Safety, Tolerability, and Immunogenicity of GS-2829 and GS-6779, a Novel Arenaviral Vectored Therapeutic Hepatitis B Vaccine: Results From a Phase 1a Study in Healthy Participants

THU-246

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Conclusions

- Alternating doses of GS-2829 and GS-6779 were safe and well tolerated in healthy participants
- GS-2829 and GS-6779 induced robust T-cell responses, including responses to hepatitis B surface antigen (HBsAg), hepatitis B core antigen (core), and polymerase (pol), along with high titres of HBsAg antibodies (anti-HBs) and no anti-vector neutralisation
  - Immunogenicity was dose-level dependent, and vaccine-elicited T-cell responses were greater among participants who received 3 vs 2 vaccine cycles
- These data support further investigation of GS-2829 and GS-6779 in participants with chronic hepatitis B virus (HBV) infection in this ongoing Phase 1 study

Plain Language Summary

- This clinical study in healthy participants investigated a novel therapeutic vaccine (GS-2829 and GS-6779) to achieve an immune response against hepatitis B virus in pursuit of a functional cure
- Overall, the vaccine was safe and well tolerated and induced a robust immune response in healthy participants
- Additional data from participants with chronic hepatitis B virus infection will be reported later this year

References: **1.** Seto WK, et al. *Lancet.* 2018;392:2313-24.
2. Schmidt S, et al. *J Infect Dis.* 2024;229:1077-87.

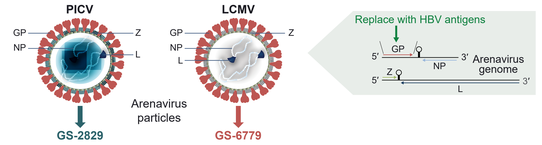
Acknowledgements: Editorial support was provided by Molly Yeager, PhD, of Red Nucleus, and funded by Gilead Sciences, Inc. This study was funded by Gilead Sciences, Inc.

Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

- Therapeutic vaccination is a promising approach to eliciting and maintaining a durable immune response against HBV, potentially contributing to functional cure, defined as sustained undetectable HBV DNA and HBsAg loss[1]
- GS-2829 and GS-6779 are nonreplicating vectors engineered to deliver highly conserved HBV antigens (HBsAg, core, and pol reverse transcriptase and ribonuclease H domains) using 2 different arenaviruses: Pichinde virus (GS-2829) and lymphocytic choriomeningitis virus (LCMV; GS-6779)
- Alternating immunisations with GS-2829 and GS-6779 elicited robust cluster of differentiation (CD) 8+ T-cell and anti-HBs responses in mice and nonhuman primates[2] with no induction of arenavirus-specific neutralising antibodies[2]

GS-2829 + GS-6779 Vaccine: Genetically Engineered Arenavirus-Based Vectors



HBV, hepatitis B virus; GP, glycoprotein; L, RNA-dependent RNA polymerase; LCMV, lymphocytic choriomeningitis virus; NP, nucleoprotein; PICV, Pichinde virus; Z, matrix protein.

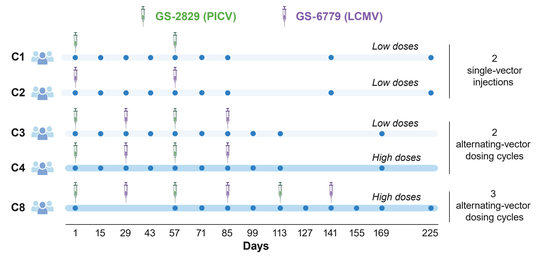
Objective

- To evaluate the safety, tolerability, and immunogenicity of GS-2829 and GS-6779 in healthy participants

Methods

- This randomised (4:1), blinded, placebo-controlled Phase 1a study (NCT05770895) was conducted at 1 centre in New Zealand in healthy participants
- Key inclusion criteria
  - Aged 18 to 60 years at the time of screening
  - Body mass index ≤32 kg/m^2 (inclusive)
  - Nondiabetic
  - No evidence of cardiac disease based on 12-lead electrocardiogram
  - No history of HBV infection and negative for HBsAg and anti-core
  - Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin at or below the upper limit of normal
  - Creatinine clearance ≥90 mL/min (using the Cockcroft-Gault method)

Study Design



Blue dots represent time points with PBMC sampling. C5, C6, and C7 enrolled participants with virally suppressed chronic hepatitis B and are not reported in this interim analysis.
C, cohort; LCMV, lymphocytic choriomeningitis virus; PBMC, peripheral blood mononuclear cells; PICV, Pichinde virus.

- Cohorts 1 and 2 received two intramuscular (IM) administrations of either a low dose of GS-2829 (cohort 1) or GS-6779 (cohort 2), or placebo, once every 8 weeks (2 low injections [inj])
- For cohorts 3, 4, and 8, alternating IM doses of GS-2829 and GS-6779, or placebo, were administered every 4 weeks as follows:
  - Cohort 3, four total low doses (2 cycles [2 × low])
  - Cohort 4, four total high doses (2 cycles [2 × high])
  - Cohort 8, six total high doses (3 cycles [3 × high])
- For both GS-2829 and GS-6779, low doses were ≥0.5 × 10^6 focus-forming units (FFU), and high doses were ≥0.5 × 10^7 FFU
- Safety and tolerability, including adverse events (AEs), serious AEs, and laboratory abnormalities, were monitored throughout the study
- Immunogenicity was evaluated via interferon-gamma enzyme-linked immunosorbent spot (ELISpot) analysis of HBV-specific T cells and by quantification of anti-HBs titres using the ADVIA Centaur anti-HBs2 assay
- For the anti-LCMV (vector) antibody assay, ARPE-19 (ie, human retinal pigment epithelial) cells were infected with green fluorescent protein–expressing LCMV in the presence of serially diluted patient serum
- Immunogenicity and anti-vector antibody analyses are reported for active treatment and pooled placebo participants in cohorts 3, 4, and 8

Results

Baseline Demographics

	Cohort 1 GS-2829 2 Low Inj (n = 8)	Cohort 2 GS-6779 2 Low Inj (n = 8)	Cohort 3 GS-2829 + GS-6779 2 × Low (n = 8)	Cohort 4 GS-2829 + GS-6779 2 × High (n = 8)	Cohort 8 GS-2829 + GS-6779 3 × High (n = 9[a])	Pooled Placebo (n = 10)	Total (N = 51)
Age, years, median (min, max)	36 (20, 50)	30 (21, 37)	32 (23, 57)	33 (25, 55)	32 (20, 46)	36 (21, 51)	33 (20, 57)
Sex, male	3 (38)	6 (75)	3 (38)	1 (13)	6 (67)	6 (60)	25 (49)
Race							
Asian	2 (25)	3 (38)	4 (50)	4 (50)	1 (11)	4 (40)	18 (35)
White	5 (63)	3 (38)	3 (38)	1 (13)	5 (56)	4 (40)	21 (41)
Native Hawaiian or Pacific Islander	0	0	0	0	2 (22)	0	2 (4)
American Indian or Alaska Native	0	0	0	0	0	1 (10)	1 (2)
Other	1 (13)	2 (25)	1 (13)	3 (38)	1 (11)	1 (10)	9 (18)
Ethnicity							
Non-Hispanic or Latino	7 (88)	6 (75)	7 (88)	5 (63)	9 (100)	10 (100)	44 (86)
BMI, kg/m^2, median (Q1, Q3)	23 (21.9, 27.8)	27 (24.1, 27.5)	25 (22.4, 26.6)	26 (23.2, 27.6)	27 (24.0, 29.3)	25 (23.9, 26.4)	25 (23.0, 27.5)

[a]One participant discontinued the study drug and withdrew consent; the participant was replaced, and 9 total participants were treated.
Data are presented as n (%) unless otherwise indicated.
BMI, body mass index; inj, injection; max, maximum; min, minimum; Q, quartile.

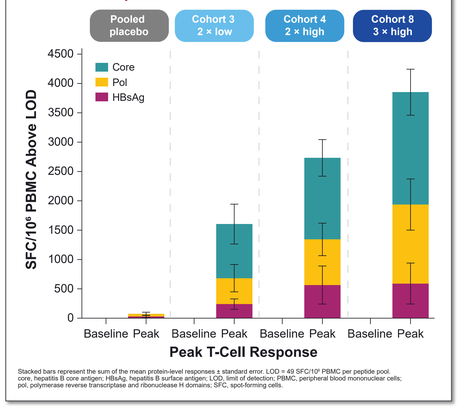
Overall Safety Summary

	Cohort 1 GS-2829 2 Low Inj (n = 8)	Cohort 2 GS-6779 2 Low Inj (n = 8)	Cohort 3 GS-2829 + GS-6779 2 × Low (n = 8)	Cohort 4 GS-2829 + GS-6779 2 × High (n = 8)	Cohort 8 GS-2829 + GS-6779 3 × High (n = 9)	Pooled Placebo (n = 10)
Any AE	8 (100)	8 (100)	8 (100)	8 (100)	9 (100)	9 (90)
Any AE related to study drug	3 (38)	7 (88)	5 (63)	8 (100)	8 (89)	8 (80)
Any Grade ≥3 AE	0	0	0	0	1 (11)[a]	0
Any SAE	0	0	0	0	1 (11)[a]	0
Any AE leading to premature d/c of study drug	0	0	0	0	0	0
Death	0	0	0	0	0	0
Common AEs (>3 participants in any cohort)						
Injection-site reaction[b]	2 (25)	5 (63)	5 (63)	8 (100)	6 (67)	3 (30)
Fatigue	1 (13)	5 (63)	3 (38)	6 (75)	4 (44)	3 (30)
Headache	3 (38)	3 (38)	1 (13)	7 (88)	4 (44)	4 (40)
Malaise	0	0	1 (13)	6 (75)	5 (56)	1 (10)
Pyrexia	1 (13)	1 (13)	2 (25)	4 (50)	2 (22)	2 (20)
Myalgia	2 (25)	0	1 (13)	5 (63)	3 (33)	0
Arthralgia	0	0	0	4 (50)	1 (11)	0
Laboratory abnormalities[c]						
Any Grade ≥1 postbaseline value	8 (100)	7 (88)	8 (100)	8 (100)	8 (89)	9 (90)
Grade 1	7 (88)	5 (63)	4 (50)	5 (63)	4 (44)	7 (70)
Grade 2	1 (13)	1 (13)	4 (50)	3 (38)	4 (44)	1 (10)
Grade 3	0	0	0	0	0	1 (10)[d]
Grade 4	0	1 (13)[d]	0	0	0	0

[a]One participant in cohort 8 experienced a Grade 3 unrelated SAE of Lisfranc fracture following a road traffic collision. [b]Injection-site reactions include pain, swelling, erythema, discomfort, induration, pruritus, and vessel puncture site bruising. [c]Grade 1 ALT elevations were observed in 1 participant each across cohorts 1–4 and 8; all were on active treatment, and none had a clear temporal association with GS-2829 or GS-6779 administration (data not shown). [d]CK elevation.
All AEs were treatment emergent.
Data are presented as n (%) unless otherwise indicated.
AE, adverse event; ALT, alanine aminotransferase; CK, creatine kinase; d/c, discontinuation; inj, injection SAE, serious adverse event.

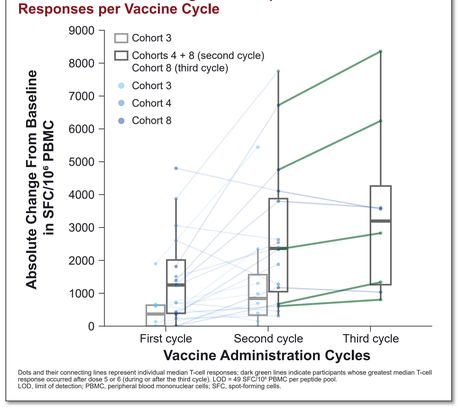
- Single and alternating vector administrations were safe and well tolerated across dose levels and numbers of injections/cycles
- Commonly reported AEs were similar between the low- and high-dose cohorts
- Importantly, no AEs led to discontinuation of study treatment

Peak T-Cell Responses



Stacked bars represent the sum of the mean protein-level responses ± standard error. LOD = 49 SFC/10^6 PBMC per peptide pool.
core, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; LOD, limit of detection; PBMC, peripheral blood mononuclear cells; pol, polymerase reverse transcriptase and ribonuclease H domains; SFC, spot-forming cells.

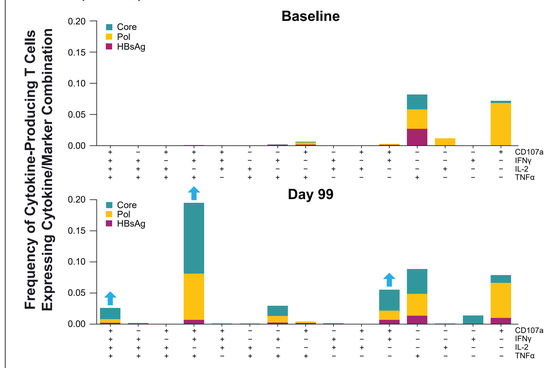
Maximum Absolute Change in Participant Total T-Cell Responses per Vaccine Cycle



Dots and their connecting lines represent individual median T-cell responses; dark green lines indicate participants whose greatest median T-cell response occurred after dose 5 or 6 (during or after the third cycle). LOD = 49 SFC/10^6 PBMC per peptide pool.
LOD, limit of detection; PBMC, peripheral blood mononuclear cells; SFC, spot-forming cells.

- Participants generated HBV-specific T cells to all vaccine-encoded HBV antigens
- Cohorts receiving the high dose vs low dose of GS-2829 and GS-6779 showed a stronger T-cell response by ELISpot assay
- On average, all cohorts demonstrated the same antigen response hierarchy: core > pol > HBsAg
- In cohort 4 (2 × high), mean response increased from undetectable at baseline to approximately 2750 spot-forming cells per 10^6 peripheral blood mononuclear cells at peak
- In several participants in cohort 8, the addition of the third vaccine cycle further increased the magnitude of T-cell responses

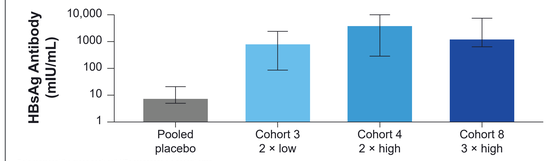
Frequency of Cytokine-Producing CD8+ T Cells at Baseline and Day 99 in Cohort 3 (2 × Low)



Blue arrows indicate HBV-specific T cells with the largest increases from baseline to day 99 in cytokine polyfunctionality and CD107a production.
CD, cluster of differentiation; core, 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, tumour necrosis factor.

- GS-2829 and GS-6779 administration increased T-cell polyfunctionality with CD107a production, indicating HBV-targeted T-cell–killing ability

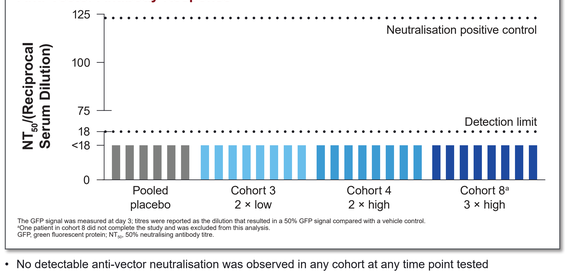
Peak Anti-HBs Responses



Data represent the mean peak anti-HBs responses ± standard error.
Anti-HBs, HBsAg antibodies; HBsAg, hepatitis B surface antigen.

- Vaccine-elicited immune responses generated high-magnitude, dose-dependent, and durable anti-HBs titres
- The additional high-dose vaccine cycle in cohort 8 enhanced the durability of anti-HBs responses (data not shown)

Anti-Vector Antibody Response



The GFP signal was measured at day 3; titres were reported as the dilution that resulted in a 50% GFP signal compared with a vehicle control.
[a]One patient in cohort 8 did not complete the study and was excluded from this analysis.
GFP, green fluorescent protein; NT$_{50}$, 50% neutralising antibody titre.

- No detectable anti-vector neutralisation was observed in any cohort at any time point tested