Baseline and On-Treatment Characteristics of HBeAg-Positive Patients and Correlates of HBeAg Loss Following GS-2829 and GS-6779 Therapeutic Vaccination in Virally Suppressed Patients With Chronic Hepatitis B

WED-580

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Viral Hepatitis B and D: New Therapies, Unapproved Therapies or Strategies

Conclusions

- In this Phase 1b cohort, high-dose GS-2829 + GS-6779 treatment resulted in a substantial rate of hepatitis B e antigen (HBeAg) loss accompanied by characteristic immunologic changes among virally suppressed HBeAg-positive patients with chronic hepatitis B (CHB)
  - The emergence of hepatitis B core antigen (HBcAg)-specific T-cell responses in patients with HBeAg loss and/or reduction may reflect potential links between antigen clearance and immune restoration
- Declines in viral antigens, including HBeAg and hepatitis B core-related antigen (HBcrAg), were observed among all HBeAg-positive patients treated with high-dose GS-2829 + GS-6779, whereas hepatitis B surface antigen (HBsAg) declines were variable and did not consistently parallel HBeAg loss. All patients who lost HBeAg did so in a consistent pattern by day 85 of study treatment
- These findings support further evaluation of GS-2829 + GS-6779 as part of combination strategies aimed at achieving functional cure in patients with CHB

Plain Language Summary

- Some patients with chronic hepatitis B who received the investigational vaccines GS-2829 + GS-6779 achieved hepatitis B e antigen loss, an important marker of antiviral activity
- Patients who lost or had decreased levels of hepatitis B e antigen showed stronger responses from a subset of hepatitis B virus–specific immune cells
- While several viral markers were reduced, clearance of hepatitis B surface antigen did not occur
- These findings support the continued study of GS-2829 + GS-6779 as part of future combination treatment approaches for patients with chronic hepatitis B

References: **1.** Lampertico P, et al. *Lancet Gastroenterol Hepatol.* 2020;5:441-53. **2.** Chan HLY, et al. *Lancet Gastroenterol Hepatol.* 2016;1(3):185-95. **3.** Chang T-T, et al. *N Engl J Med.* 2006;354(10):1001-10. **4.** Marcellin P, et al. *N Engl J Med.* 2008;359(23):2442-55. **5.** Gane EJ, et al. Poster presented at AASLD: The Liver Meeting; November 7–11, 2025; Washington, DC, USA. Poster 0197.

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Introduction

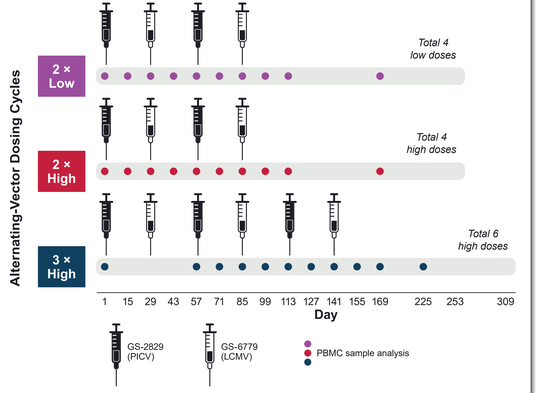
- HBeAg loss is an important milestone towards functional cure (defined as sustained loss of HBsAg and undetectable hepatitis B virus [HBV] DNA after treatment discontinuation) of CHB
- With current first-line oral nucleos(t)ide analogue therapy, HBeAg loss occurs in approximately 6% to 8% of virally suppressed patients and in 12% to 22% of viraemic patients after 1 year of oral antiviral treatment in Phase 3 studies, while HBsAg loss is rare (≤3%)[1-4]
- In a Phase 1b study, 5 of 11 (45%) HBeAg-positive patients treated with high-dose GS-2829 + GS-6779 exhibited a consistent pattern of HBeAg loss by day 85, with concurrent declines in HBeAg and HBcrAg, and vaccine-elicited immune responses; however, no patients achieved functional cure[5]

Objective

- To identify differences in baseline characteristics and immunologic changes in HBeAg-positive patients enrolled in a Phase 1b study by treatment group (where applicable) and on-treatment HBeAg status up to posttreatment week 24

Methods

Study Design



For both GS-2829 and GS-6779, low doses were ≥0.5 × 10^8 FFU, and high doses were ≥0.5 × 10^7 FFU.
FFU, focus-forming units; LCMV, lymphocytic choriomeningitis virus; PBMC, peripheral blood mononuclear cell; PICV, Pichinde virus.

- A randomised (4:1), blinded, placebo-controlled, Phase 1b study (NCT05770895) was conducted in New Zealand and Taiwan to evaluate the safety, tolerability, immunogenicity, and antiviral efficacy of GS-2829 + GS-6779
- Population:
  - Adults with virally suppressed CHB without cirrhosis
  - HBsAg greater than the lower limit of quantitation (0.05 IU/mL) and ≤5000 IU/mL
  - Alanine aminotransferase <3 × the upper limit of normal
- Enrolment was not restricted by HBeAg status; this subanalysis includes patients who were HBeAg positive at baseline
- Baseline characteristics and on-treatment changes in quantitative HBeAg, HBsAg, and HBcrAg levels and HBV-specific T-cell responses (ex vivo interferon gamma enzyme-linked immunosorbent spot [ELISpot]) were assessed through posttreatment week 24 using descriptive statistics
- Among HBeAg-positive patients randomized to active treatment, all 11 (100%) were enrolled in high-dose GS-2829 + GS-6779 cohorts; no HBeAg-positive patients were randomised to low-dose treatment. HBeAg-positive pooled placebo patients were included as a comparator where relevant (n = 2)
- HBeAg loss was defined as a change from HBeAg positive at baseline to negative at any postbaseline visit. HBeAg seroconversion was defined as HBeAg loss with development of anti-HBe antibodies

Results

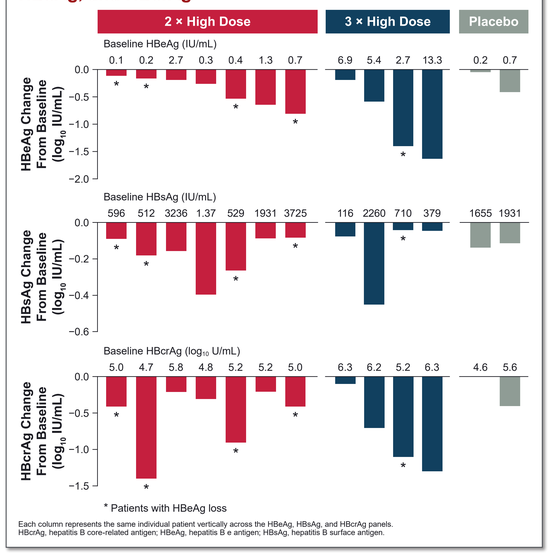
Baseline Demographics and Characteristics of HBeAg-Positive Patients

	HBeAg Loss (n = 5)	No HBeAg Loss (n = 6)
Age, years, median (range)	45 (28, 56)	45 (37, 62)
Male, n (%)	4 (80)	4 (67)
Years since HBV diagnosis, median (range)	23 (10, 45)	17 (8, 38)
HBsAg, IU/mL, median (range)	596 (512, 3725)	1155 (1, 3236)
HBeAg, IU/mL, median (range)	0.37 (0.14, 2.71)	4.05 (0.25, 13.31)
ALT, U/L, median (range)	20 (14, 51)	18 (13, 32)
HBV genotype, n (%)		
B	4 (80)	1 (17)
C	1 (20)	4 (67)
Unclassified	0	1 (17)
Duration of oral antiviral treatment, weeks, median (range)	144 (16, 967)	271 (132, 392)

The 2 HBeAg-positive participants who received placebo are not included in the table.
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

- Baseline characteristics were generally similar between patients with and without HBeAg loss; however, lower baseline HBeAg and HBsAg levels, along with differences in genotype distribution, were observed among patients who subsequently achieved HBeAg loss
- Five of 11 (45%) HBeAg-positive patients in the high-dose cohorts achieved HBeAg loss with seroconversion to 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

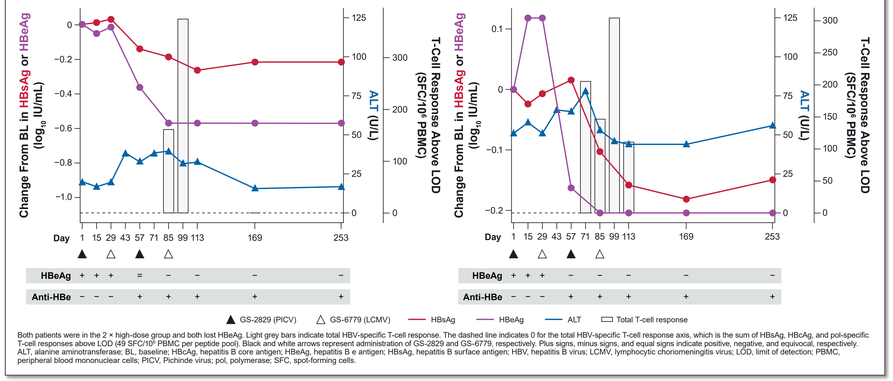
Individual Maximum Change From Baseline in HBeAg, HBsAg, and HBcrAg



Each column represents the same individual patient vertically across the HBeAg, HBsAg, and HBcrAg panels.
HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

- Declines in HBeAg and HBcrAg were observed among HBeAg-positive patients treated with high-dose GS-2829 + GS-6779, with greater declines generally observed among patients who achieved HBeAg loss
- Changes in HBsAg were modest and more variable across HBeAg-positive patients

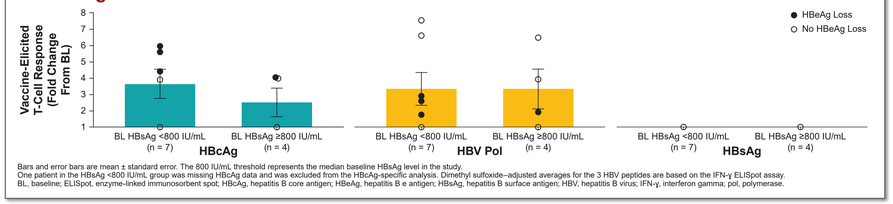
Representative Examples of HBeAg Loss



Both patients were in the 2 × high-dose group and both lost HBeAg. Light grey 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. Plus signs, minus signs, and equal signs indicate positive, negative, and equivocal, respectively.
ALT, alanine aminotransferase; BL, baseline; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LCMV, lymphocytic choriomeningitis virus; LOD, limit of detection; PBMC, peripheral blood mononuclear cells; PICV, Pichinde virus; pol, polymerase; SFC, spot-forming cells.

- HBeAg loss occurred in a characteristic pattern by day 85 (prior to the end of the second dosing cycle), with early reductions in HBeAg followed by loss and seroconversion to anti-HBe
- HBeAg loss was accompanied by declines in HBcrAg and transient elevations in alanine aminotransferase, a pattern also observed in other patients with HBeAg loss (not shown) and consistent with vaccine-mediated immune pressure targeting transcriptionally active, covalently closed circular DNA–positive hepatocytes

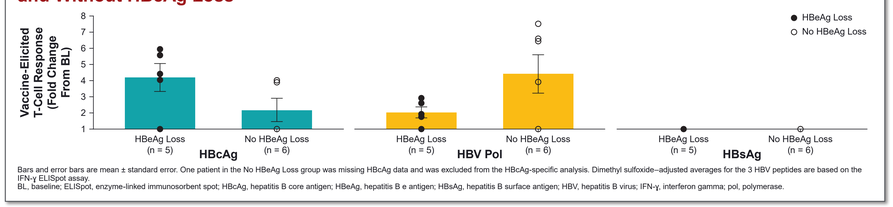
Peak Magnitude of Vaccine-Elicited IFN-γ+ T-Cell Responses in Vaccine-Treated Patients With BL HBsAg <800 or ≥800 IU/mL



Bars and error bars are mean ± standard error. The 800 IU/mL threshold represents the median baseline HBsAg level in the study.
One patient in the HBsAg <800 IU/mL group was missing HBcAg data and was excluded from the HBcAg-specific analysis. Dimethyl sulfoxide–adjusted averages for the 3 HBV peptides are based on the IFN-γ ELISpot assay.
BL, baseline; ELISpot, enzyme-linked immunosorbent spot; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN-γ, interferon gamma; pol, polymerase.

- Patients with baseline HBsAg <800 IU/mL exhibited more pronounced HBcAg-specific T-cell responses compared with those with baseline HBsAg ≥800 IU/mL, while no corresponding increase in the magnitude of HBsAg-specific T-cell responses was observed; polymerase (pol)-specific responses were similar between groups

Peak Magnitude of Vaccine-Elicited IFN-γ+ T-Cell Responses in Vaccine-Treated Patients With and Without HBeAg Loss



Bars and error bars are mean ± standard error. One patient in the No HBeAg Loss group was missing HBcAg data and was excluded from the HBcAg-specific analysis. Dimethyl sulfoxide–adjusted averages for the 3 HBV peptides are based on the IFN-γ ELISpot assay.
BL, baseline; ELISpot, enzyme-linked immunosorbent spot; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN-γ, interferon gamma; pol, polymerase.

- A trend towards stronger HBeAg-specific T-cell responses was observed among patients with HBeAg loss, while those without HBeAg loss showed relatively stronger pol-specific responses; these observations are based on a small sample size and warrant confirmation in larger studies
- Additional investigation of transcriptional signatures and immune mechanisms associated with HBeAg loss following GS-2829 + GS-6779 vaccination are presented in poster WED-578