Gene Editing Therapy for Chronic Hepatitis B, Demonstrates Safety and Antiviral Activity in Early Cohorts

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November 10, 2025

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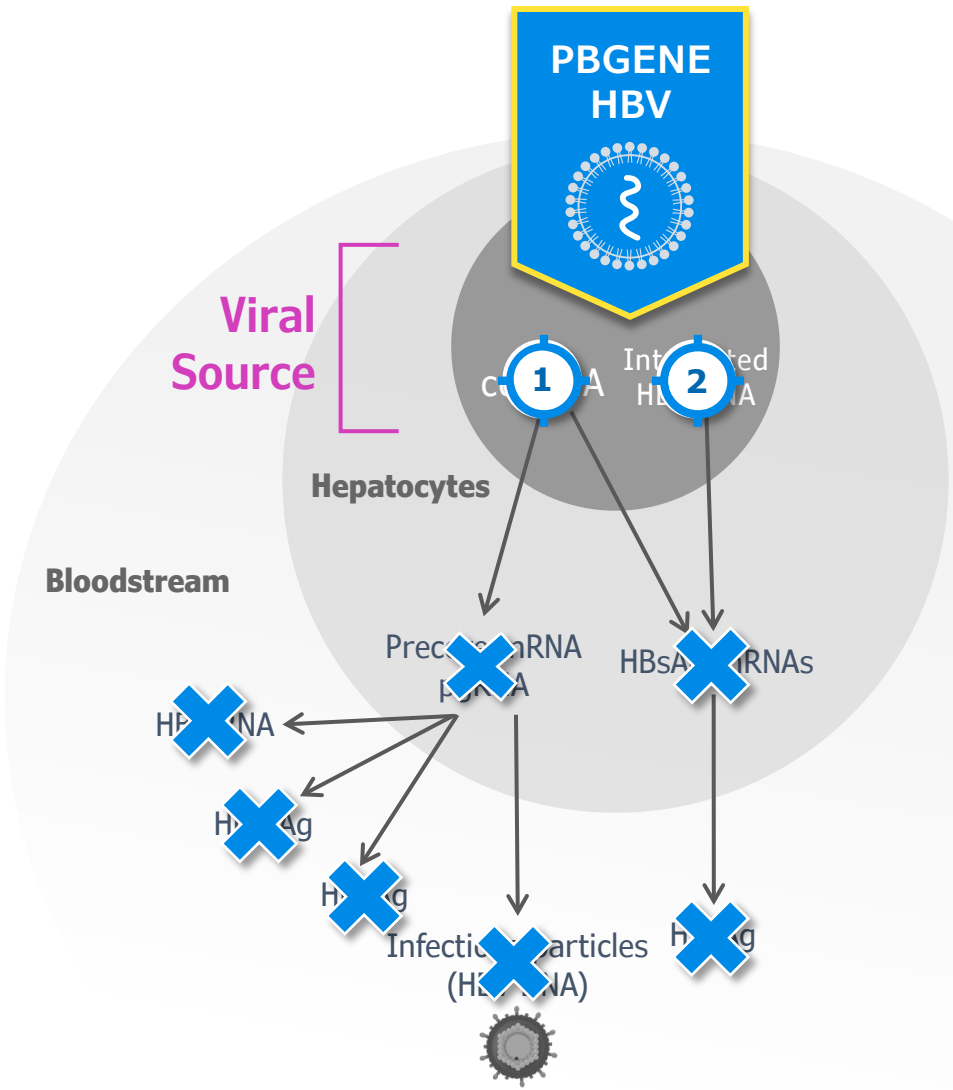
- **Advisory committee member:**
  Aligos Therapeutics, AiCuris, Arbutus Biopharma, Clear B Therapeutics, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Roche, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology and Visirna Therapeutics
- **Speaker:**
  Aligos Therapeutics, Fujirebio Incorporation, Gilead Sciences, GlaxoSmithKline, Roche and Sysmex Corporation
- **Research grants:**
  AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Fujirebio Incorporation, Gilead Sciences, Immunocore, Precision Biosciences, Sysmex Corporation and Roche

HBV Cure Requires a Novel Approach Targeting the Viral Replication Source

Eliminating cccDNA has a Clear Biologic Rationale for Cure

- ① Eliminates cccDNA
- ② Inactivates Integrated HBV DNA through insertions and deletions
- ✖ Treatment at the Source of the Viral Pathway Results in Reductions of Downstream Markers



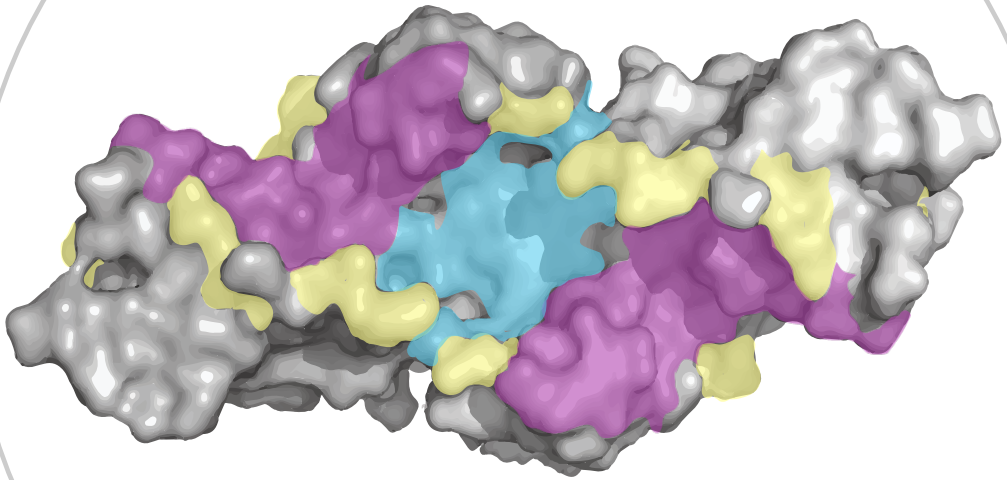
"The ideal therapeutic strategy for curative approaches includes reduction or elimination of the whole cccDNA pool."

—Ligat et al. 2020

PBGENE-HBV is uniquely designed to achieve a complete cure by eliminating cccDNA and inactivating integrated DNA at the source of HBV, preventing the chance of viral relapse

cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; mRNA, messenger RNA; NUCs, nucleos(t)ide analogs; pgRNA, pregenomic RNA; RNA, ribonucleic acid; siRNA, small interfering RNA.

PBGENE-HBV:
First in Class Gene Editor Designed To Eliminate cccDNA and Inactivate Integrated HBV DNA



ARCUS protein with DNA interface in color

PBGENE-HBV is a lipid nanoparticle (LNP) delivered mRNA encoding an ARCUS gene editing nuclease that uniquely eliminates the root cause of HBV with curative intent

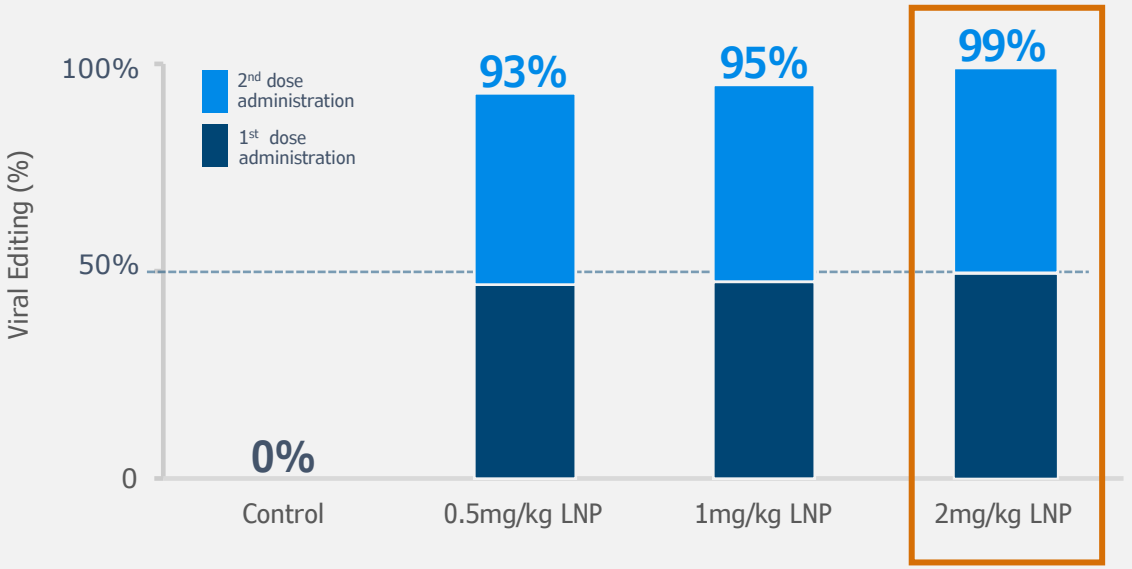
- PBGENE-HBV specifically recognizes a highly conserved target sequence within the in the Enhancer 1 element present in both cccDNA and integrated HBV DNA
- Proprietary ARCUS nuclease is ideal for HBV
  - Small size enables delivery efficiency and accessibility to cccDNA
  - Single component gene editor enables direct interaction with cccDNA
- PBGENE-HBV preclinical safety:
  - specificity with no increased risks of translocations or integrations with multiple administrations
  - No adverse changes in NHPs over multiple administrations with rapid clearance after each dose administration

Lipid nanoparticle technology for PBGENE-HBV has been provided by Acuitas Therapeutics Inc.

PBGENE-HBV Preclinical Data Demonstrates cccDNA Elimination and integrated HBV DNA Inactivation

cccDNA Elimination (NHP AAV Model)

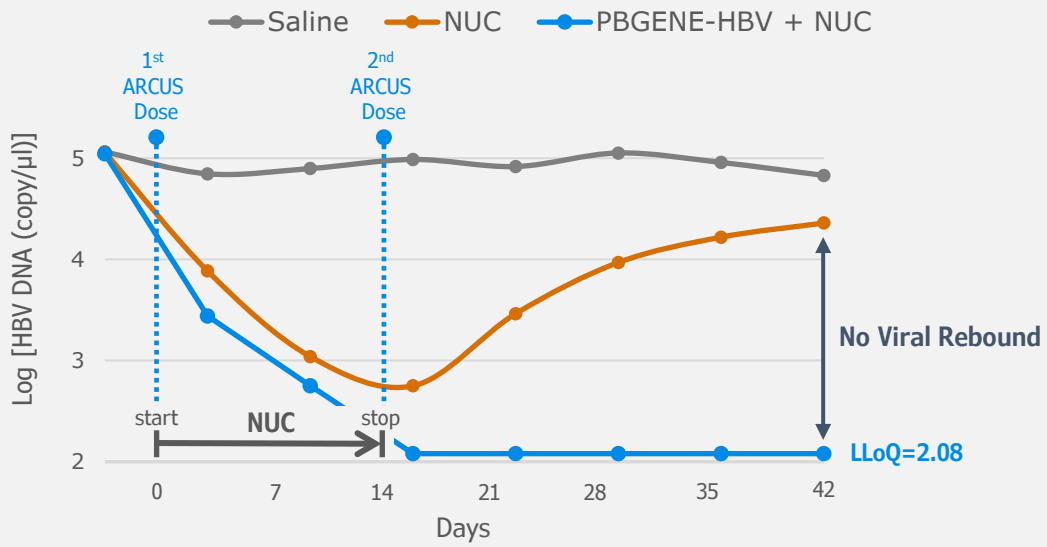
Cumulative editing with 99% viral editing after two doses



~50% viral editing after 1 dose and up to 99% viral editing with 2nd dose in NHP model where AAV is used as a surrogate for cccDNA

Integrated HBV DNA Inactivation (HBV Transgenic Mouse Model)

Significant HBV DNA reduction with no viral rebound



Sustainable reduction of HBV DNA in HBV transgenic mouse model

PBGENE-HBV shows cccDNA elimination and integrated HBV DNA inactivation with multiple administrations

Notes: Final optimized candidate nuclease derived from prior optimized nuclease - only one amino acid difference with similar efficacy
LLoQ=lower limit of quantitation; LNP=lipid nanoparticle; NHP=nonhuman primate; NUC=nucleos(t)ide analog; AAV=adeno-associated virus

Phase 1 Study to Evaluate Safety and Antiviral Activity of PBGENE-HBV in HBeAg Negative Patients With Chronic Hepatitis B

(NCT06680232) Objectives

Primary Objective:

- To evaluate the safety of PBGENE-HBV in participants with Chronic Hepatitis B (CHB)

Secondary Objectives:

- To further evaluate the safety and tolerability of PBGENE-HBV in participants with CHB
- To evaluate the pharmacokinetics (PK) of PBGENE-HBV in participants with CHB
- To evaluate the antiviral activity of PBGENE-HBV in participants with CHB

Phase 1 Study to Evaluate Safety and Antiviral Activity of PBGENE-HBV in HBeAg Negative Patients With Chronic Hepatitis B

(NCT06680232) Endpoints

Primary Endpoint

Safety determined by:

- Frequency and severity of dose-limiting toxicities (DLTs)

DLT Definition

A **DLT** is defined as any organ-specific, treatment-emergent adverse event (AE) ≥ Grade 3 that does not decrease to ≤ Grade 2 within 7 days and is related to study medication.

- Isolated, asymptomatic laboratory or ECG abnormalities that do not meet the above criteria do not necessarily fulfill this DLT criterion.
- ALT flares will only be considered as a DLT if the ALT Flare Committee determines so

DLT Period: 28 days post dose administration.

Secondary Endpoints

Additional safety determined by:

- Frequency and severity of adverse events and changes in physical examinations, vital signs, and safety labs (hematology, chemistry, and urinalysis)
- Pharmacokinetic parameters of PBGENE-HBV determined by: AUC, Tmax, Cmax, Cmin, and t1/2

Efficacy determined by:

- Change from baseline in:
  - HBsAg and anti-HBs levels
  - hepatitis B virus (HBV) DNA and HBV RNA levels
- Proportion of participants who:
  - Can discontinue nucleos(t)ide analog (NA) therapy
  - Achieve functional cure[1] or partial cure

Key Inclusion / Exclusion Criteria

Inclusion Criteria

- HBeAg-negative cHBV (~80% patients on NUCs[1])
- cHBV infection documented by serum HBsAg-positivity for ≥ 12 months
- Serum HBsAg ≥200 IU/mL at screening with no upper limit
- Virologically suppressed and currently on nucleos(t)ide analog treatment
  - HBV DNA < 20 IU/mL at screening and on one occasion at least 6 months prior
- Serum ALT ≤ 1.5× ULN
- Have a FibroScan™ liver stiffness measurement ≤8.5 kPa within 6 months prior to screening or at the time of screening

Exclusion Criteria

- No history of liver cirrhosis regardless of any subsequent improvement in histology
- No hepatitis A virus infection, hepatitis D virus infection, hepatitis E virus infection, HIV type 1 or type 2 infection, and no history or current hepatitis C infection
- Must not have any evidence of liver disease of non-HBV etiology or evidence of decompensation at any time point prior to or at the time of screening
- Must not have signs of hepatocellular carcinoma
- No prior investigational agents within 6 months of screening except for siRNA therapeutics, which cannot have been administered within 1 year of screening

1. Chan HLY, et al. Long-term treatment with tenofovir alafenamide for chronic hepatitis B results in high rates of viral suppression and favorable renal and bone safety. Am J Gastroenterol. 2024;119(3):486-496.

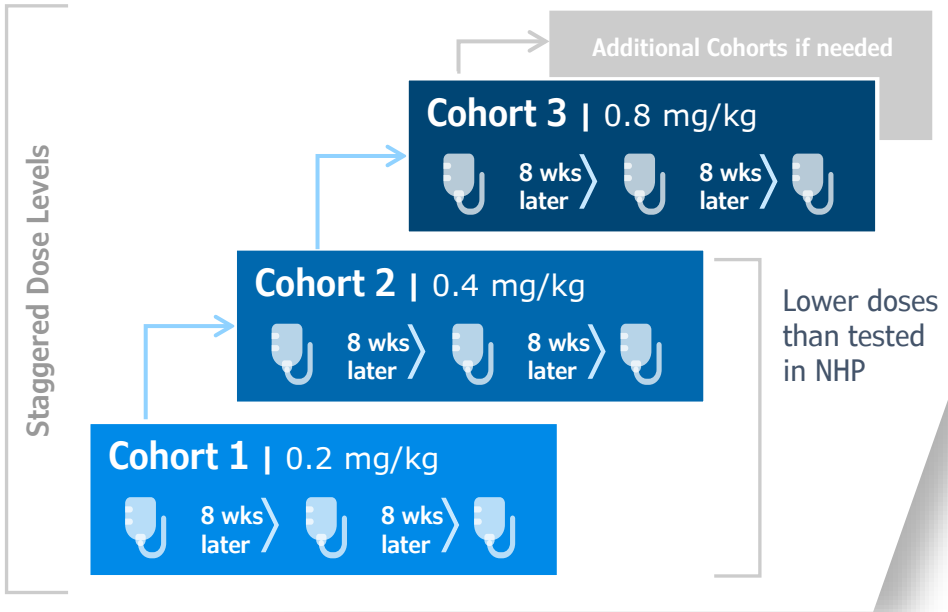
Phase 1 Study Design (NCT06680232)

Part 1: Multiple Ascending Dose Escalation

Finite Treatment: Patient receives up to 3 dose administrations

HBeAg negative patients on NUCs

N=3 dosed at each cohort



Safety & Efficacy Evaluation

Part 2: Dose Expansion

Advance optimized dose and schedule to eliminate cccDNA and drive cure

Go Forward Dose

Optimal
- Dose level
- Number of doses
- Time between doses

N = Up to 45 patients total across both Part 1 and 2 of Phase 1 study

GOAL: Establish a finite treatment course enabling stopping NUCs and cure

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; mg/kg, milligram per kilogram; N, total number of patients; NHP, non-human primate; NUCs, nucleos(t)ide analogs; wks, weeks.

Demographics and Baseline Characteristics

Sex	Number	Percent
Male	10	100
Ethnicity/Race		
Caucasian	5	50
Asian	4	40
Native Hawaiian or Other Pacific Islander	1	10

	Mean	Range
Age (years)	51	39 - 66
Time with HBV (years)	22	7 - 39
Time on NUCs (years)	10	4 - 25
Baseline HBsAg (IU/mL)	2,217*	370 - 11,813

*HBsAg levels representative of HBeAg negative patients on NUCs: In U.S. and Europe[1,2] 86% of patients have HBsAg < 3,000 IU/mL and **66% of patients have HBsAg < 1,000 IU/mL**. In Asia[3] 98% of patients have HBsAg < 3,000 IU/mL and **73% of patients have HBsAg < 1,000 IU/mL**.

1. RETRACT-B Study – European and USA subgroup analysis; Jeng WJ, Papatheodoridi M, Lok ASF, et al. Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study). Gastroenterology. 2022;162(3):757-771.e4. doi:10.1053/j.gastro.2021.11.002
2. Triangulated with GSK 2023 Epidemiology Report based on secondary research and not real-world patient data
3. Large-scale profile study on hepatitis B surface antigen levels in chronic hepatitis B: implications for drug development targeting functional cure," published online August 5, 2025, Gut; Rex Wan-Hin Hui, Lung-Yi Mak, Ka-Shing Cheung, James Fung, Wai-Kay Seto, and Man-Fung Yuen.

PBGENE-HBV Safety: Treatment Related Adverse Events

Patients Experiencing Treatment Related Adverse Events

Events Occurring in at Least 2 Patients or ≥ Grade 3 (n =10)

Preferred Term	All Grades (%)	Grade 3 (%)
Pyrexia	9 (90)	0 (0)
Chills	8 (80)	0 (0)
Headache	6 (60)	0 (0)
Myalgia	5 (50)	0 (0)
Dizziness	3 (30)	0 (0)
Hypotension	4 (40)	4 (40)
Sinus tachycardia	3 (30)	0 (0)
Vomiting	3 (30)	0 (0)
Rigors	3 (30)	0 (0)
Fatigue	2 (20)	0 (0)
Drug hypersensitivity	1 (10)	1 (10)
Aspartate aminotransferase increased	1 (10)	1 (10)

No DLTs have been observed across all 22 doses given

AEs were transient and generally resolved within 12 hours

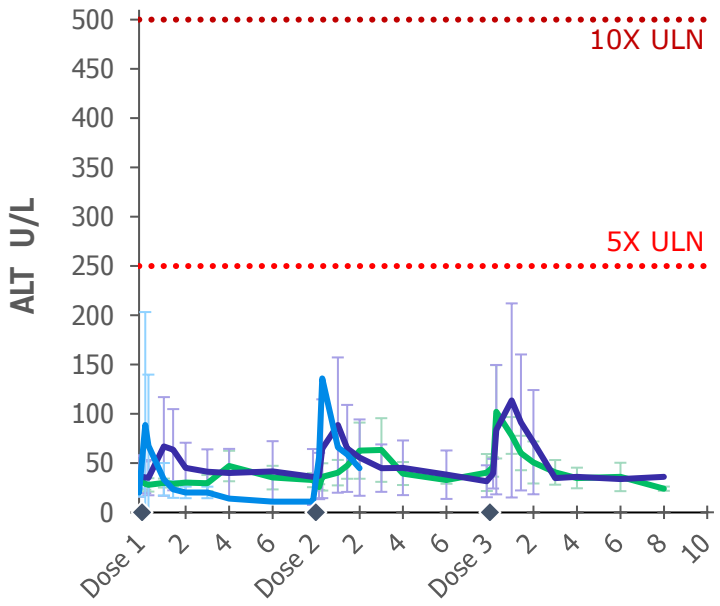
Grade 3 AST elevation resolved within ~3 days; was reviewed by independent ALT Flare Committee and deemed not dose-limiting. Hypotension events resolved in <24 hours post dosing.

AEs were consistent with infusion related reactions and were predictable and manageable

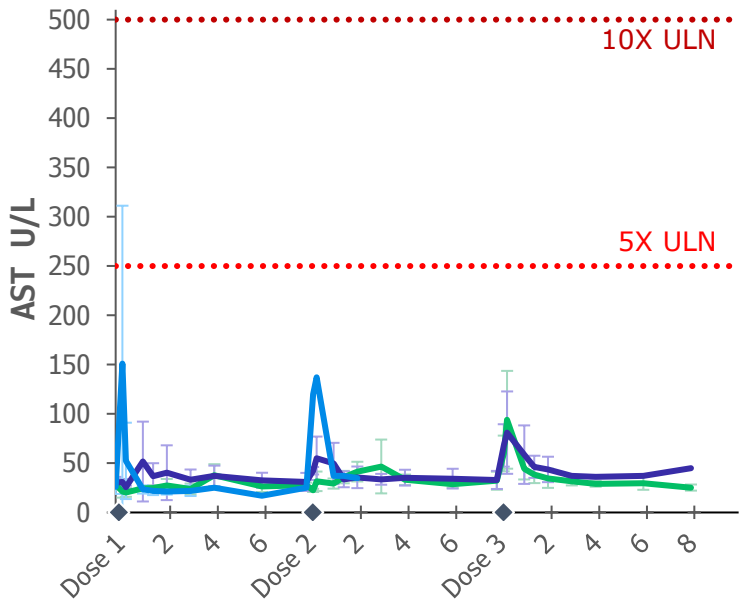
*One participant did not complete dosing due to a transient, reversible infusion reaction. The DMC did not deem this to be dose-related or dose-limiting.
ALT/AST elevations graded per DAIDS criteria (Grade 2 = 2.5–5× ULN, Grade 3 = 5–10× ULN, Grade 4 = >10× ULN).
1. Hypotension was transient, occurring immediately after PBGENE-HBV infusion, and responsive to IV normal saline.
AE, adverse event; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; HBV, hepatitis B virus; SAE.

SAFETY: PBGENE-HBV Hepatic Safety Lab Results Across cohorts

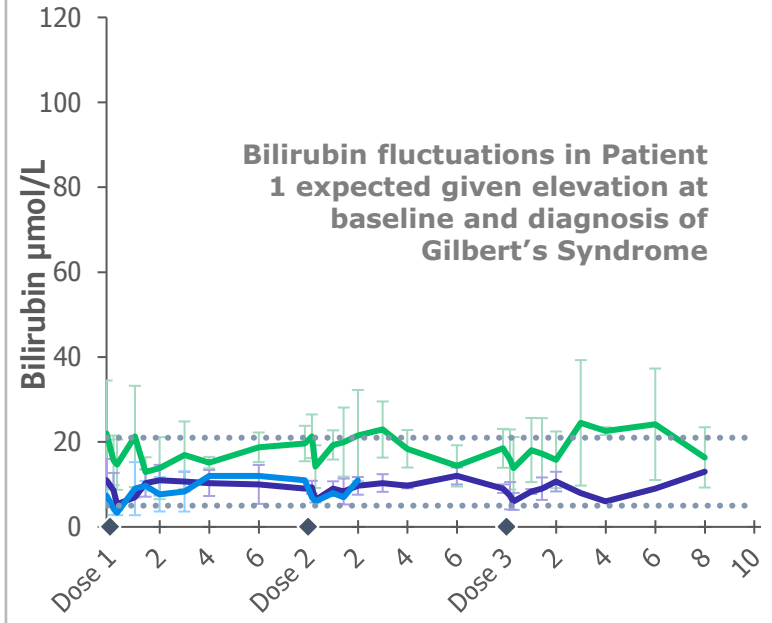
ALT elevations <5X ULN with no sustained elevations



Transient AST elevations resolved quickly



Bilirubin fluctuations near normal range



Cohort 1 — Cohort 2 — Cohort 3 ◆ Dosing ····· Reference Range

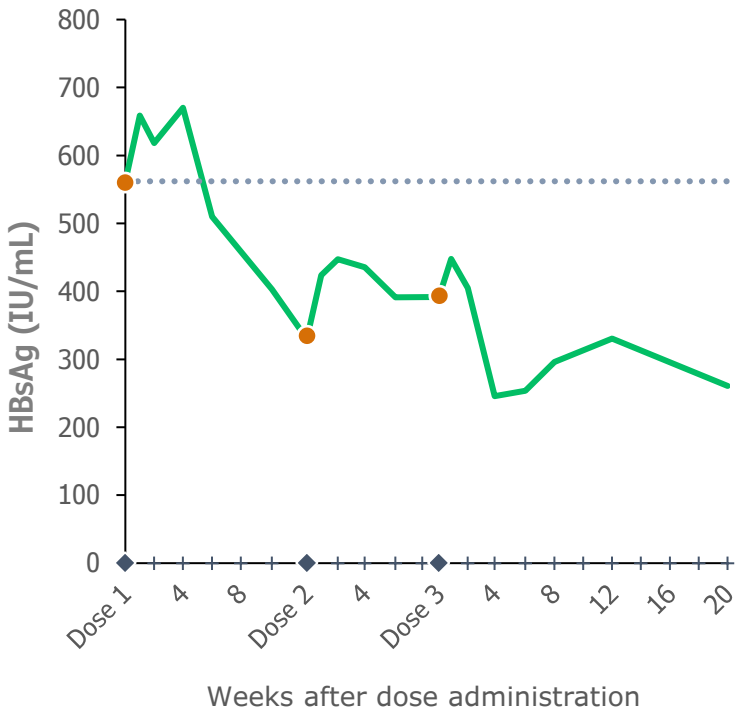
- Transaminase elevations were transient with no associated changes in bilirubin and no evidence of liver dysfunction
- No changes in transaminases outside of normal limits after 8 weeks post 3rd administration

Platelet fluctuations have been **transient and asymptomatic**

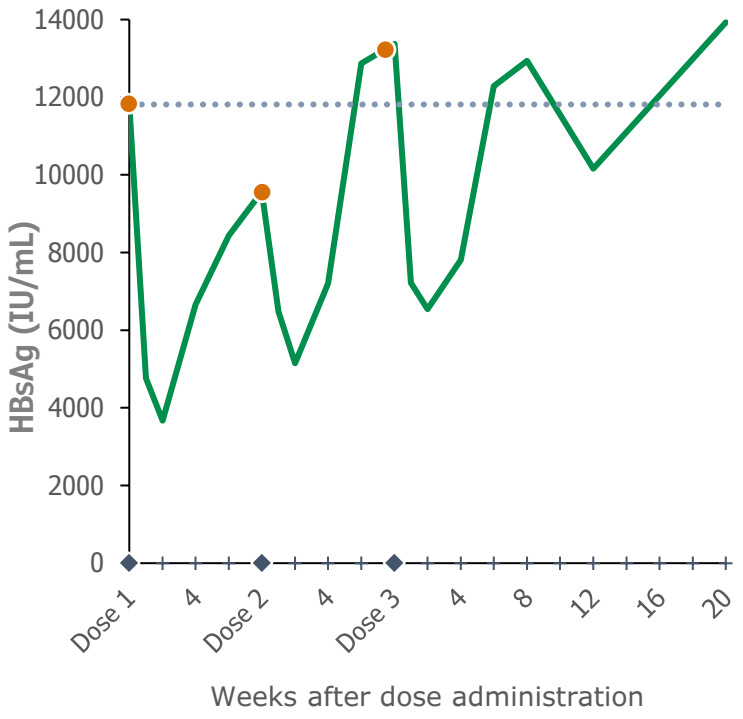
ALT, alanine aminotransferase; AST, aspartate aminotransferase; L, liter; LNP, lipid nanoparticle; U, unit; ULN, upper limit of normal; µmol, micromole.
Data shown represent mean +/- standard deviation. ULN ranges across labs: ALT: 45-58 U/L, AST: 38-50 U/L, Bilirubin: 21-25 µmol/L

EFFICACY: PBGENE-HBV HBsAg Results for Cohort 1 (0.2 mg/kg)

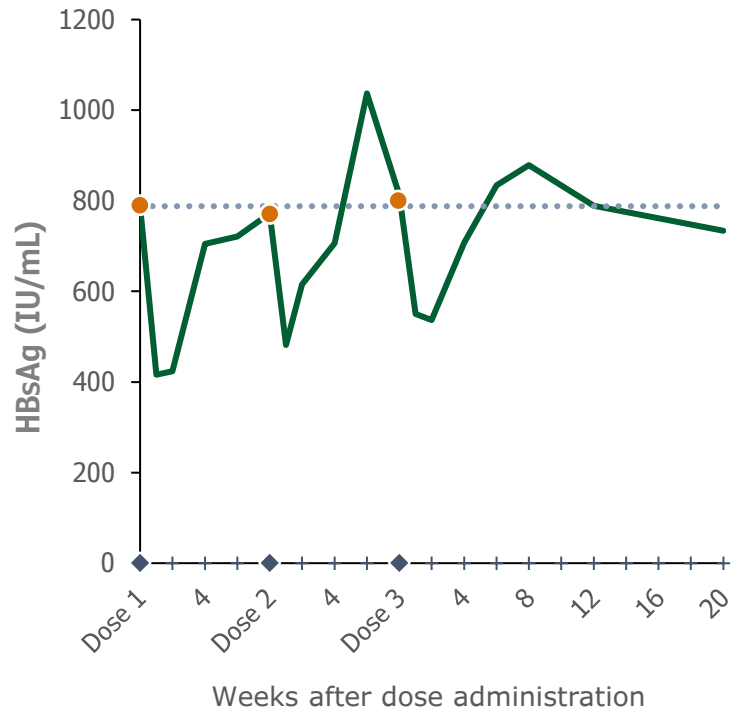
Patient 1
(Deepest HBsAg reduction: 56%, 0.36log)



Patient 2
(Deepest HBsAg reduction: 69%, 0.51log)



Patient 3
(Deepest HBsAg reduction: 47%, 0.28log)



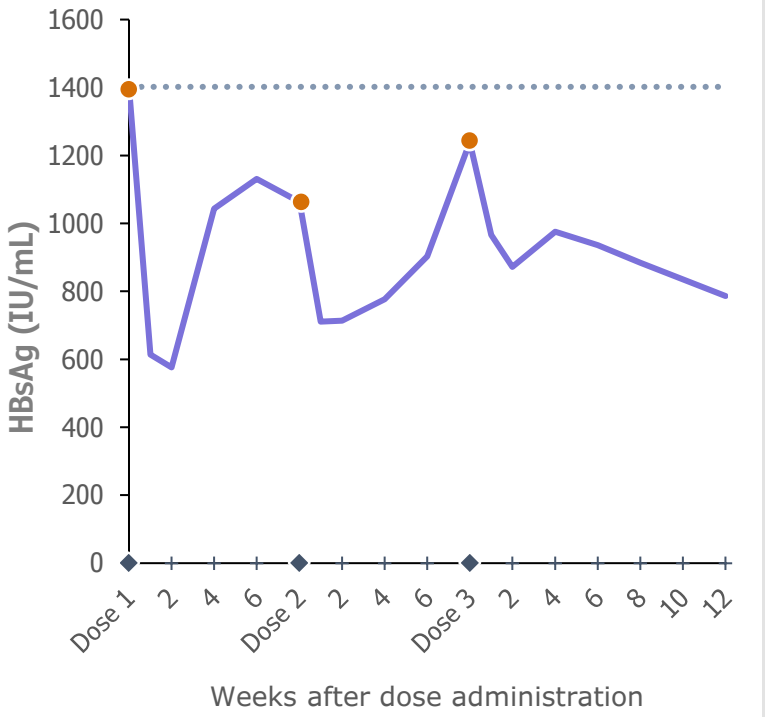
Base Line

At 0.2 mg/kg All Patients Showed Activity and One Showed Durable HBsAg reductions

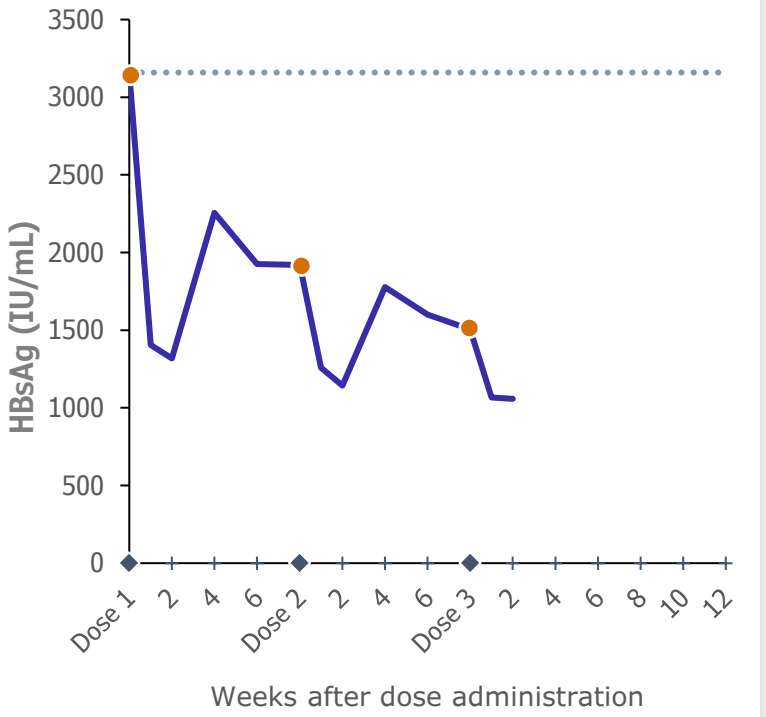
DNA, deoxyribonucleic acid; EASL, European Organization for Hepatology; HBsAg, Hepatitis B surface antigen; IU, international units; mg/kg, milligram per kilogram; NUCs, nucleo(t)side analogs.

EFFICACY: PBGENE-HBV HBsAg Results for Cohort 2 (0.4 mg/kg)

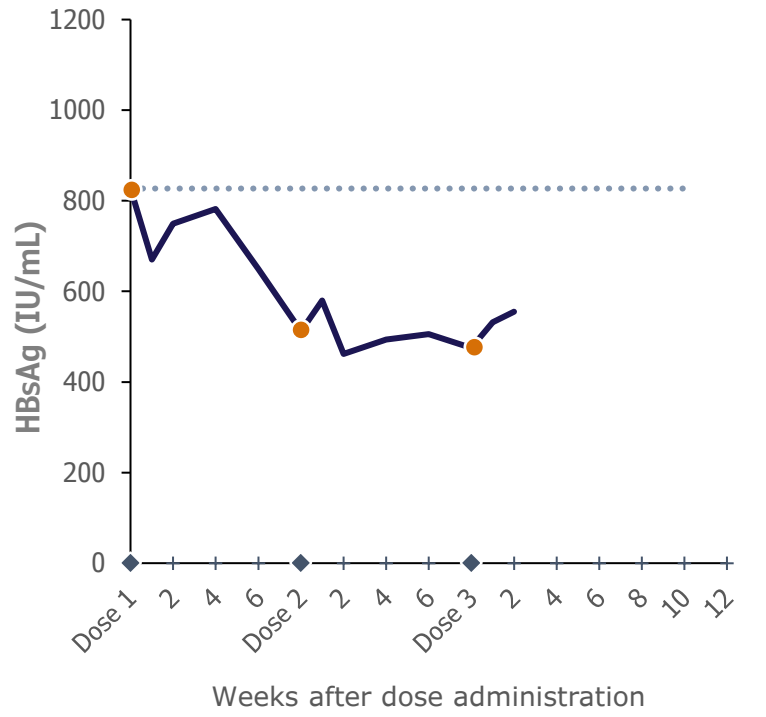
Patient 4
(Deepest HBsAg reduction: 59%, 0.39log)



Patient 5
(Deepest HBsAg reduction: 66%, 0.47log)



Patient 6
(Deepest HBsAg reduction: 44%, 0.25log)



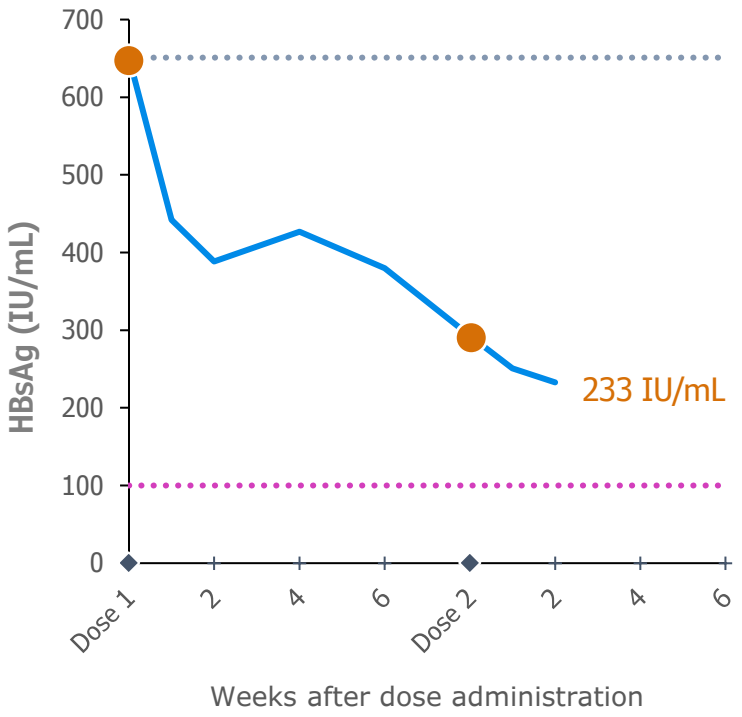
Base Line

At 0.4 mg/kg All Patients Demonstrated Persistent Antiviral Activity

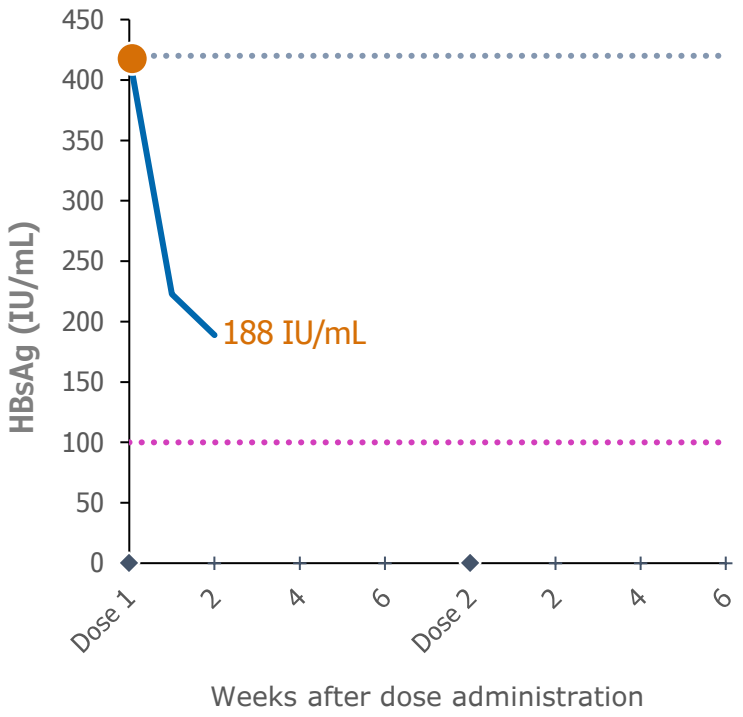
DNA, deoxyribonucleic acid; HBsAg, Hepatitis B surface antigen; IU, international units; mg/kg, milligram per kilogram; NUCs, nucleo(t)side analogs.

EFFICACY: PBGENE-HBV HBsAg Results for Cohort 3 (0.8 mg/kg)

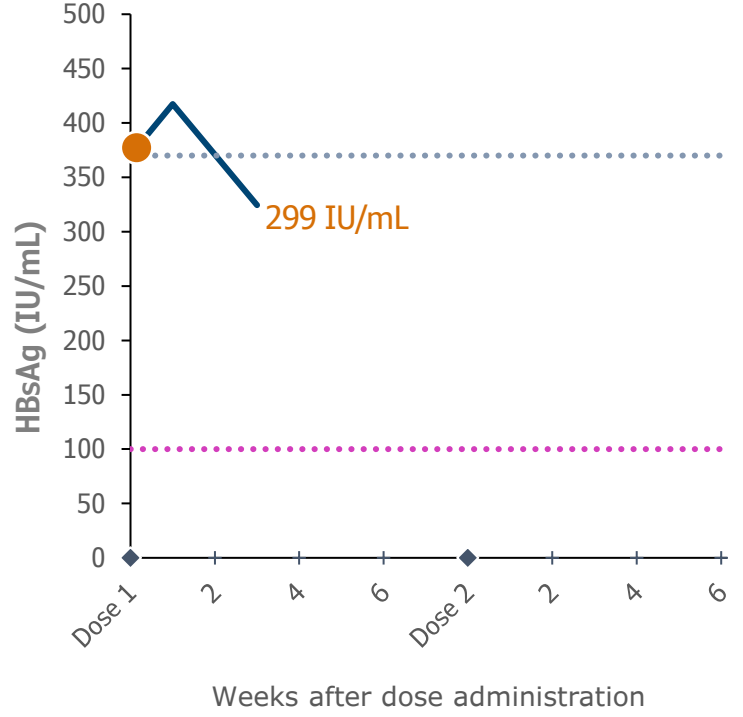
Patient 7
(Deepest HBsAg reduction: 62%, 0.41log)



Patient 8
(Deepest HBsAg reduction: 55%, 0.35log)



Patient 9
(Deepest HBsAg reduction: 19%, 0.09log)



Base Line Consider Stopping NUCs

At 0.8 mg/kg Further Dose Dependent Antiviral Effects Emerging

Interim day 21 HBsAg data was collected for patients 8 and 9 but not for patient 7 or any patients in prior cohorts. That data, which awaits final confirmation from the clinical lab, shows a similar trend to patient 7 between days 14 and 28 after the first administration.

EASL, European Organization for Hepatology; HBsAg, Hepatitis B surface antigen; IU/mL, international units per milliliter; NUCs, nucleo(t)side analogs.

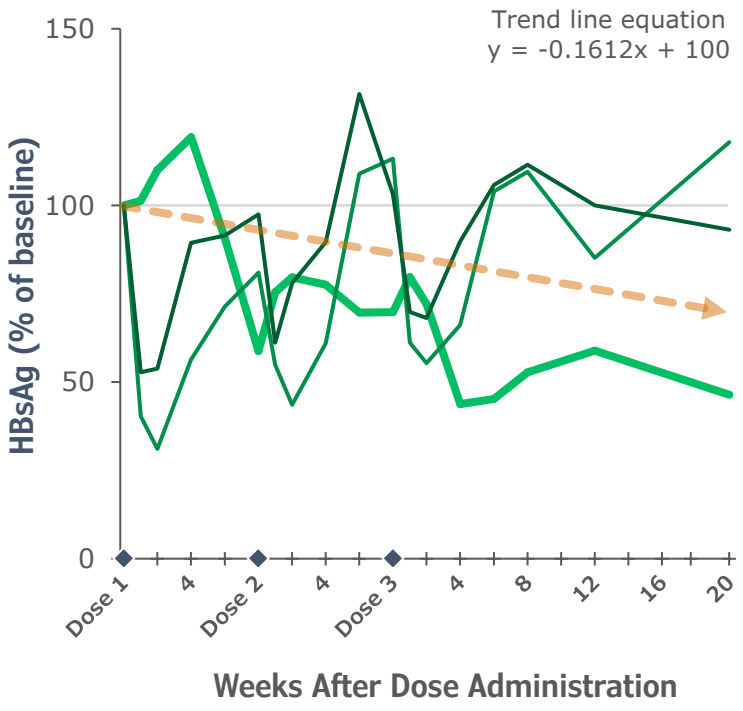
EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatology. 2025;83(2):502-583.

Efficacy: PBGENE-HBV HBsAg Lab Results Across Cohorts

Cohort 1 | 0.2 mg/kg

Activity in 3 of 3 patients

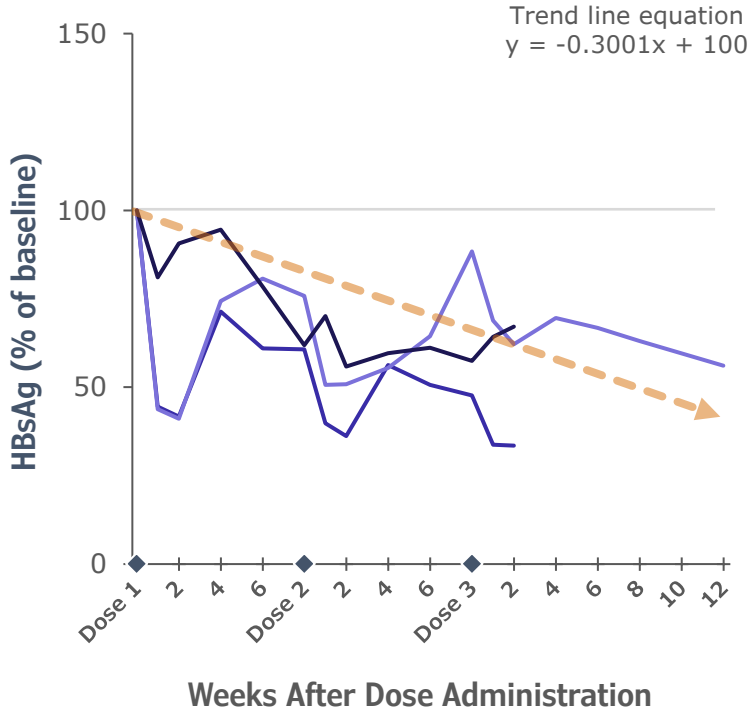
Durable response in 1 of 3 patients



Cohort 2 | 0.4 mg/kg

Activity in 3 of 3 patients

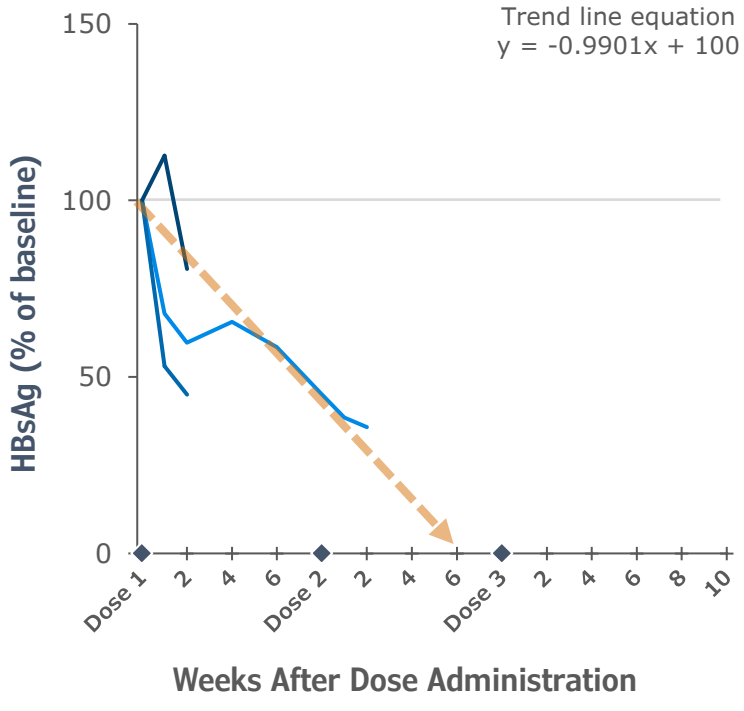
Durable response in 3 of 3 patients



Cohort 3 | 0.8 mg/kg

Activity in 3 of 3 patients

Dose dependent effect established

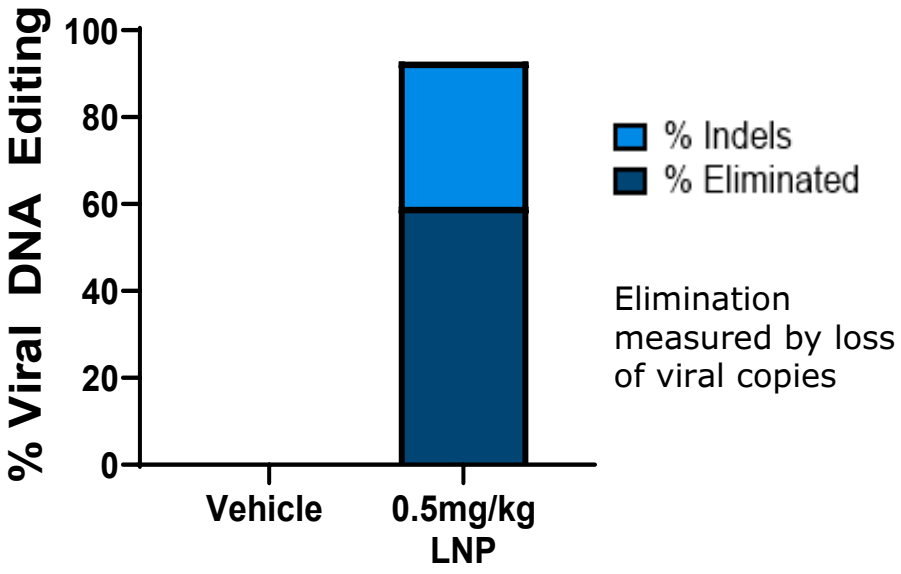


Cohort 1: Patient 1 — Patient 2 — Patient 3 **Cohort 2:** Patient 4 — Patient 5 — Patient 6 **Cohort 3:** Patient 7 — Patient 8 — Patient 9 ◆ Dosing — Baseline → Trendline

Interim day 21 HBsAg data was collected for patients 8 and 9 but not for patient 7 or any patients in prior cohorts. That data, which awaits final confirmation from the clinical lab, shows a similar trend to patient 7 between days 14 and 28 after the first administration.
HBsAg, hepatitis B surface antigen; mg/kg, milligram per kilogram.

Proof of Mechanism: Evidence of PBGENE-HBV editing viral DNA

Preclinical NHP Viral DNA Editing
(Two Admins at 0.5 mg/kg)



Clinical Biopsy Data from Patient #5
(Two Admins at 0.4 mg/kg)

Inactivation with indels in remaining viral DNA	**28%**
Elimination of viral DNA	**Data pending** (pgRNA and cccDNA quantitation)

Preclinical data demonstrates viral DNA elimination is primary outcome after editing with PBGENE-HBV, elimination data from clinical sample is pending assay validation

*Preclinical NHP data showed 92% total viral DNA editing (indels + elimination) after 2 administrations at 0.5 mg/kg. Assay development underway for clinical biopsy evaluation of viral DNA elimination.
cccDNA, covalently closed circular DNA; indels, insertions and deletions; mg/kg, milligram per kilogram; HBV, hepatitis B virus; W, week. IU/mL, international units per milliliter.

Conclusions

Safety:

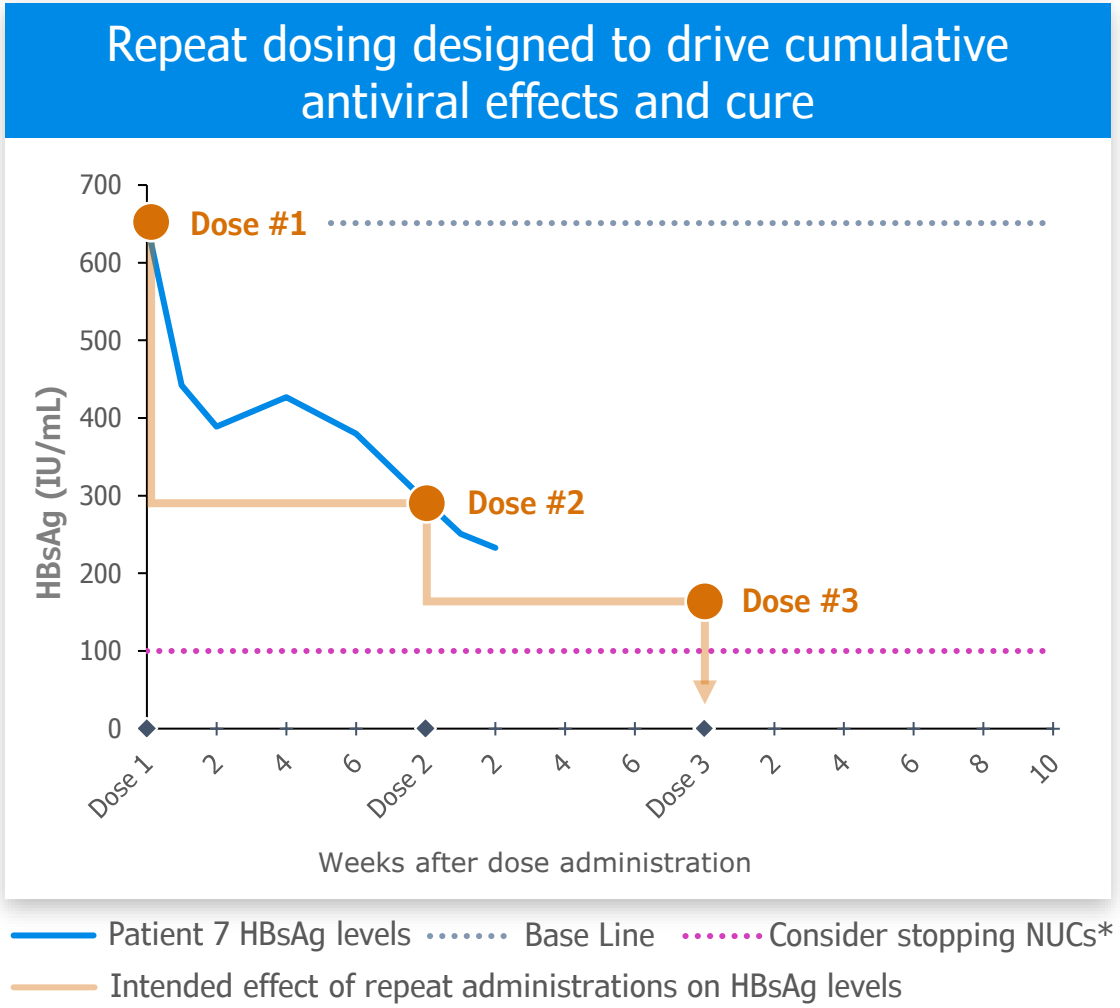
- PBGENE-HBV at doses as high as 0.8 mpk administered every 8 weeks has not resulted in a DLT in the initial 3 dose cohorts tested
- Repeat administrations were well tolerated

Efficacy:

- Antiviral activity was demonstrated after PBGENE-HBV treatment in all patients
- Dose responsive durability was consistently observed across all cohorts, with promising early results at 0.8 mg/kg
- HBV DNA remained suppressed in all patients
- First clinical proof of gene editing in Hepatitis B achieved with PBGENE-HBV confirmed with biopsy

Next Steps:

- Continue dosing optimization to determine ideal dose level and interval for stopping NUCs with the goal of developing a finite curative regimen for Hepatitis B and commencing expansion in Part 2 of ELIMINATE-B



HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU/mL, international units per milliliter; NUCs, nucleo(t)side analogs.
*EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatology.* 2025;83(2):502-583.

We thank the study **participants**, **investigators**, and **clinical site staff** for their participation and support in the ELIMINATE-B study. We also acknowledge the important contributions of the clinical operations and other functional teams, as well as our partners in the HBV field who have shared valuable insights on the trial design.

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