Safety, Tolerability, Immunogenicity, and Antiviral Efficacy of GS-2829 and GS-6779, a Novel, Arenaviral-Vectored, Therapeutic Hepatitis B Vaccine: Results From a Phase 1b Study in Virally Suppressed Patients With Chronic Hepatitis B

Edward J Gane[1], Chi-Yi Chen[2], Tsung-Hui Hu[3], Ching-Chu Lo[4], Pin-Nan Cheng[5], Tung-Hung Su[6], Ming-Lung Yu[7], Frida Abramov[8], Dana Tedesco[8], Mario Cortese[8], David Z Pan[8], Scott Balsitis[8], Teri Chew[8], Sarah Arterburn[8], Christopher Richards[8], Anu O Osinusi[8], Wen-Juei Jeng[9,10], Yao-Chun Hsu[11]

[1]University of Auckland, Auckland, New Zealand; [2]Division of Gastroenterology and Hepatology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan; [3]Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, St. Martin De Porres Hospital, Chiayi City, Taiwan; [5]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [6]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [7]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [8]Gilead Sciences, Inc., Foster City, CA, USA; [9]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou, Taiwan; [10]College of Medicine, Chang Gung University, Taoyuan, Taiwan; [11]Department of Medical Research, E-Da Hospital, School of Medicine, I-Shou University, Kaohsiung, Taiwan

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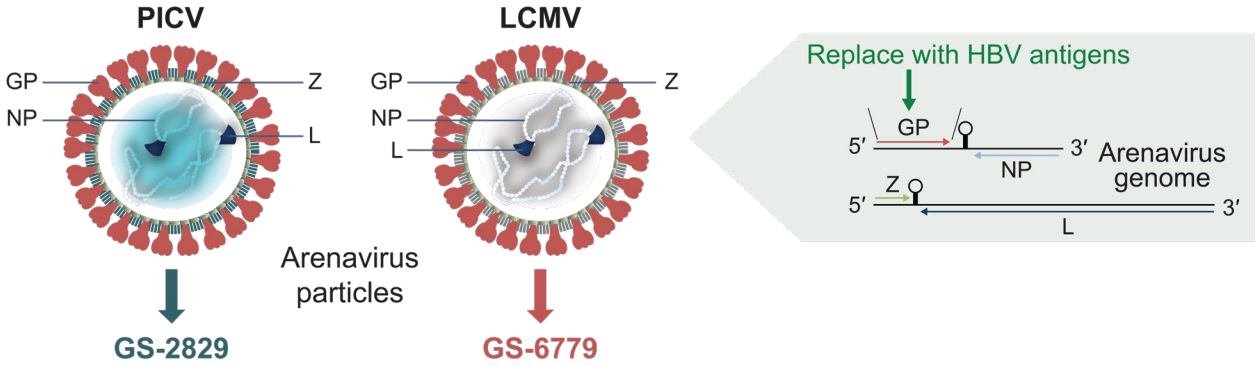
Background

- CHB remains a global health challenge,[1] with current therapies rarely achieving functional cure—defined as sustained loss of HBsAg and HBV DNA <LLOQ off therapy[2]
- Therapeutic vaccines represent a promising approach to boost HBV-specific immune responses, which may be an essential component of HBV cure regimens[3]

CHB, chronic hepatitis B; **HBV**, hepatitis B virus; **HBsAg**, hepatitis B surface antigen; **LLOQ**, lower limit of quantitation.

1. Wong GLH, et al. *J Hepatol*. 2025;82:918-25. **2**. Ghany MG, et al. *Hepatology*. 2023;78:1654-73. **3**. Feld JJ, et al. *Clin Gastroenterol Hepatol*. 2023;21:2040-50.

Background



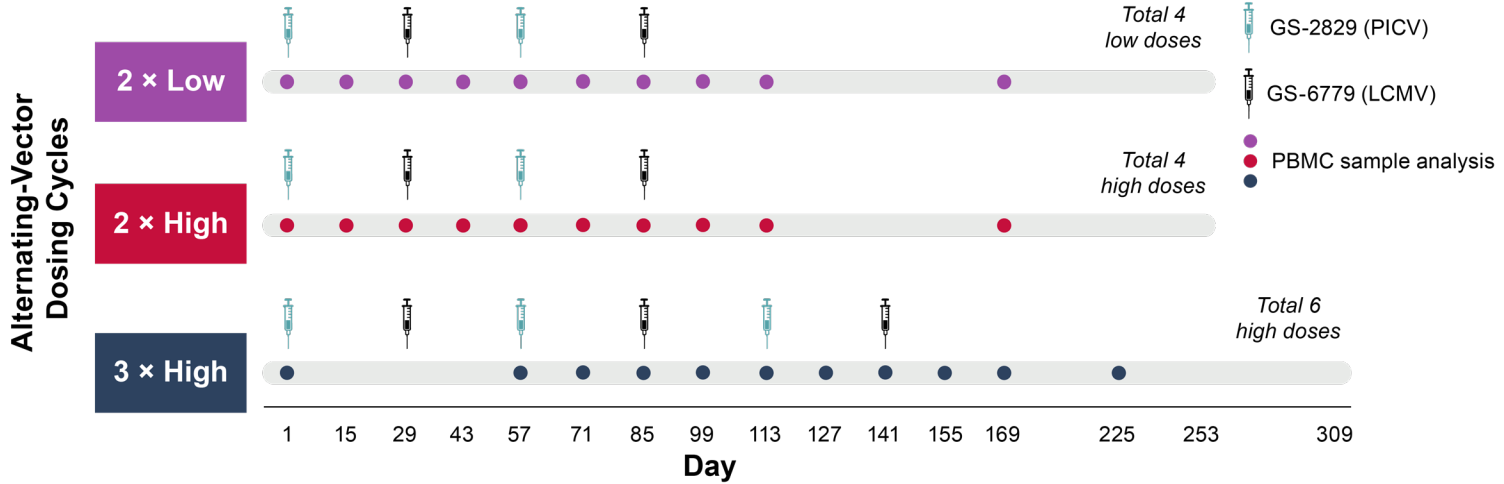
- GS-2829 (PICV) and GS-6779 (LCMV) are nonreplicating arenaviral-vectored vaccines engineered to deliver conserved HBV antigens (HBsAg, HBcAg, and pol)
- In healthy adults, alternating doses of GS-2829 and GS-6779 were safe and well tolerated, and induced robust HBV-specific T-cell responses without anti-vector neutralization[1]

GP, glycoprotein; **HBV**, hepatitis B virus; **HBcAg**, hepatitis B core antigen; **HBsAg**, hepatitis B surface antigen; **L**, RNA-dependent RNA polymerase; **LCMV**, lymphocytic choriomeningitis virus; **NP**, nucleoprotein; **PICV**, Pichinde virus; **pol**, polymerase reverse transcriptase and ribonuclease H domains; **Z**, matrix protein.

1. Gane EJ, et al. *J Hepatology*. 2025;82(S1):S831.

Objective and Study Design

- **Objective:** Safety, tolerability, immunogenicity, and antiviral efficacy of GS-2829 and GS-6779
- **Design:** Randomized (4:1), blinded, placebo-controlled, Phase 1b study (NCT05770895) conducted in New Zealand and Taiwan



- **Population:**
  - Adults with virally suppressed CHB without cirrhosis
  - HBsAg >LLOQ and ≤5000 IU/mL
  - ALT <3 × ULN

For both GS-2829 and GS-6779, low doses were ≥0.5 × 10^6 FFU, and high doses were ≥0.5 × 10^7 FFU.
ALT, alanine aminotransferase; **CHB**, chronic hepatitis B; **FFU**, focus-forming units; **HBsAg**, hepatitis B surface antigen; **LCMV**, lymphocytic choriomeningitis virus; **LLOQ**, lower limit of quantitation; **PBMC**, peripheral blood mononuclear cell; **PICV**, Pichinde virus; **ULN**, upper limit of normal.

Endpoints

Safety: AEs and laboratory abnormalities

Virologic and Serologic Response:

- Evaluated change from baseline in HBcrAg and HBsAg levels in all patients and HBeAg levels in HBeAg-positive patients
- Development of HBsAg antibodies and HBeAg antibodies to confirm seroconversion

HBV-specific T-Cell Analysis:

- Immunogenicity evaluated via IFNγ ELISpot
- Polyfunctionality assessed by flow cytometry via intracellular cytokine staining

AE, adverse event; **ELISpot,** enzyme-linked immunosorbent spot analysis; **HBcrAg**, hepatitis B core-related antigen; **HBeAg**, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **IFN**, interferon.

Baseline Demographic and Disease Characteristics

Parameter	GS-2829 + GS-6779			Placebo
	2 × Low (n = 8)	2 × High (n = 8)	3 × High (n = 8)	(n = 6)
Age, years, median (min, max)	57 (41, 59)	45 (28, 56)	45 (37, 62)	51 (30, 56)
Sex, male, n (%)	5 (63)	5 (63)	7 (88)	2 (33)
Race, Asian, n (%)	8 (100)	8 (100)	8 (100)	6 (100)
BMI, kg/m^2, median (Q1, Q3)	22.5 (19.1, 24.1)	25.6 (23.2, 27.1)	24.5 (23.0, 29.4)	22.6 (20.7, 24.8)
HBsAg, IU/mL, median (min, max)	1579 (1, 3737)	863 (1, 3725)	401 (25, 2260)	1079 (7, 1931)
HBeAg positive, n (%)	0	7 (88)	4 (50)	2 (33)
HBV DNA <LLOQ[a], n (%)	7 (88)	7 (88)	8 (100)	6 (100)
HBV genotype, n (%)				
B	4 (50)	4 (50)	3 (38)	2 (33)
C	2 (25)	2 (25)	4 (50)	3 (50)
Unclassified	2 (25)	2 (25)	1 (13)	1 (17)
ALT, U/L, median (Q1, Q3)	15 (14, 23)	21 (17, 34)	28 (17, 30)	17 (14, 24)
Prior interferon, n (%)	2 (25)	0	0	0

[a]All patients had HBV DNA <LLOQ at screening, as it was an inclusion criterion (LLOQ = 10 IU/mL).

ALT, alanine aminotransferase; **BMI**, body mass index; **HBeAg**, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **LLOQ**, lower limit of quantitation; **max**, maximum; **min**, minimum; **Q**, quartile.

Overall Safety Summary – Adverse Events

Adverse Events, n (%)	GS-2829 + GS-6779			Placebo (n = 6)
	2 × Low (n = 8)	2 × High (n = 8)	3 × High (n = 8)	
Any AE	6 (75)	5 (63)	6 (75)	3 (50)
Any AE related to study drug	4 (50)	3 (38)	5 (63)	2 (33)
Any Grade ≥3 AE, SAE, or death	0	0	0	0
Any AE leading to premature d/c	0	0	0	0
Common AEs (≥2 in any cohort)				
Injection-site reaction[a]	3 (38)	3 (38)	3 (38)	2 (33)
Fatigue	3 (38)	3 (38)	3 (38)	1 (17)
Headache	2 (25)	1 (13)	1 (13)	2 (33)
Malaise	1 (13)	1 (13)	3 (38)	1 (17)
Myalgia	2 (25)	2 (25)	2 (25)	0
Cough	0	3 (38)	1 (13)	1 (17)
Arthralgia	2 (25)	0	1 (13)	0
COVID-19	0	0	0	2 (33)

[a]Injection-site reactions included pain, swelling, erythema, and induration.
AE, adverse event; **d/c**, discontinuation; **SAE**, serious adverse event.

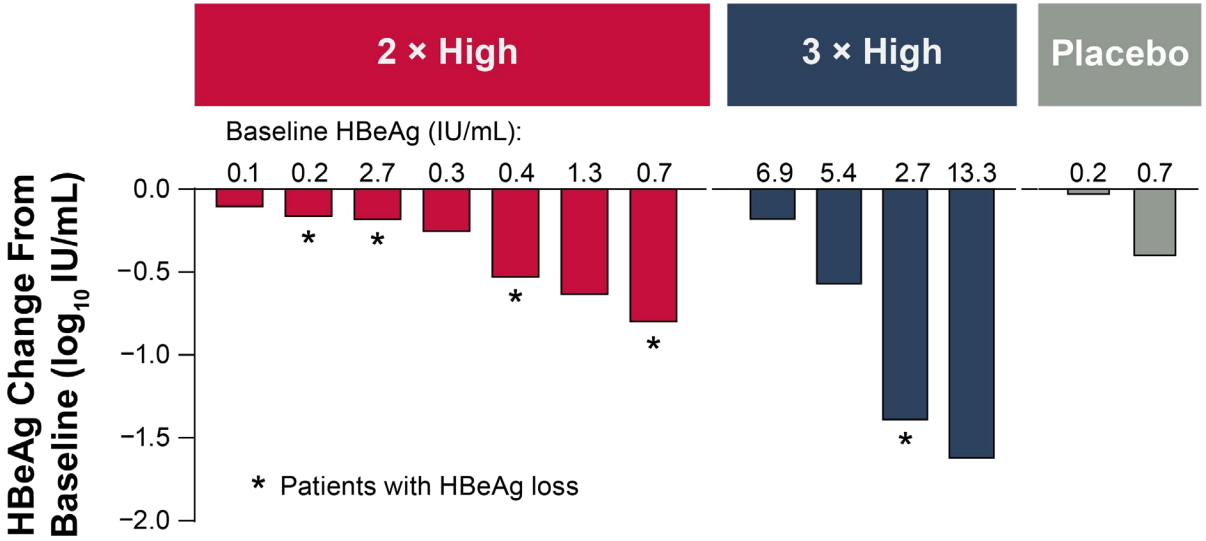
Overall Safety Summary – Laboratory Abnormalities

Patients, n (%)	GS-2829 + GS-6779			Placebo (n = 6)
	2 × Low (n = 8)	2 × High (n = 8)	3 × High (n = 8)	
Any Grade ≥1 postbaseline value	7 (88)	8 (100)	8 (100)	6 (100)
Grade 1	4 (50)	5 (63)	6 (75)	5 (83)
Grade 2	2 (25)	3 (38)	1 (13)	1 (17)
Grade 3	1 (13)	0	1 (13)	0
Grade 4	0	0	0	0

- Grade 3 abnormalities were observed in 2 patients:
  - Creatine kinase elevation (2 × low): patient reported increased exercise or physical activity prior to blood sampling
  - Lymphocyte count decline (3 × high): patient had Grade 2 lymphopenia at screening

Patients were counted once at their highest-grade laboratory abnormality.

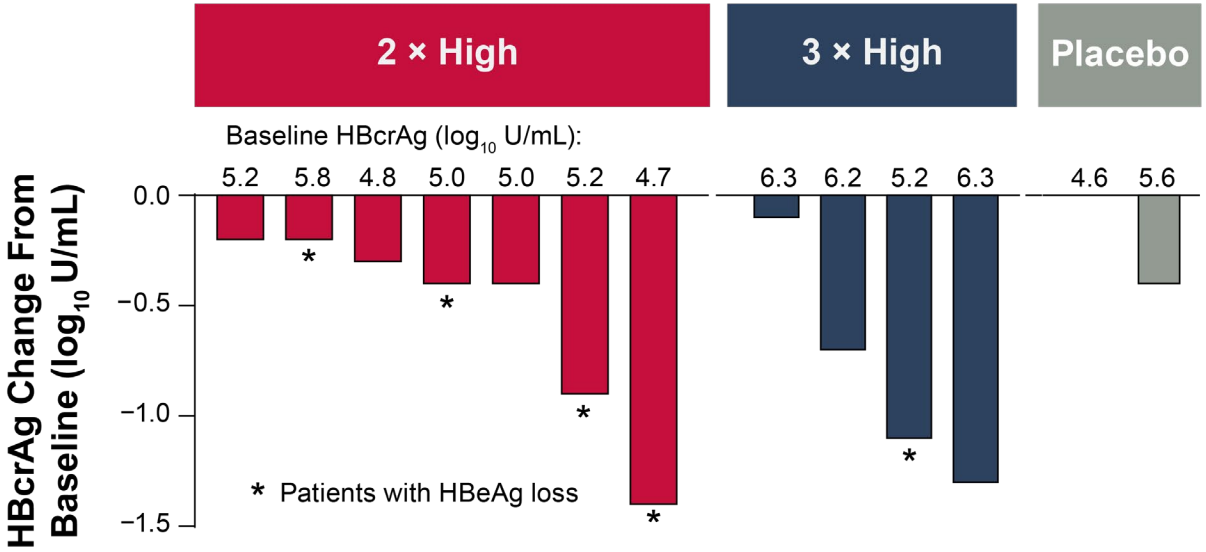
Maximum qHBeAg Decline From Baseline in HBeAg-Positive Patients (n = 13)



- All HBeAg-positive patients in high-dose cohorts showed declines in qHBeAg
- Five of 11 (45%) HBeAg-positive patients in high-dose cohorts lost HBeAg and developed anti-HBe
  - — One patient (3 × high) lost anti-HBe but remained HBeAg negative
  - — One patient (2 × high) had HBeAg seroreversion but remained anti-HBe positive

anti-HBe, hepatitis B e antigen antibody; **HBeAg**, hepatitis B e antigen; **qHBeAg**, quantitative hepatitis B e antigen.

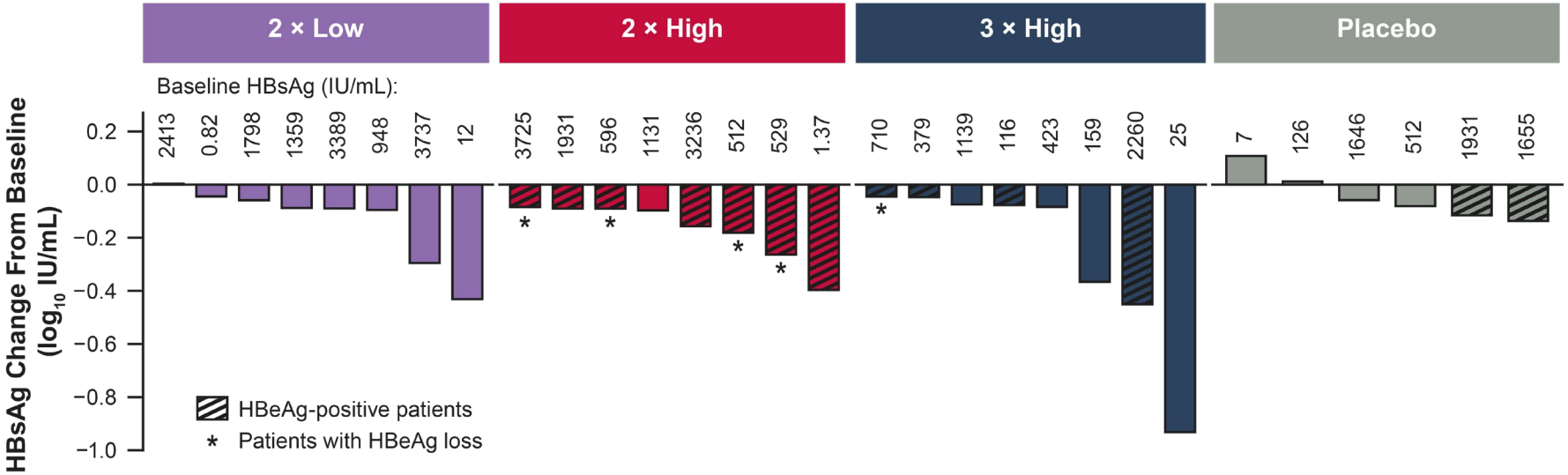
Maximum HBcrAg Decline From Baseline in HBeAg-Positive Patients (n = 13)



- All HBeAg-positive patients in high-dose cohorts showed declines in HBcrAg

HBcrAg, hepatitis B core-related antigen; **HBeAg**, hepatitis B e antigen.

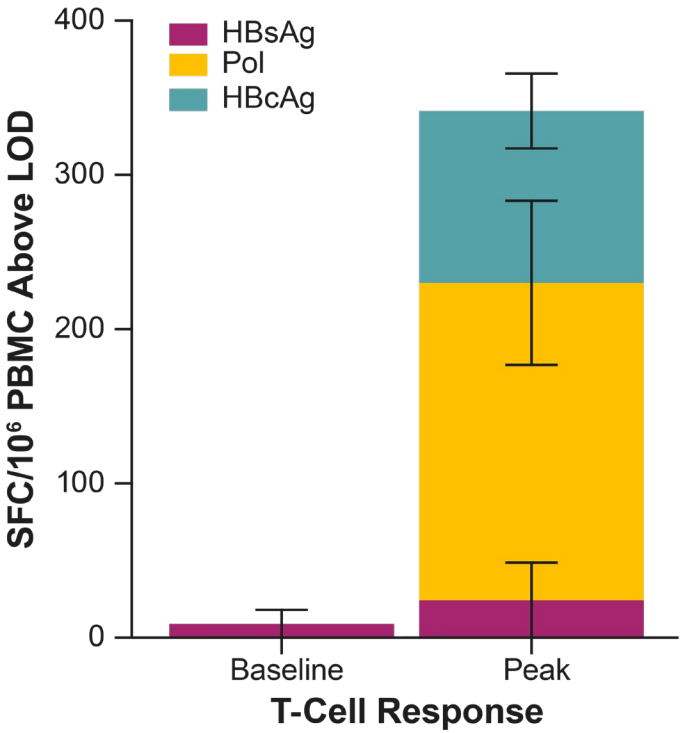
Maximum HBsAg Decline From Baseline in All Patients (n = 30)



- HBsAg declines were observed for all patients in the high-dose cohorts
- No patients achieved HBsAg loss

ALT, alanine aminotransferase; **HBeAg**, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen.

Combined HBV-Specific T-Cell Responses in High-Dose Cohorts

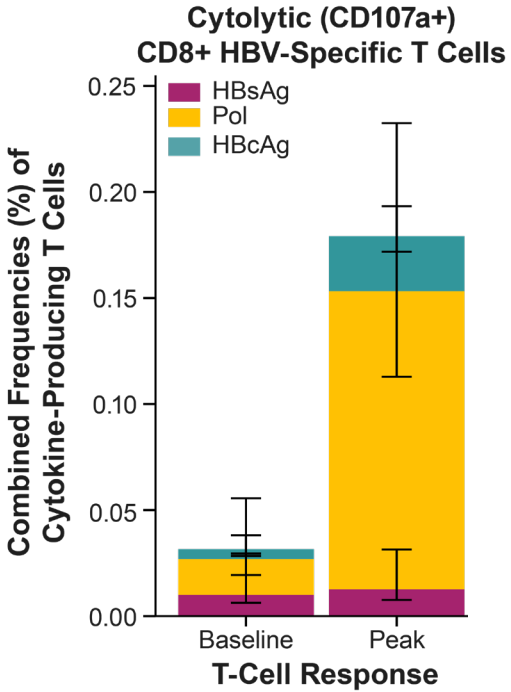


- GS-2829 and GS-6779 induced increases in HBV-specific, IFNγ-producing, T-cell responses, as measured by ex vivo ELISpot
- The majority of the HBV-specific T-cell response was directed against HBcAg and pol peptide pools

Data represent the mean ± SE for ex vivo HBV-specific T-cell responses above the LOD (49 SFC/10^6 PBMC per peptide pool) at baseline and peak for patients on active treatment in the 2 × high and 3 × high cohorts; baseline, n = 16; peak response, n = 16. **ELISpot,** enzyme-linked immunosorbent spot analysis; **HBcAg**, hepatitis B core antigen; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **IFN**, interferon; **LOD**, limit of detection; **PBMC**, peripheral blood mononuclear cells; **pol**, polymerase reverse transcriptase and ribonuclease H domains; **SFC**, spot-forming cells.

Cytokine-Producing CD8+ T Cells at Baseline and at Peak Response in High-Dose Cohorts

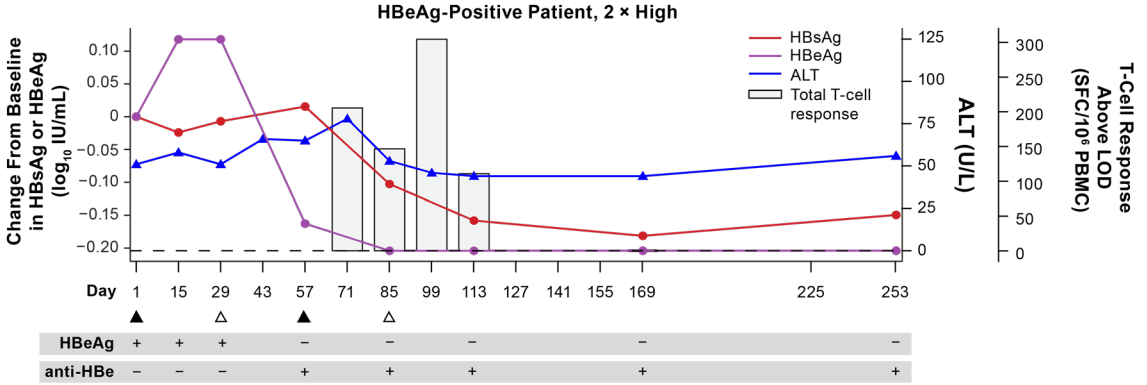
- Administration of GS-2829 and GS-6779 resulted in the generation of HBV-specific CD8+ T cells with increased cytolytic (CD107a+) capacity and high polyfunctionality



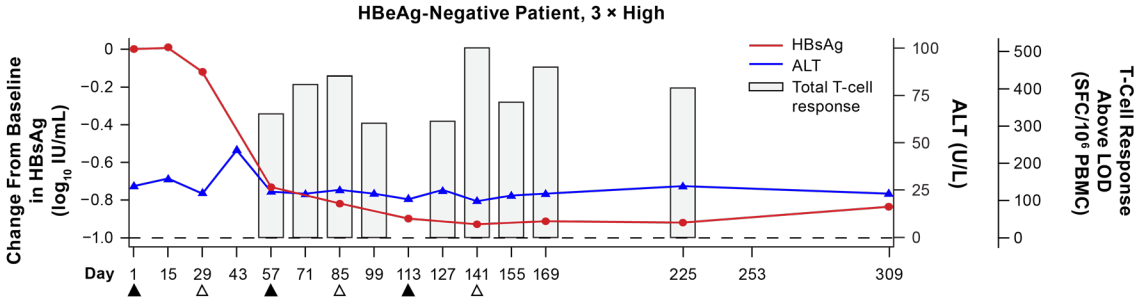
At baseline, n = 15; at peak response, n = 15. T cell responses from patients with CHB were grouped based on the expression of CD107a, alone or in combination with IFNγ, IL-2, and TNFα. The bar and pie charts represent the median frequency of cytokine-producing HBV-specific T cells. **CD**, cluster of differentiation; **CHB**, chronic hepatitis B; **HBcAg**, hepatitis B core antigen; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **IFN**, interferon; **IL**, interleukin; **pol**, polymerase reverse transcriptase and ribonuclease H domains; **TNF**, tumor necrosis factor.

Example Cases: HBV-Specific T-Cell Response in an HBeAg-Positive and an HBeAg-Negative Patient

- **HBeAg-positive patients:** HBV-specific T-cell responses often coincided with antigen declines and mild ALT increases, supporting immune-mediated antiviral activity



- **HBeAg-negative patients:** A similar pattern of T-cell response was observed in HBeAg-negative patients



Light gray bars indicate total HBV-specific T-cell response. The dashed line indicates 0 for the total HBV-specific T-cell response axis, which is the sum of HBsAg, HBcAg, and pol-specific T-cell responses above LOD (49 SFC/10^6 PBMC per peptide pool). Black and white arrows represent administration of GS-2829 and GS-6779, respectively. **ALT**, alanine aminotransferase; **anti-HBe**, hepatitis B e antigen antibody; **HBcAg**, hepatitis B core antigen; **HBeAg**, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **LOD**, limit of detection; **PBMC**, peripheral blood mononuclear cells; **pol**, polymerase reverse transcriptase and ribonuclease H domains; **SFC**, spot-forming cells.

Key Takeaways

- Alternating doses of GS-2829 and GS-6779 were safe and well tolerated in virally suppressed patients with CHB
- High-dose vaccination induced HBV-specific immune responses, accompanied by reductions in HBV antigens and mild ALT increases, indicating that the vaccine is targeting transcriptionally active cccDNA-positive hepatocytes
- GS-2829 and GS-6779 will be combined with other novel therapies to achieve a functional cure for patients with CHB

ALT, alanine aminotransferase; **cccDNA**, covalently closed circular DNA; **CHB,** chronic hepatitis B; **HBV**, hepatitis B virus.

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- Correspondence: Edward J Gane, MD, FAASLD, EdGane@adhb.govt.nz