CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1a/1b Study to Evaluate the Safety and Tolerability of Repeated Doses of Nonreplicating Arenavirus Vector Therapeutic Vaccines GS-2829 and GS-6779 in Healthy Participants and Participants With Chronic Hepatitis B (CHB)
Short Title:	Study of HBV Therapeutic Vaccines GS-2829 and GS-6779 in Healthy Participants and Participants With Chronic Hepatitis B
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EudraCT Number:** **ClinicalTrials.gov ID:**	Not Applicable Not Applicable NCT05770895
Indication:	Chronic Hepatitis B (CHB)
Protocol ID:	GS-US-642-5670
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 01 September 2022 Amendment 1: 22 November 2022 Amendment 2: 20 July 2023

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

CONFIDENTIALITY STATEMENT

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BMI	body mass index
CD4	clusters of differentiation 4
CD8	clusters of differentiation 8
CFR	Code of Federal Regulations
CHB	chronic hepatitis B
CK	creatine kinase
CL_{cr}	creatinine clearance
CMV	cytomegalovirus
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISpot	enzyme-linked immunospot assay
ESLD	end-stage liver disease
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FFU	focus-forming unit
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GLP	Good Laboratory Practice
HAV	hepatitis A virus
HBcrAg	hepatitis B core-related antigen
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEPES	N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid
HEV	hepatitis E virus

HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IFN	interferon
IFN-γ	interferon gamma
Ig	immunoglobulin
IND	investigational new drug
INR	international normalized ratio
IRT	Interactive Response Technology
LCMV	lymphocytic choriomeningitis virus
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	nucleos(t)ide analogues
PBMC	peripheral blood mononuclear cell
PBO	placebo
PCR	polymerase chain reaction
PICV	Pichinde virus
PIMMC	potential immune-mediated condition
PS	Patient Safety
PT	preferred term
QT (interval)	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
rHSA	recombinant human serum albumin
rLCMV	replication-deficient lymphocytic choriomeningitis virus
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SRT	Safety Review Team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US, USA	United States, United States of America

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Foster City, CA 94404
USA

Study Title: A Phase 1a/1b Study to Evaluate the Safety and Tolerability of Repeated Doses of Nonreplicating Arenavirus Vector Therapeutic Vaccines GS-2829 and GS-6779 in Healthy Participants and Participants With Chronic Hepatitis B (CHB)

Short Title: Study of HBV Therapeutic Vaccines GS-2829 and GS-6779 in Healthy Participants and Participants With Chronic Hepatitis B

IND Number: Not Applicable
EudraCT Number: Not Applicable
ClinicalTrials.gov Identifier: NCT05770895

Study Centers Planned: This is a multicenter study to be conducted at 1 site in New Zealand for Phase 1a activities and approximately 15 sites globally for Phase 1b activities.

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the safety and tolerability of repeated dosing of GS-2829 and GS-6779 in healthy participants and in virally suppressed participants with CHB	• Proportion of participants with treatment-emergent adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities
Secondary Objective	**Secondary Endpoints**
• To evaluate the immunogenicity of repeated dosing of GS-2829 and GS-6779 in healthy participants and in virally suppressed participants with CHB	• Incidence and magnitude of vaccine-induced T-cell responses

Study Design:

This protocol is a blinded, placebo-controlled, randomized Phase 1a and Phase 1b study to evaluate the safety, tolerability, and immunogenicity of repeated doses of GS-2829 and GS-6779 administered by intramuscular injection in healthy participants (Phase 1a) and participants with CHB (Phase 1b). The study will comprise 8 cohorts, which will enroll up to 10 participants each, with a 4:1 randomization to either the active viral vectors GS-2829 and/or GS-6779 or placebo (PBO).

An overview of the study design is described below and shown in Figure 1, Figure 2, Figure 3, and Figure 4.

The investigational products GS-2829 and GS-6779 are available as $\geq 1.0 \times 10^7$ focus-forming units (FFU)/mL. There are 2 doses in this study: high dose (0.5 mL of the undiluted solution) and low dose (0.5 mL of the 10-fold dilution of the high dose).

Following completion of screening, eligible participants will be randomized to receive the investigational product (viral vector or PBO) as shown below:

Phase 1a Healthy Participant Cohorts

- Cohort 1 – Single low dose of GS-2829 or PBO on Day 1 and Day 57.
- Cohort 2 – Single low dose of GS-6779 or PBO on Day 1 and Day 57.
- Cohort 3 – Single low dose of GS-2829 or PBO on Day 1 and Day 57; and single low dose of GS-6779 or PBO on Day 29 and Day 85.
- Cohort 4 – Single high dose of GS-2829 or PBO on Day 1 and Day 57; and single high dose of GS-6779 or PBO on Day 29 and Day 85.
- Cohort 8 – Single high dose of GS-2829 or PBO on Day 1, Day 57, and Day 113; and single high dose of GS-6779 or PBO on Day 29, Day 85, and Day 141.

Phase 1b Virally Suppressed CHB Participant Cohorts

- Cohort 5 – Single low dose of GS-2829 or PBO on Day 1 and Day 57; and single low dose of GS-6779 or PBO on Day 29 and Day 85.
- Cohort 6 – Single high dose of GS-2829 or PBO on Day 1 and Day 57; and single high dose of GS-6779 or PBO on Day 29 and Day 85.
- Cohort 7 – Single high dose of GS-2829 or PBO on Day 1, Day 57, and Day 113; and single high dose of GS-6779 or PBO on Day 29, Day 85, and Day 141.

Cohorts 1, 2, and 3

Cohorts 1 and 2 will enroll concurrently and will receive investigational product in 2 groups, a sentinel group (2 active and 1 PBO, randomly assigned) and the remainder (6 active and 1 PBO), for a total of approximately 10 healthy participants per cohort. Dosing the remainder of Cohorts 1 and 2 and initiation of Cohort 3 will commence at the discretion of the investigator in consultation with the sponsor's medical monitor upon evaluation of available safety data through at least 14 days after the first dose of investigational product in Cohort 1 and 2 sentinel participants. The duration of this review period may be increased based on emerging preliminary safety data. Decisions to initiate a higher dose level cohort and any required revisions to postdose monitoring will be made upon the review of all available safety data by the Safety Review Team (SRT).

Cohorts 4 and 5

Initiation of Cohorts 4 and 5, which will run concurrently, will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 Days after the initial dose of both investigational products for all participants enrolled in Cohort 3), in addition to all available safety data from Cohorts 1 and 2. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT

charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 8

Initiation of Cohort 8 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after all participants in Cohort 3 have completed the initial dose of both investigational products), in addition to all available safety data from prior cohorts. Initiation of a third dose of 2-vector combination, therapy will be determined at the discretion of the SRT based on the evaluation of the available safety data through Day 99 (14 days after all participants in Cohort 4 have completed the second dose of both investigational products), in addition to all available safety data. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 6

Initiation of Cohort 6 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after initial dose of both the investigational products for all participants enrolled in Cohort 4), available safety data from participants enrolled in Cohort 5, and all available safety data from all dosed cohorts, and dosing will be initiated only in the absence of dose-limiting toxicity and/or meeting any prespecified stopping criteria. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 7

Initiation of Cohort 7 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after initial dose of both the investigational products for all participants enrolled in Cohort 4), available safety data from participants enrolled in Cohort 5, and all available safety data from all dosed cohorts. Initiation of the third dose of 2 vector combination therapy will be determined at the discretion of SRT based on the evaluation of the available safety data through Day 99 (14 days after all participants in Cohort 4 have completed the second dose of both investigational products), in addition to all available safety data. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

Number of Participants Planned: Approximately 80 participants are planned for 8 cohorts. of 10 participants each: 50 healthy participants for Phase 1a activities and 30 participants diagnosed with CHB for Phase 1b activities.

Target Population:

Phase 1a: Healthy male and nonpregnant, nonlactating female participants, aged 18 through 60 years, inclusive

Phase 1b: Male and nonpregnant, nonlactating female participants diagnosed with CHB, aged 18 through 65 years, inclusive

Duration of Intervention:

- Cohorts 1 and 2 will receive 2 total doses over 56 days (Days 1 and 57).
- Cohorts 3, 4, 5, and 6 will receive 4 total doses over 84 days (Days 1, 29, 57, and 85).
- Cohorts 7 and 8 will receive 6 total doses over 140 days (Days 1, 29, 57, 85, 113, and 141).
- All participants will be followed for safety for 24 weeks following their last dose of investigational product (through Day 225 for Cohorts 1 and 2; through Day 253 for Cohorts 3, 4, 5, and 6; and Day 309 for Cohorts 7 and 8).

Diagnosis and Main Eligibility Criteria:

Phase 1a: Eligible participants will include those assigned male sex at birth or those who are nonpregnant, nonlactating, assigned female at birth, aged 18 through 60 years inclusive, with a body mass index (BMI) of ≤ 32.0 kg/m^2, with normal or nonclinically significant 12-lead electrocardiogram (ECG) evaluations, and no significant medical history. Participants will also be in good general health as determined by the investigator and have no prior history of hepatitis B virus (HBV) infection as demonstrated with a negative hepatitis B surface antigen (HBsAg) and hepatitis B core antibody test. Participants are prohibited from receipt of any investigational product or vaccine within 3 months of screening (with the exception of influenza and SARS-CoV-2 vaccines, which if needed, should be administered at least 14 days before or after an investigational product administration; participants should be encouraged to receive any needed vaccinations prior to enrollment) and should not receive ongoing therapy with any prohibited medications listed in the protocol.

Phase 1b: Eligible participants will include those assigned male sex at birth or those who are nonpregnant, nonlactating, assigned female at birth, aged 18 through 65 years, inclusive, with a BMI of ≤ 32.0 kg/m^2, and with normal or nonclinically significant 12-lead ECG evaluations. Participants must have documented evidence of CHB based on one of the following: positive HBsAg or HBV DNA at least 6 months prior to the screening visit; or historical liver biopsy consistent with CHB infection. Participants must have no evidence of advanced fibrosis by FibroScan. Participants are prohibited from receipt of any investigational product or vaccine within 3 months of screening (with the exception of influenza and SARS-CoV-2 vaccines, which, if needed, should be administered at least 14 days before or after an investigational product administration; participants should be encouraged to receive any needed vaccinations prior to enrollment) and should not receive ongoing therapy with any prohibited medications listed in the protocol.

Phase 1b participants in Cohorts 5, 6, and 7 must be receiving an approved HBV-active oral antiviral agent for ≥ 6 months prior to screening with HBV DNA less than the lower limit of quantification (LLOQ) for ≥ 3 months prior to screening with no plan to stop HBV-active antivirals during the study.

Study Procedures/Frequency:

All participants will provide informed consent, complete all screening procedures and assessments, and must meet all eligibility criteria prior to administration of investigational product on Day 1.

Study procedures including investigational product administration, safety follow-up via collection of AEs, laboratory assessments, participant diary review, immunogenicity, and biomarker assessments, HBV genomic sequencing and phenotyping, and other procedures are described in the protocol Sections 5 and 6 and the scheduling and frequency of these procedures are detailed in the study assessment tables (Table 1, Table 2, and Table 3).

Test Product, Dose, and Mode of Administration:

GS-2829 – Low-dose intramuscular administration will be $\geq 0.5 \times 10^6$ FFU

GS-6779 – Low-dose intramuscular administration will be $\geq 0.5 \times 10^6$ FFU

GS-2829 – High-dose intramuscular administration will be $\geq 0.5 \times 10^7$ FFU

GS-6779 – High-dose intramuscular administration will be $\geq 0.5 \times 10^7$ FFU

Reference Therapy, Dose, and Mode of Administration:

The comparator will be an inactive PBO comprising a solution of human serum albumin with visual characteristics similar to the investigational products to be administered intramuscularly at the same volume as the investigational products.

Statistical Methods:

All analyses and summaries will be presented by population and treatment group. Data from participants who receive PBO may be pooled across cohorts within the same population.

The AE data will be listed by participant. The incidence of treatment-emergent AEs, SAEs, and AEs leading to discontinuation of investigational product will be summarized by treatment, system organ class, high-level term (if applicable), and preferred term using the current version of the MedDRA.

Listings of individual participant laboratory results will be provided. Laboratory results and change from baseline values for selected laboratory tests will be summarized by scheduled visits. The incidence of treatment-emergent laboratory abnormalities will be summarized by population and treatment.

Vital signs and ECG data will be summarized by population, treatment group, and visit.

The immunogenicity analysis will be based on the proportion of participants with investigational product-induced HBV-specific T-cell response, as determined by the interferon

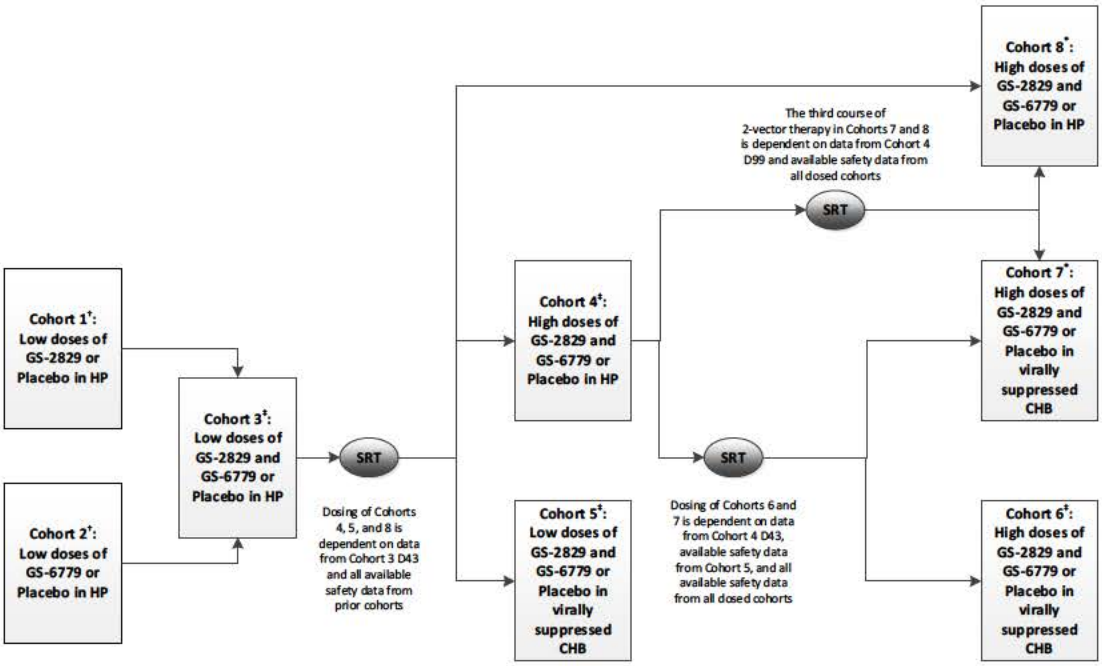
gamma (IFN-γ) enzyme-linked immunospot assay (ELISpot) assay and will be summarized by population and treatment group. The magnitude of the total investigational product-induced HBV-specific T-cell response, as determined by the IFN-γ ELISpot assay, will be summarized by population and treatment group.

Sample Size:

The sample size in this study is determined based on practical considerations and empirical experience with similar types of studies. No formal power and sample size calculation were performed. Overall, a total sample size of approximately 80 participants (10 participants per cohort, including 8 active and 2 PBO) is expected to provide a suitable assessment of the safety, tolerability, and immunogenicity of treatment with the investigational product.

STUDY SCHEMA

Figure 1. Overall Study Schema, Phase 1a and Phase 1b



† Total 2 doses
‡ Total 4 doses
* Total of 6 doses

Cohorts 1, 2, and 3: Cohorts 1 and 2 will enroll concurrently and will receive investigational product in 2 groups, a sentinel group (2 active and 1 PBO, randomly assigned) and the remainder (6 active and 1 PBO), for a total of approximately 10 healthy participants per cohort. Dosing the remainder of Cohorts 1 and 2 and initiation of Cohort 3 will commence at the discretion of the investigator in consultation with the sponsor's medical monitor upon evaluation of available safety data through at least 14 days after the first dose of investigational product in Cohort 1 and 2 sentinel participants. The duration of this review period may be increased based on emerging preliminary safety data. Decisions to initiate a higher dose level cohort and any required revisions to postdose monitoring will be made upon the review of all available safety data by the SRT.

Cohorts 4 and 5: Initiation of Cohorts 4 and 5, which will run concurrently, will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 Days after the initial dose of both investigational products for all participants in enrolled in Cohort 3), in addition to all available safety data from Cohorts 1 and 2. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

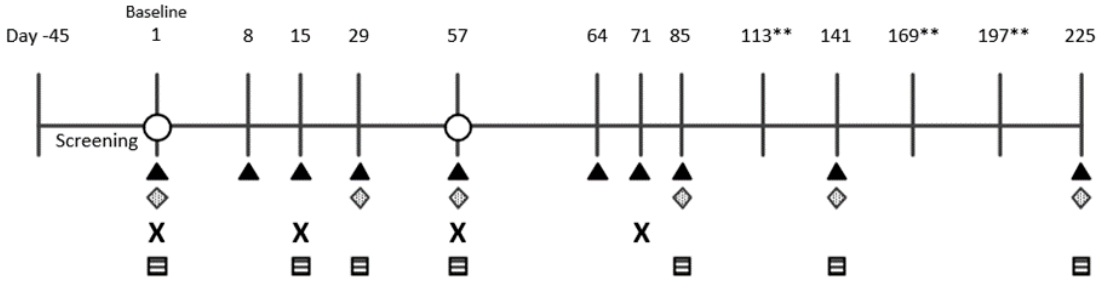
Cohort 8: Initiation of Cohort 8 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after all participants in Cohort 3 have completed the initial dose of both investigational products), in addition to all available safety data from prior cohorts. Initiation of a third dose of 2-vector combination, therapy will be determined at the discretion of the SRT based on the evaluation of the available safety data through Day 99 (14 days after all participants in Cohort 4 have completed the second dose of both investigational products), in addition to all available safety data. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 6: Initiation of Cohort 6 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after initial dose of both the investigational products for all participants enrolled in Cohort 4), available safety data from participants enrolled in Cohort 5, and all available safety data from all dosed cohorts, and dosing will be initiated only in the absence of dose-limiting toxicity and/or meeting any prespecified stopping criteria. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 7: Initiation of Cohort 7 will be determined at the discretion of the SRT based on the evaluation of available safety data through 14 days (Day 43) after initial dose of both the investigational products for all participants enrolled in Cohort 4, available safety data from participants enrolled in Cohort 5, and all available safety data from all dosed cohorts. Initiation of the third dose of 2 vector combination therapy will be determined at the discretion of SRT based on the evaluation of the available safety data through Day 99 (14 days after all participants in Cohort 4 have completed the second dose of both investigational products), in addition to all available safety data. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

CHB = chronic hepatitis B; D = Day; HBV = hepatitis B virus; HP = healthy participant; SRT = Safety Review Team

Figure 2. Schema for Cohorts 1 and 2 (Two Total Doses)



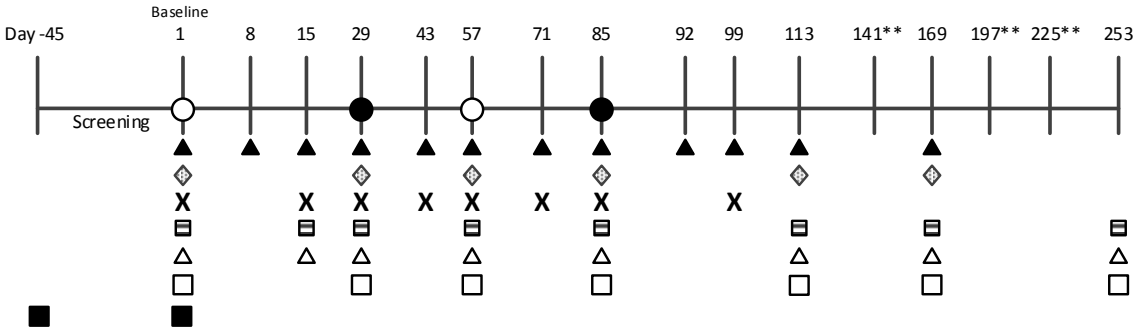
Phase 1a

- Cohort 1: Low Doses of GS-2829 or Placebo in HP
- Cohort 2: Low Doses of GS-6779 or Placebo in HP

GS-2829 or GS-6779 dose or Placebo
PBMC for Biomarker Cellular Assays
Serum for HBV-Targeting Antibody Measurements
X Whole Blood for Biomarker Analysis
HBV Neutralizing Antibody and Antivector Antibody Assessment
** Day 113, Day 169 and Day 197 visits are only required for female participants of childbearing potential

HBV = hepatitis B virus; HP = healthy participant; PBMC = peripheral blood mononuclear cell
Note: A follow-up phone call will be performed on Days 2, 3, 58, and 59.

Figure 3. Schema for Cohorts 3, 4, 5, and 6 (Four Total Doses)



Phase 1a

- Cohort 3: Low Doses of GS-2829 and GS-6779 or Placebo in HP
- Cohort 4: High Doses of GS-2829 and GS-6779 or Placebo in HP

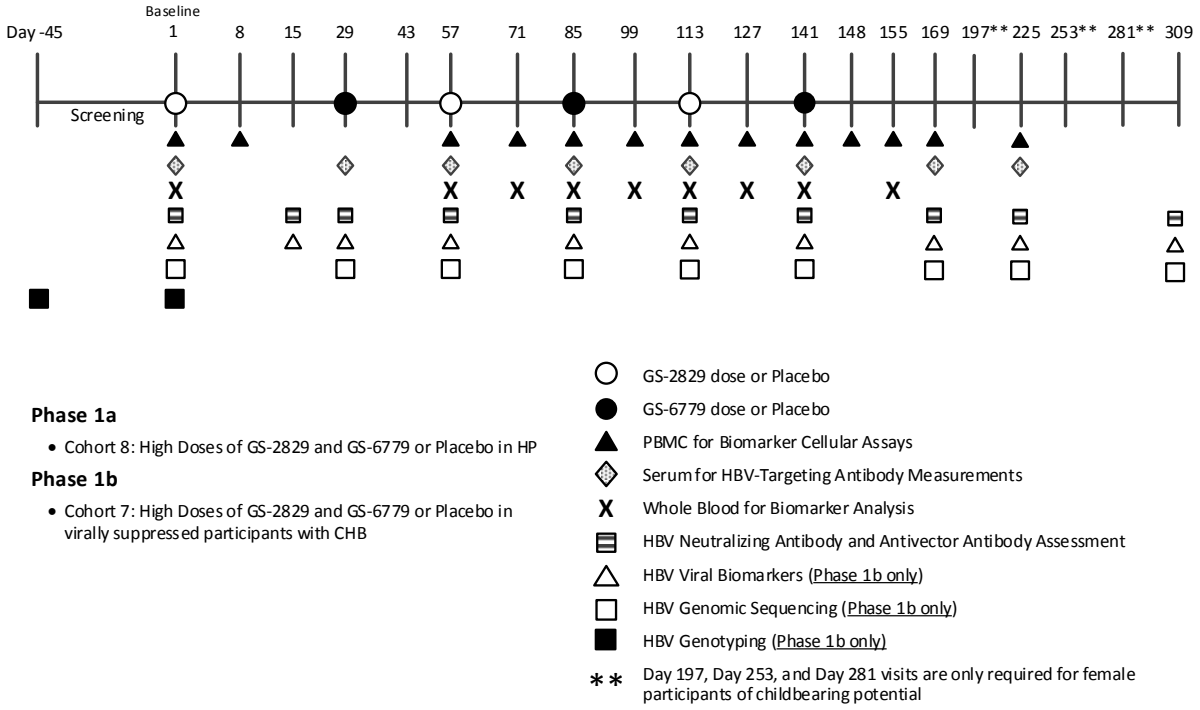
Phase 1b

- Cohort 5: Low Doses of GS-2829 and GS-6779 or Placebo in virally suppressed participants with CHB
- Cohort 6: High Doses of GS-2829 and GS-6779 or Placebo in virally suppressed participants with CHB

GS-2829 dose or Placebo
GS-6779 dose or Placebo
PBMC for Biomarker Cellular Assays
Serum for HBV-Targeting Antibody Measurements
X Whole Blood for Biomarker Analysis
HBV Neutralizing Antibody and Antivector Antibody Assessment
HBV Viral Biomarkers (Phase 1b only)
HBV Genomic Sequencing (Phase 1b only)
HBV Genotyping (Phase 1b only)
** Day 141, Day 197 and Day 225 visits are only required for female participants of childbearing potential

CHB = chronic hepatitis B; HBV = hepatitis B virus; HP = healthy participant; PBMC = peripheral blood mononuclear cell
Note: A follow-up phone call will be performed on Days 2, 3, 30, 31, 58, 59, 86, and 87.

Figure 4. Schema for Cohorts 7 and 8 (Six Total Doses)



CHB = chronic hepatitis B; HBV = hepatitis B virus; HP = healthy participant; PBMC = peripheral blood mononuclear cell
Note: A follow-up phone call will be performed on Days 2, 3, 30, 31, 58, 59, 86, 87, 114, 115, 142, and 143..

STUDY PROCEDURES TABLES

Table 1. Schedule of Assessments, Phase 1a – Cohorts 1 and 2 (Two Total Doses)

Study Period	Screen	Active Dosing					Safety Follow-up								
Study Day		**Baseline Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 57**	**Day 64**	**Day 71**	**Day 85**	**Day 113[a]**	**Day 141**	**Day 169[a]**	**Day 197[a]**	**Day 225**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 3**	**± 1**	**± 1**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**8**	**9**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	
Dosing (PBO or IP)[b]		X				X									
Written informed consent; I/E criteria; medical history	X														
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
General Assessments and Laboratory Assessments															
Complete physical examination[c]	X	X				X								X	X
Symptom-directed physical examination[d]			X	X	X		X	X	X		X				
HIV-1, HBV, and HCV testing	X	X[c]				X[c,e]								X[e]	X
Height	X														
Weight	X	X				X								X	X
12-lead ECG	X													X	X
Vital signs	X	X[f]	X	X	X	X[f]	X	X	X		X			X	X
Urinalysis	X	X[c]		X	X	X[c]		X	X		X			X	X
Hematology[g]	X	X[c]		X	X	X[c]		X	X		X			X	X
FSH[h]	X														
Serum pregnancy test[i]	X	X[c]			X	X[c]			X	X	X	X	X	X	X
Urine pregnancy test[i]		X				X									

Study Period	Screen	Active Dosing					Safety Follow-up								
Study Day		**Baseline Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 57**	**Day 64**	**Day 71**	**Day 85**	**Day 113[a]**	**Day 141**	**Day 169[a]**	**Day 197[a]**	**Day 225**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 3**	**± 1**	**± 1**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**8**	**9**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	
Urine drug and alcohol screen	X	X[c]													
Chemistry and liver function tests[j]	X	X[c]		X	X	X[c]		X	X		X			X	X
Creatinine clearance[k]	X	X			X	X								X	X
Coagulation[l]	X	X[c]		X	X	X[c]		X	X		X			X	X
Local and Systemic Reactogenicity															
Dispense participant diary[m]		X				X									
Review Participant diary[m]			X	X			X	X							
Immunology and Biomarkers															
PBMC collection for biomarker cellular assays		X[c]	X	X	X	X[c]	X	X	X		X			X	X
Serum collection for HBV-targeting antibody measurements		X[c]			X	X[c]			X		X			X	X
Whole blood collection for biomarker analysis		X[c]		X		X[c]		X							X
Clinical Virology															
Serum collection for HBV neutralizing antibody and antivector antibody assessment		X[c]		X	X	X[c]			X		X			X	X

ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus type 1; I/E = inclusion/exclusion; IP = investigational product; N/A = not applicable; PBMC = peripheral blood mononuclear cell; PBO = placebo; Screen = screening

a These visits are only required for pregnancy testing for women of childbearing potential. Participants who are able to access an at-home urine pregnancy test from the clinical site may conduct their pregnancy test at home and will be contacted by site staff to confirm the result. If urine pregnancy results are equivocal or positive, a serum pregnancy test will be required.
b Participant shall receive the appropriate investigational product or PBO, as detailed in Section 5.3 and Table 8. Sentinel participants will be observed at the study site for at least 8 hours after investigational product administration on Day 1, and for at least 4 hours following each administration of investigational product for all subsequent doses. All other Phase 1a participants will be monitored in the clinic for at least 4 hours following each dose of investigational product. Participants will receive a follow-up phone call for 2 consecutive days following each dose to review protocol restrictions, adverse events, any concomitant medication usage, and completion of participant diaries.
c Collection of vital signs, physical examination, and blood/urine samples should be completed prior to investigational product administration.
d Symptom-driven physical examinations shall be performed as deemed necessary.
e At the discretion of the investigator.
f Indicated assessment shall be performed prior to dosing and within 15 to 30 minutes following investigational product administration.
g Hematology assessments are listed in Section 6.4.5.
h An FSH test is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.
i For participants assigned female at birth and of childbearing potential. On days of investigational product administration, urine pregnancy testing is also required to determine pregnancy status prior to dosing.
j Chemistry and liver function assessments are listed in Section 6.4.5.
k Central laboratory will calculate creatinine clearance.
l Coagulation assessments are listed in Section 6.4.5.
m Participants will be asked to record potential vaccine reactions based on solicited events via diary for 7 days following each administration of investigational product. Review of participant reactogenicity data will occur at each visit after vaccination up to 7 days postdose or beyond for cases with ongoing events after 7 days postdose.

Table 2. Schedule of Assessments, Phase 1a – Cohorts 3, 4 and Phase 1b - Cohorts 5 and 6 (Four Total Doses)

Study Period	**Screen**	**Active Dosing**								**Safety Follow-up**								
Study Day		**Baseline Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 92**	**Day 99**	**Day 113**	**Day 141[a]**	**Day 169**	**Day 197[a]**	**Day 225[a]**	**Day 253**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**13**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	
Dosing (PBO or IP)[b]		X			X		X		X									
Written informed consent; I/E criteria; medical history	X																	
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
General Assessments and Laboratory Assessments																		
Complete physical examination[c]	X	X			X		X		X								X	X
Symptom-directed physical examination[d]			X	X		X		X		X	X	X		X				
HIV-1 testing	X																X[e]	X
HBV testing[p]	X	X[c]							X[c,e]								X[e]	X
HCV testing	X																X[e]	X
HDV testing[l]	X																	
Height	X																	
Weight	X	X			X		X		X								X	X
12-lead ECG	X								X								X	X
Vital signs	X	X[f]		X	X[f]	X	X[f]	X	X[f]	X	X	X		X			X	X
Urinalysis	X	X[c]			X[c]		X[c]	X	X[c]		X	X		X			X	X
Hematology[g]	X	X[c]		X	X[c]	X	X[c]	X	X[c]		X	X		X			X	X
FSH[h]	X																	
Serum pregnancy test[i]	X	X[c]			X[c]		X[c]		X[c]			X	X	X	X	X	X	X

Study Period	Screen	Active Dosing								Safety Follow-up								
Study Day		**Baseline Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 92**	**Day 99**	**Day 113**	**Day 141[a]**	**Day 169**	**Day 197[a]**	**Day 225[a]**	**Day 253**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**13**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	
Urine pregnancy test[i]		X[c]			X[c]		X[c]		X[c]									
Urine drug and alcohol screen	X	X																
Chemistry and liver function tests[j]	X	X[c]		X	X[c]	X	X[c]	X	X[c]		X	X		X			X	X
Creatinine clearance[k]	X	X			X		X		X								X	X
Autoantibody test[l]		X																
FibroScan for participants with none in past 6 months[l]	X																	
Coagulation[m]	X	X[c]		X	X[c]	X	X[c]	X	X[c]		X	X		X			X	X
Local and Systemic Reactogenicity																		
Dispense participant diary[n]		X			X		X		X									
Review participant diary[n]			X	X		X		X		X	X							
Immunology and Biomarkers																		
PBMC collection for biomarker cellular assays		X[c]	X	X	X[c]	X	X[c]	X	X[c]	X	X	X		X				X
Serum collection for HBV-targeting antibody measurements		X[c]			X[c]		X[c]		X[c]			X		X				X
Whole blood collection for biomarker analysis		X[c]		X	X[c]	X	X[c]	X	X[c]		X							X

Study Period	Screen	Active Dosing								Safety Follow-up								
Study Day		**Baseline Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 92**	**Day 99**	**Day 113**	**Day 141[a]**	**Day 169**	**Day 197[a]**	**Day 225[a]**	**Day 253**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**13**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	
Clinical Virology																		
HBV neutralizing antibody and antivector antibody assessment		X[c]		X	X[c]		X[c]		X[c]			X		X			X	X
HBV viral biomarkers[o,l]		X[c]		X	X[c]		X[c]		X[c]			X		X			X	X
HBV genomic sequencing[l]		X[c]			X[c]		X[c]		X[c]			X		X			X	X
HBV genotyping[l]	X	X[c]																

DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV-1 = human immunodeficiency virus type 1; I/E = inclusion/exclusion; IP = investigational product; N/A = not applicable; PBMC = peripheral blood mononuclear cell; PBO = placebo; RNA = ribonucleic acid; Screen = screening

a These visits are only required for pregnancy testing for women of childbearing potential. Participants who are able to access an at-home urine pregnancy test from the clinical site may conduct their pregnancy test at home and will be contacted by site staff to confirm the result. If urine pregnancy results are equivocal or positive, a serum pregnancy test will be required.

b Participant shall receive the appropriate investigational product or PBO, as detailed in Section 5.3 and Table 8. Participants in Cohorts 3 and 4 will be monitored in the clinic for at least 4 hours following each dose of investigational product. Participants in Cohorts 5 and 6 will be monitored in the clinic for at least 2 hours following each dose of investigational product. Participants may be required to remain in the clinic for additional observation at the discretion of the investigator. Participants will receive a follow-up phone call for 2 consecutive days following each dose to review protocol restrictions, adverse events, any concomitant medication usage, and completion of participant diaries.

c Collection of vital signs, physical examinations, and blood/urine samples should be completed prior to investigational product administration.

d Symptom-driven physical examinations shall be performed as deemed necessary.

e At the discretion of the investigator.

f Indicated assessment shall be taken prior to dosing and within 15 to 30 minutes following investigational product administration.

g Hematology assessments are listed in Section 6.4.5.

h An FSH test is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.

i For participants assigned female at birth and of childbearing potential. On days of investigational product administration, urine pregnancy testing is also required to determine pregnancy status prior to dosing.

j Chemistry and liver function assessments are listed in Section 6.4.5.

k Central laboratory will calculate creatinine clearance.

l Required for Phase 1b only.

m Coagulation assessments are listed in Section 6.4.5.
n Participants will be asked to record potential vaccine reactions based on solicited events via diary for 7 days following each administration of investigational product. Review of participant reactogenicity data will occur at each visit after vaccination up to 7 days postdose or beyond for cases with ongoing events after 7 days postdose.
o To include the assessments of: HBV DNA, quantitative HBsAg, anti-HBsAg antibody, HBcrAg, HBeAg, HBV RNA.
p Phase 1a: HBV testing is for HBsAg with reflex to HBV DNA, and hepatitis B core antibody. Phase 1b: HBV testing is for HBsAg, hepatitis B core antibody, HBV DNA, and quantitative HBsAg.

Table 3. Schedule of Assessments, Phase 1a – Cohort 8 and Phase 1b - Cohort 7 (Six Total Doses)

Study Period	Screen	Active Dosing												Safety Follow-up								
Study Day		**Base-line Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 127**	**Day 141**	**Day 148**	**Day 155**	**Day 169**	**Day 197[a]**	**Day 225**	**Day 253[a]**	**Day 281[a]**	**Day 309**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**	**24**	**28**	**32**	**36**	**40**	**44**	
Dosing (PBO or IP)[b]		X			X		X		X		X		X									
Written informed consent; I/E criteria; medical history	X																					
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
General Assessments and Laboratory Assessments																						
Complete physical examination[c]	X	X			X		X		X		X		X								X	X
Symptom-directed physical examination[d]			X	X		X		X		X		X		X	X	X		X				
HIV-1 testing	X																				X[e]	X
HBV testing[p]	X	X[e]							X[c,e]												X[e]	X
HCV testing	X																				X[e]	X
HDV testing[l]	X																					
Height	X																					
Weight	X	X			X		X		X		X		X								X	X
12-lead ECG	X								X				X								X	X

Study Period	**Screen**	**Active Dosing**												**Safety Follow-up**								
Study Day		**Base-line Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 127**	**Day 141**	**Day 148**	**Day 155**	**Day 169**	**Day 197[a]**	**Day 225**	**Day 253[a]**	**Day 281[a]**	**Day 309**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**	**24**	**28**	**32**	**36**	**40**	**44**	
Vital signs	X	X[f]		X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X	X		X			X	X
Urinalysis	X	X[e]			X[e]		X[e]	X	X[e]	X	X[e]	X	X[e]		X	X		X			X	X
Hematology[g]	X	X[e]		X	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]		X	X		X			X	X
FSH[h]	X																					
Serum pregnancy test[i]	X	X[e]			X[e]		X[e]		X[e]		X[e]		X[e]			X	X	X	X	X	X	X
Urine pregnancy test[i]		X[e]			X[e]		X[e]		X[e]		X[e]		X[e]									
Urine drug and alcohol screen	X	X																				
Chemistry and liver function tests[j]	X	X[e]		X	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]		X	X		X			X	X
Creatinine clearance[k]	X	X			X		X		X		X		X					X			X	X
Autoantibody test[l]		X																				
FibroScan for participants with none in past 6 months[l]	X																					
Coagulation[m]	X	X[e]		X	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]		X	X		X			X	X
Local and Systemic Reactogenicity																						
Dispense participant diary[n]		X			X		X		X		X		X									

Study Period	Screen	Active Dosing												Safety Follow-up								
Study Day		**Base-line Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 127**	**Day 141**	**Day 148**	**Day 155**	**Day 169**	**Day 197[a]**	**Day 225**	**Day 253[a]**	**Day 281[a]**	**Day 309**	**ET**
Visit Window (Days)	**45 Days**	**N/A**	**± 1**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**N/A**
Study Weeks		**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**	**24**	**28**	**32**	**36**	**40**	**44**	
Review participant diary[n]			X	X		X		X		X		X			X							
Immunology and Biomarkers																						
PBMC collection for biomarker cellular assays		X[c]	X				X[c]	X	X[c]	X	X[c]	X	X[c]	X	X	X		X				X
Serum collection for HBV-targeting antibody measurements		X[c]			X[c]		X[c]		X[c]		X[c]		X[c]			X		X				X
Whole blood collection for biomarker analysis		X[c]					X[c]	X	X[c]	X	X[c]	X	X[c]		X							X
Clinical Virology																						
HBV neutralizing antibody and antivector antibody assessment		X[c]		X	X[c]		X[c]		X[c]		X[c]		X[c]			X		X			X	X
HBV viral biomarkers[o,l]		X[c]		X	X[c]		X[c]		X[c]		X[c]		X[c]			X		X			X	X
HBV genomic sequencing[l]		X[c]			X[c]		X[c]		X[c]		X[c]		X[c]			X		X			X	X
HBV genotyping[l]	X	X[c]																				

DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV-1 = human immunodeficiency virus type 1; I/E = inclusion/exclusion; IP = investigational product; N/A = not applicable; PBMC = peripheral blood mononuclear cell; PBO = placebo; RNA = ribonucleic acid; Screen = screening

a These visits are only required for pregnancy testing for women of childbearing potential. Participants who are able to access an at-home urine pregnancy test from the clinical site may conduct their pregnancy test at home and will be contacted by site staff to confirm the result. If urine pregnancy results are equivocal or positive, a serum pregnancy test will be required.

b Participant shall receive the appropriate investigational product or PBO, as detailed in Section 5.3 and Table 8. Participants in Cohort 7 will be monitored in the clinic for at least 2 hours following each dose of investigational product. Participants may be required to remain in the clinic for additional observation at the discretion of the investigator. Participants will receive a follow-up phone call for 2 consecutive days following each dose to review protocol restrictions, adverse events, any concomitant medication usage, and completion of participant diaries.

c Collection of vital signs, physical examinations, and blood/urine samples should be completed prior to investigational product administration.

d Symptom-driven physical examinations shall be performed as deemed necessary.

e At the discretion of the investigator.

f Indicated assessment shall be taken prior to dosing and within 15 to 30 minutes following investigational product administration.

g Hematology assessments are listed in Section 6.4.5.

h An FSH test is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.

i For participants assigned female at birth and of childbearing potential. On days of investigational product administration, urine pregnancy testing is also required to determine pregnancy status prior to dosing.

j Chemistry and liver function assessments are listed in Section 6.4.5.

k Central laboratory will calculate creatinine clearance.

l Required for Phase 1b only.

m Coagulation assessments are listed in Section 6.4.5.

n Participants will be asked to record potential vaccine reactions based on solicited events via diary for 7 days following each administration of investigational product. Review of participant reactogenicity data will occur at each visit after vaccination up to 7 days postdose or beyond for cases with ongoing events after 7 days postdose.

o To include the assessments of: HBV DNA, quantitative HBsAg, anti-HBsAg antibody, HBcrAg, HBeAg, HBV RNA.

p HBV testing is for HBV surface antigen and antibody.

Table 4, Table 5, and Table 6 are for biomarker collections only.

Table 4. Sampling for Biomarker Assessments for Phase 1a – Cohorts 1 and 2 (Two Total Doses)

		Active Dosing					Safety Follow-up					
Sample Type		**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 57**	**Day 64**	**Day 71**	**Day 85**	**Day 141**	**Day 225**	**ET**
Visit Window (Days)		**N/A**	**± 1**	**± 1**	**± 3**	**± 3**	**± 1**	**± 1**	**± 3**	**± 7**	**± 7**	**N/A**
Study Weeks	**Biomarker Assay**	**1**	**1**	**2**	**4**	**8**	**9**	**10**	**12**	**20**	**32**	
PBMC	HBV-specific IFN-γ T-cell ELISpot	X		X	X	X		X	X	X	X	X
PBMC	T-cell ICS	X		X	X	X		X	X			X
PBMC	HBV-specific B-cells	X	X			X	X					X
PBMC	CyTOF	X		X		X		X				X
PBMC	Single cell multiomics	X		X		X		X				X
PBMC	TCR repertoire	X		X		X		X				X
Serum	HBV-specific antibodies	X			X	X			X	X	X	X
Serum	Immune complexes	X			X	X			X	X	X	X
Plasma	Cytokine analysis	X		X		X		X				X
Whole blood	Bulk gene expression	X		X		X		X				X

CyTOF = cytometry by time of flight; ELISpot = enzyme-linked immunospot assay; ET = early termination; HBV = hepatitis B virus; ICS = intracellular cytokine staining; IFN-γ = interferon gamma; N/A = not applicable; PBMC = peripheral blood mononuclear cell; TCR = T-cell receptor

Table 5. Sampling for Biomarker Assessments for Phase 1a – Cohorts 3 and 4 and Phase 1b - Cohorts 5 and 6 (Four Total Doses)

Sample Type	Biomarker Assay	Active Dosing								Safety Follow-up				
		Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 92	Day 99	Day 113	Day 169	ET
Visit Window (Days)		N/A	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 3	± 7	N/A
Study Weeks		1	1	2	4	6	8	10	12	13	14	16	24	
PBMC	HBV-specific IFN-γ T-cell ELISpot	X		X	X	X	X	X	X		X	X	X	X
PBMC	T-cell ICS	X		X	X	X	X	X	X		X	X		X
PBMC	HBV-specific B-cells	X	X						X	X				X
PBMC	CyTOF	X		X		X		X			X			X
PBMC	Single cell multiomics	X		X	X	X	X	X	X		X		X	X
PBMC	TCR repertoire	X		X		X		X			X		X	X
Serum	HBV-specific antibodies	X			X		X		X			X	X	X
Serum	Immune complexes	X			X		X		X			X	X	X
Plasma	Cytokine analysis	X		X	X	X	X	X	X		X			X
Whole blood	Bulk gene expression	X		X	X	X	X	X	X		X			X

CyTOF = cytometry by time of flight; ELISpot = enzyme-linked immunospot assay; ET = early termination; HBV = hepatitis B virus; ICS = intracellular cytokine staining; IFN-γ = interferon gamma; N/A = not applicable; PBMC = peripheral blood mononuclear cell; TCR = T-cell receptor

Table 6. Sampling for Biomarker Assessments for Phase 1a – Cohort 8 and Phase 1b - Cohort 7 (Six Total Doses)

		Active Dosing										Safety Follow-up				
Sample Type		**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 127**	**Day 141**	**Day 148**	**Day 155**	**Day 169**	**Day 225**	**ET**
Visit Window (Days)		**N/A**	**± 1**	**± 3**	**± 3**	**± 1**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**N/A**
Study Weeks	**Biomarker Assay**	**1**	**1**	**4**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**	**24**	**32**	
PBMC	HBV-specific IFN-γ T-cell ELISpot	X			X	X	X	X	X	X	X		X	X	X	X
PBMC	T-cell ICS	X			X	X	X	X	X	X	X		X	X		X
PBMC	HBV-specific B-cells	X	X				X		X		X	X				X
PBMC	CyTOF	X				X		X		X			X			X
PBMC	Single cell multiomics	X			X	X	X	X	X	X	X		X		X	X
PBMC	TCR repertoire	X				X		X		X			X		X	X
Serum	HBV-specific antibodies	X		X	X		X		X		X			X	X	X
Serum	Immune complexes	X		X	X		X		X		X			X	X	X
Plasma	Cytokine analysis	X			X	X	X	X	X	X	X		X			X
Whole blood	Bulk gene expression	X			X	X	X	X	X	X	X		X			X

CyTOF = cytometry by time of flight; ELISpot = enzyme-linked immunospot assay; ET = early termination; HBV = hepatitis B virus; ICS = intracellular cytokine staining; IFN-γ = interferon gamma; N/A = not applicable; PBMC = peripheral blood mononuclear cell; TCR = T-cell receptor

1. INTRODUCTION

1.1. Background

Chronic hepatitis B (CHB) is the most prevalent viral hepatitis disease, globally affecting close to 296 million individuals {World Health Organization (WHO) 2021}. Most people living with CHB are in the Western Pacific Region and Sub-Saharan Africa, where 116 and 82 million people, respectively, are chronically infected. The International Agency for Research on Cancer estimates that, globally, 1 in 3 of all cases of hepatocellular carcinoma (HCC) are secondary to CHB. In Africa and East Asia, the proportion is closer to 60% {Singal 2020}. There are currently several prophylactic hepatitis B virus (HBV) vaccines commercially available with efficacies approaching 95% in some populations. Coverage has improved significantly since 2019 but is not optimal {Pattyn 2021} as there is still a high rate of new cases of HBV annually in many regions of the world. Chronic infection with HBV has multiple clinical sequelae such as chronic liver disease that progresses to cirrhosis, and end-stage liver disease (ESLD) in approximately 7% of cases even with nucleos(t)ide analogues (NAs) therapy {Liaw 2004}.

Currently, 2 classes of drugs have been approved for treatment of CHB, NAs, and interferons (IFNs). Nucleos(t)ide analogues are very effective at suppressing viral replication and reducing the risk of complications of CHB, but for those who meet current treatment criteria, lifelong therapy is required. Additionally, concerns of adherence, cost, and potential HBV reactivation secondary to treatment interruptions have limited use of NAs to only a subset of patients with CHB. Pegylated IFN-based therapies have achieved modest levels of HBV DNA suppression and hepatitis B surface antigen (HBsAg) loss in the range of 3% to 3.5%, ie, functional cure (defined as HBV DNA suppression, HBsAg loss with or without anti-HBsAg seroconversion) {Ren 2019}. This treatment unfortunately is poorly tolerated. Combinations of NAs and IFNs have been evaluated in prior studies attempting to achieve HBV functional cure but HBsAg loss has been achieved in only up to 9% of patients {Ren 2019}.

Immune correlates of functional cure in individuals with resolved acute HBV and CHB on NA therapy show that cure is associated with increases in HBV-specific CD4+ and CD8+ T-cells {Boni 2012, Hoogeveen 2022, Hoogeveen 2019, Maini 2018}. Consistent with the clinical observations, studies in CD8-depleted nonhuman primates suggest that HBV-specific CD8+ T-cells are critical for eliminating existing HBV-infected hepatocytes {Thimme 2003}. Furthermore, numerous studies show that HBV-specific CD8+ T-cell responses are associated with improved viral control and functional cure {Chen 2020, de Niet 2016, Fisicaro 2010, Pallett 2017}. Therefore, therapeutic strategies, such as vaccination, will need to induce a strong CD8+ T-cell response to maximize the likelihood of achieving a functional cure {Boni 2012, Chen 2020, de Niet 2016, Fisicaro 2010, Hoogeveen 2019, Maini 2018, Pallett 2017}. Induction of anti-HBsAg antibody responses is also highly desirable for patients with CHB, as viral rebound is less likely to occur after HBsAg loss in patients who also achieve anti-HBsAg seroconversion {Yip 2018}.

Different combinations of investigational products are currently in clinical testing for their ability to induce HBV functional cure {Roca Suarez 2021}. Functional cure is expected to significantly reduce risk of progression to ESLD and HCC. These treatment concepts usually include 3 main components: (1) viral antigen reduction strategies, (2) immune system modulation with the aim of reversing T-cell exhaustion, and (3) stimulation of an HBV-specific immune response targeted at viral elimination. Therapeutic vaccines are considered a key component of such treatment strategies {Cargill 2021}. In this effort, therapeutic vaccines are used to stimulate an individual's immune system by stimulating HBV-specific responses against infected hepatocytes. Consequently, current efforts to develop HBV therapeutic vaccines seek to induce a polyfunctional response through the activation of HBV-specific T-cell responses and the induction of cross-reactive antibodies against different genotypes of HBV circulating globally. In a recent Phase 1b/2a study, the heterologous vector-based investigational therapeutic vaccine VTP-300 comprising chimpanzee adenoviral vector (ChAdOx1-HBV) and modified vaccinia Ankara boost HBV (MVA-HBV) induced a sustained decline in HBsAg levels both as monotherapy and combined with nivolumab with no vaccine-related serious adverse events (SAEs). One individual being treated with vaccine combined with nivolumab achieved HBsAg loss {Evans 2022}.

The investigational therapeutic vaccine proposed for this study is based on a nonreplicating arenavirus vector encoding 3 highly conserved HBV proteins: the HBV core, HBsAg, and a truncated inactive version of the HBV polymerase. A prior Phase 1 clinical study investigating a cytomegalovirus (CMV) vaccine based on a similar platform revealed that vaccinated individuals mounted both CD8+ and CD4+ T-cell responses that were specific for vaccine vector-encoded CMV glycoprotein B and phosphoprotein 65 {Schwendinger 2022}. These arenavirus vector vaccines use the platform used in the CMV vaccine, which has a safety profile similar to the current standard of care vaccines {Schwendinger 2022}. As detailed in Section 1.2.1.2 and the investigator's brochure (IB), GS-2829 and GS-6779 induce potent HBV-specific T-cell and anti-HBsAg responses and have the potential to promote functional cure, either as monotherapy in select patients or in combination with other agents.

1.2. Background on Investigational Product

The investigational product is a vaccine developed on a nonreplicating arenavirus vector platform. A CMV vaccine developed on a similar arenavirus vector platform has been shown to induce indication-specific dose-dependent immune responses {Schwendinger 2022}. The proposed product is delivered sequentially as an alternating 2-vector therapy using different arenavirus viral vectors (GS-2829 and GS-6779) and will be compared with an inactive placebo (PBO).

A list of study interventions and their authorization status is provided in Appendix 11.2.

1.2.1. GS-2829 and GS-6779

1.2.1.1. General Information

GS-2829 is an HBV-specific immunotherapy consisting of 2 coformulated nonreplicating arenavirus vectors derived from Pichinde virus (PICV). GS-1164202 encodes the HBV core and HBsAg proteins separated by a translational skip site {Liu 2017}, while GS-1164203 encodes a truncated and inactive version of the HBV polymerase. GS-2829 is also referred to as a "therapeutic vaccine" because it is intended to utilize the patient's own immune system to induce a strong CD8+ T-cell response against HBV, along with HBV-specific CD4+ T-cells and anti-HBsAg antibodies.

GS-2829 vectors were generated by replacing the glycoprotein gene of a wild-type arenavirus with an HBV antigen of interest, leaving the RNA replication and protein expression machinery intact while preventing the production of any new virions. These vectors are capable of entering cells, expressing the encoded HBV proteins, and eliciting an HBV-specific immune response, but are incapable of forming new infectious particles. Consequently, GS-2829 vectors are described as "nonreplicating" vectors.

GS-6779 is an HBV-specific immunotherapy consisting of 2 coformulated nonreplicating arenavirus vectors derived from lymphocytic choriomeningitis virus (LCMV). GS-1069374 encodes the HBV core and HBsAg proteins separated by a translational skip site {Liu 2017} while GS-1069370 encodes a truncated and inactive version of the HBV polymerase. GS-6779 is also referred to as a "therapeutic vaccine" because it is intended to utilize the patient's own immune system to induce a strong CD8+ T-cell response against HBV, along with HBV-specific CD4+ T-cells and anti-HBsAg antibody.

GS-6779 vectors were generated by replacing the glycoprotein gene of a wild-type arenavirus with an HBV antigen of interest, leaving the RNA replication and protein expression machinery intact while preventing the production of any new virions. GS-6779 vectors are capable of entering cells, expressing the encoded HBV proteins, and eliciting an HBV-specific immune response, but are incapable of forming new infectious particles. Consequently, GS-6779 vectors are described as "nonreplicating" vectors.

Immunizations of nonhuman primates with GS-2829 and GS-6779 in an alternating, sequential manner led to consistent, high-magnitude, HBV-specific CD8+ T-cell responses against all 3 encoded HBV antigens, and further induced high titers of anti-HBsAg antibody. As strong CD8+ T-cell responses and anti-HBsAg antibodies are associated with immune clearance and long-term control of CHB {Boni 2012, Hoogeveen 2022, Yip 2018}, therapeutic vaccination with GS-2829 and GS-6779 may mediate functional cure in patients with CHB. For further information on GS-2829 and GS-6779, refer to the IB, including information on the following:

- Nonclinical pharmacology and toxicology

1.2.1.2. Nonclinical Pharmacology and Toxicology

GS-2829 and GS-6779 have been evaluated for pharmacodynamic effect (immunogenicity) in nonhuman primates and have been shown to induce robust and consistent T-cell and antibody responses to HBV antigens. The number and schedule of GS-2829 and GS-6779 doses were optimized in cynomolgus macaque studies. Nonclinical toxicology was evaluated in a repeated-dose Good Laboratory Practice (GLP)-compliant toxicity and local tolerability study in cynomolgus macaques and alternating 2-vector therapy with GS-2829 and GS-6779 was well tolerated at 2.65×10^7 focus-forming unit (FFU)/dose GS-2829 and 1.59×10^7 FFU/dose GS-6779. Nonadverse findings were limited to transient increased body temperature and very slight edema and/or slight erythema and minimal to moderate mixed cell infiltration at the injection sites. These are typical vaccine-related effects.

The biodistribution and persistence of replication-deficient LCMV (rLCMV)-based vector (ie, the vector used in GS-6779) was evaluated in C57BL/6 mice following a single intramuscular injection. Quantifiable rLCMV vector genome was detected starting at 1-hour postdose (first sampling time point) and was below the quantifiable level in blood and tissues by Day 28, except the injection sites for males that remained quantifiable on Day 56, demonstrating clearance from blood and tissues.

The biodistribution of the PICV-based vector (ie, the vector used in GS-2829) is being evaluated in an ongoing study in Wistar Han rats following a single intramuscular injection. Similar to the LCMV vector used in GS-6779, the PICV-based vector is also a nonreplicating arenavirus-based vector that is expected to be cleared from injection site, blood, and tissues and would not raise any nonclinical safety concern.

Further overviews of the nonclinical pharmacology and toxicology for GS-2829 and GS-6779 are provided in the IB.

1.2.2. Information About Comparator (Placebo)

The comparator will be an inactive PBO comprising a solution of human serum albumin with visual characteristics similar to GS-2829 and GS-6779.

1.2.3. Information About Auxiliary Medicinal Products

Treatment cohorts are described in Section 3.1. There will be no auxiliary medicinal products (AxMPs) used for participants in Cohorts 1 through 4 and in Cohort 8.

Auxiliary medicinal products will only be used in Cohorts 5 through 7, as participants in these cohorts are required to continue to receive NA therapy for HBV. Although prior studies have shown improvement in HBV-specific immune response after NA therapy {Stoop 2007}, the rate of HBsAg loss remains very low (approximately 0.5% to 1.0% per year in CHB) {Liaw 1991} {Chu 2007}. In this study, NA therapy is considered to be background treatment, thus, is an AxMP. Commercially available HBV NA therapy (ie, tenofovir and entecavir-based therapies), either as single agents or in combination will be appropriate in Cohort 5 through Cohort 7. These HBV active NAs have been used extensively in the treatment of HBV globally, have a well characterized safety profile, and have been shown to be well tolerated.

1.3. Rationale for This Study

Current standard of care for HBV treatment, though effective at reducing progression to advanced liver disease and HCC, requires lifelong therapy. The nonreplicating arenavirus vectors GS-2829 and GS-6779 given as an alternating 2-vector therapy have shown broad polyfunctional HBV-specific T-cell and antibody response in nonclinical studies (Section 1.2.1.1). These results suggest that GS-2829 and GS-6779 may induce HBsAg loss and HBsAg seroconversion as monotherapy or combined with other agents.

This study will evaluate the safety of these products in both healthy participants and subsequently in virally suppressed individuals with CHB. The study will be a randomized blinded clinical study evaluating the safety, tolerability, and immunogenicity of GS-2829 and/or GS-6779 compared with PBO. Participants will be randomized in a 4:1 ratio of active to PBO to ensure a clear comparison.

The primary goal is to establish the safety and tolerability profile of alternating 2-vector therapy of GS-2829 and GS-6779 in healthy participants (Phase 1a) and virally suppressed participants with CHB (Phase 1b). This will be evaluated in a stepwise manner in the Phase 1a based on the following in healthy participants:

- Individual vector monotherapy (Cohorts 1 and 2), administered once every 8 weeks
- Alternating 2-vector combination therapy (GS-2829, followed by GS-6779), administered once every 4 weeks at the low-dose (Cohort 3) and high-dose levels (Cohort 4)
- Extension of the high-dose level alternating 2-vector combination therapy with an additional administration of each investigational product (Cohort 8)

Study drug administration is further detailed in Section 3.2, Table 8.

Phase 1b will evaluate the safety and tolerability profile of the alternating 2-vector therapy with GS-2829 and GS-6779 in virally suppressed CHB patients as follows:

- Alternating 2-vector combination therapy, administered once every 4 weeks at the low-dose (Cohort 5) and high-dose (Cohort 6) levels
- Extension of the high-dose level alternating 2-vector combination therapy to include an additional administration of each investigational product (Cohort 7)

Study drug administration is further detailed in Section 3.2, Table 8.

Dose level, and the number of doses of 2-vector combination therapy has the potential to augment the vaccine-elicited immune response. It is critical to optimize the magnitude and durability of the HBV-specific immune response, believed to be a fundamental component of achieving an HBV cure, that is generated by the vaccine. Secondary to establishing the safety and tolerability profile, the magnitude and durability of the HBV-specific immune responses elicited by the alternating 2-vector therapy will be explored in healthy (Phase 1a) and virally suppressed CHB participants (Phase 1b).

1.4. Rationale for the Dose Selection of the Investigational Product

In the GLP tolerability study (TX-488-2009), 1-vector repeat administration and alternating 2-vector therapy with 2.65×10^7 FFU/dose GS-2829 and/or 1.59×10^7 FFU/dose GS-6779 every 2 weeks for a total of 6 doses in cynomolgus monkeys were well tolerated and no dose-limiting safety signals were identified.

Administration of the alternating 2-vector therapy with GS-2829 and GS-6779 in cynomolgus monkeys every 4 weeks induced robust HBV-specific T-cell responses at both dose levels as measured by interferon gamma (IFN-γ) enzyme-linked immunospot assay (ELISpot). The cumulative 4 total dose regimen at a frequency of dosing of every 4 weeks elicited the highest immune response compared with every 2-week dosing and alternating 2- and 4-week dosing.

Extension of treatment (one additional dose of 2-vector therapy) had a comparable safety profile with a potential increase in the magnitude of the elicited immune response. Please refer to the IB for further details on the effect of increasing the number of total doses.

Starting dose levels for GS-2829 and GS-6779 were selected to achieve a 10-fold lower dose than the well-tolerated dose in cynomolgus monkeys, consistent with a lower pharmacodynamic effect noted in previous clinical experience with arenavirus vectors using a 10-fold dose range {Schwendinger 2022}. In nonhuman primate studies up to the target dose for both vectors, the most common vaccination-related adverse effects were transient elevated body temperature and edema/erythema at the injection sites. The elevated body temperature was self-limiting and resolved by 24 hours postdose, whereas edema/erythema resolved by 72 hours postdose. Further details for these studies are provided in the IB.

1.5. Risk/Benefit Assessment for the Study

Potential risks of a participant's study involvement include unknown adverse events (AEs), general risks associated with frequent clinic visits and laboratory blood draws, local events of injection including site pain, swelling, and erythema, as well as systemic events of fatigue, fever, arthralgia, myalgia, headache, and nausea. Strategies to mitigate these risks include close monitoring of participants' clinical status, laboratory values, and AEs in the immediate postdose period and beyond. Parameters for discontinuation of the investigational product due to AEs will be well defined and closely followed.

This is a first-in-human study and there may be unknown risks associated with the investigational product. This may include allergic and hypersensitivity reactions and/or anaphylaxis, which have been observed in similar vaccines. Due to these risks, sentinel participants will be observed at the study site for at least 8 hours after investigational product administration on Day 1, and for at least 4 hours following each administration of investigational product for all subsequent doses. All other Phase 1a participants will be monitored in the clinic for at least 4 hours following each dose of investigational product. Participants in Cohorts 5, 6, and 7 will be monitored in the clinic for at least 2 hours following each dose of investigational product. Participants may be required to remain in the clinic for additional observation at the discretion of the investigator. Participants who experience hypersensitivity or anaphylaxis will discontinue the investigational product and will not be rechallenged. The duration of the monitoring period may be revised based on recommendations of the Safety Review Team (SRT).

As described in Section 1.3, the safety profile will be established in a stepwise manner in healthy participants in the Phase 1a portion of the study. Specific information on the study design, safety data to be evaluated by the SRT, and stopping rules is detailed in Section 3. In addition to the monitoring strategy described previously in this section for this first-in-human study, the following will be implemented to support the safety profile and manage the unknown risks associated with of the investigational products as monotherapy, combination therapy at low- and high-dose levels, and extension of the treatment duration to include an additional administration of 2-vector therapy (detailed in Section 3.2, Table 8):

- The investigational products will be first tested in the monotherapy setting to evaluate the safety of repeated low-dose levels of the vectors (Cohorts 1 and 2).
- As detailed in Section 3.2, Table 8, alternating 2-vector combination therapy will be administered once every 4 weeks and will be first evaluated at the low-dose level (Cohort 3), and then at the high-dose level (Cohort 4).
- The low-dose level safety profile will be established first in healthy participants (Phase 1a, Cohort 3) after a cumulative evaluation of Day 43 safety data (2 weeks after the completion of the first dose of the 2-vector combination therapy) and the available cumulative safety data from all prior cohorts, before initiating the alternating 2-vector therapy at the high-dose level in healthy participants (Cohorts 4 and 8), and the low-dose level in virally suppressed CHB participants (Cohort 5, Phase 1b).
- The safety profile of the high-dose level will be established in healthy participants (Cohort 4, Phase 1a) based on evaluation of Day 43 safety data (2 weeks after completion of the first dose of each investigational product of the 2-vector combination therapy) and the available cumulative safety data from all prior cohorts, before initiating the high-dose level in virally suppressed CHB participants (Cohorts 6 and 7, Phase 1b).
- The decision to extend the treatment duration to a third dose of each investigational product of 2-vector combination therapy (Cohort 8, Phase 1a and/or Cohort 7, Phase 1b) will be based on evaluation of all the Cohort 4 Day 99 (2 weeks after completion of the second dose of 2-vector therapy) safety data, in addition to all other available cumulative safety data from all dosed cohorts.

This stepwise, gated approach will mitigate any unknown risks of dose-level increases, and the additional dose of alternating 2-vector therapy. Based on the current information (included in the IB), it is anticipated that the overall benefit-risk profile is comparable between 2 versus 3 doses of 2-vector combination therapy in healthy participants, and participants with CHB.

Immune-mediated conditions have been reported in some studies and in clinical use of some vaccines. In this early-stage protocol, individuals with a history of autoimmune diseases are excluded. Investigational product will be stopped for any participant with a new onset or worsening of any potentially immune-mediated condition, regardless of assessment of relationship to study vaccination. Management of such events will be based on the best available local standard of care. A list of potential immune-mediated conditions is provided in Appendix 11.7.

The investigational product has induced HBV-specific immune responses in nonhuman primate studies indicating a potential to mediate functional cure in individuals with CHB. There is however no clinical data suggesting any known direct benefit to participants in this study. The data from this study will, however, support the development of GS-2829 and GS-6779, products that when used in combination therapy could help achieve a curative treatment for HBV.

An infectious disease pandemic may pose additional risks to investigational product availability, study visit schedule, and adherence to protocol-specified safety- monitoring or laboratory assessments. Refer to Appendix 11.3 for further details on the risks and risk mitigation strategy.

Considering the above, the benefit-risk balance for this study is considered positive.

1.6. Compliance

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are outlined in Table 7.

Table 7. Study Objectives and Endpoints

Primary Objective	Primary Endpoint
• To evaluate the safety and tolerability of repeated dosing of GS-2829 and GS-6779 in healthy participants and in virally suppressed participants with CHB	• Proportion of participants with treatment-emergent AEs, SAEs, and laboratory abnormalities
Secondary Objective	**Secondary Endpoints**
• To evaluate the immunogenicity of repeated dosing of GS-2829 and GS-6779 in healthy participants and in virally suppressed participants with CHB	• Incidence and magnitude of vaccine-induced T-cell responses
Exploratory Objectives	**Exploratory Endpoints**
• To further evaluate the T- and B-cell immunogenicity and mechanism of action of GS-2829 and GS-6779 in healthy participants and in virally suppressed participants with CHB	• Postvaccination changes in T-cell subset frequencies and activation status from baseline levels • Postvaccination changes in HBV-specific B-cell subset frequencies from baseline levels • Postvaccination changes in HBV antigen-antibody immune complexes from baseline levels • Postvaccination changes in HBV-specific antibodies from baseline levels • Postvaccination changes in HBV-specific neutralizing antibodies from baseline levels
• To evaluate the impact of GS-2829 and GS-6779 on HBV-specific viral biomarkers in participants with CHB	• Change in HBsAg from baseline • Proportion of participants with HBsAg loss with or without HBsAg seroconversion • Changes in quantitative HBV RNA, HBV DNA, hepatitis B core-related antigen (HBcrAg), hepatitis B e antigen (HBeAg), and other HBV viral biomarkers from baseline • Genomic sequencing of HBV in virally suppressed participants as needed
• To characterize the relationship between immunologic changes and circulating HBV viral markers	• Correlation between changes in immunological biomarkers and circulating HBV viral markers from baseline
• To evaluate the presence of antivector antibodies and their impact on immunogenicity and virologic endpoints	• Postvaccination changes in vector-specific antibodies from baseline levels

3. STUDY DESIGN

3.1. Study Design

This protocol describes a blinded, placebo-controlled, randomized Phase 1a and Phase 1b study to evaluate the safety, tolerability, and immunogenicity of repeated doses of GS-2829 and GS-6779 in healthy participants (Phase 1a) and participants with CHB (Phase 1b). The study will comprise 8 cohorts, which will enroll approximately 10 participants each, with a 4:1 randomization either active viral vectors GS-2829 and/or GS-6779 or PBO. The dosing schedules by cohort are provided in Table 8.

Healthy participants aged 18 through 60 years will be enrolled into the Phase 1a part of the study; and participants with CHB aged 18 through 65 years will be enrolled into the Phase 1b part of the study. To ensure there is enough information to assess any differential for safety and tolerability by sex at birth, enrollment of participants of both sexes is encouraged.

An overview of the study design is described below and shown in Figure 1, Figure 2, and Figure 3.

The investigational products GS-2829 and GS-6779 are available as $\geq 1.0 \times 10^7$ FFU/mL. There are 2 dose levels in this study: high dose (0.5 mL of the undiluted solution) and low dose (0.5 mL of the 10-fold dilution of the high dose).

Phase 1a activities will be performed in healthy participants at a single study site. Healthy participants will be enrolled into 1 of 5 cohorts to receive the investigational product as follows:

- Cohort 1 – Single low dose of GS-2829 or PBO on Day 1 and Day 57.
- Cohort 2 – Single low dose of GS-6779 or PBO on Day 1 and Day 57.
- Cohort 3 – Single low dose of GS-2829 or PBO on Day 1 and Day 57; and single low dose of GS-6779 or PBO on Day 29 and Day 85.
- Cohort 4 – Single high dose of GS-2829 or PBO on Day 1 and Day 57; and single high dose of GS-6779 or PBO on Day 29 and Day 85.
- Cohort 8 – Single high dose of GS-2829 or PBO on Day 1, Day 57, and Day 113; and single high dose of GS-6779 or PBO on Day 29, Day 85, and Day 141.

Phase 1b activities will be performed at multiple study sites (approximately 15) in participants diagnosed with CHB who are virally suppressed (Cohort 5, 6, and 7). These participants will be enrolled into 1 of 3 cohorts to receive the investigational product as follows:

- Cohort 5 – Single low dose of GS-2829 or PBO on Day 1 and Day 57; and single low dose of GS-6779 or PBO on Day 29 and Day 85.

- Cohort 6 – Single high dose of GS-2829 or PBO on Day 1 and Day 57; and single high dose of GS-6779 or PBO on Day 29 and Day 85.

- Cohort 7 - Single high dose of GS-2829 or PBO on Day 1, Day 57 and Day 113; and single high dose of GS-6779 or PBO on Day 29, Day 85, and Day 141.

Cohorts 1, 2, and 3

Cohorts 1 and 2 will enroll concurrently and will receive investigational product in 2 groups, a sentinel group (2 active and 1 PBO, randomly assigned) and the remainder (6 active and 1 PBO), for a total of approximately 10 healthy participants per cohort. Dosing the remainder of Cohorts 1 and 2 and initiation of Cohort 3 will commence at the discretion of the investigator in consultation with the sponsor's medical monitor upon evaluation of available safety data through at least 14 days after the first dose of investigational product in Cohort 1 and 2 sentinel participants. The duration of this review period may be increased based on emerging preliminary safety data. Decisions to initiate a higher dose level cohort and any required revisions to postdose monitoring will be made upon the review of all available safety data by the SRT.

Cohorts 4 and 5

Initiation of Cohorts 4 and 5, which will run concurrently, will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 Days after the initial dose of both investigational products for all participants enrolled in Cohort 3), in addition to all available safety data from Cohorts 1 and 2. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 8

Initiation of Cohort 8 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after all participants in Cohort 3 have completed the initial dose of both investigational products), in addition to all available safety data from prior cohorts. Initiation of a third dose of 2-vector combination therapy will be determined at the discretion of the SRT based on the evaluation of the available safety data through Day 99 (14 days after all participants in Cohort 4 have completed the second dose of both investigational products), in addition to all available safety data. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 6

Initiation of Cohort 6 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after initial dose of both the investigational products for all participants enrolled in Cohort 4), available safety data from participants enrolled

in Cohort 5, and all available safety data from all dosed cohorts, and dosing will be initiated only in the absence of dose-limiting toxicity and/or meeting any prespecified stopping criteria. The duration of this review period may be increased based on the emerging and cumulative safety data.

Cohort 7

Initiation of Cohort 7 will be determined at the discretion of the SRT based on the evaluation of available safety data through Day 43 (14 days after initial dose of both the investigational products for all participants enrolled in Cohort 4), available safety data from participants enrolled in Cohort 5, and all available safety data from all dosed cohorts. Initiation of the third dose of 2-vector combination therapy will be determined at the discretion of SRT based on the evaluation of the available safety data through Day 99 **(**14 days after all participants in Cohort 4 have completed the second dose of both investigational products), in addition to all available safety data. The decision on cohort initiation will be based on prespecified criteria agreed upon by the SRT and documented in the SRT charter. The duration of this review period may be increased based on the emerging and cumulative safety data.

3.1.1. Safety Review Team and Charter

An SRT will make decisions on initiating enrollment of higher dose cohorts and initiating the third dose of both investigational products based on available safety data in prior study cohorts as described in Section 3.1. There will be 3 planned SRT reviews in this protocol. Ad hoc reviews can be convened at the discretion of the SRT during the study based on new safety concerns and/or the protocol stopping rules (Section 3.3.3).

An SRT charter defining the team membership, meeting conduct, and decision-making process will be agreed upon by all team members before the first meeting. The data reviewed at the team meetings to make cohort transition decisions will be defined in the charter. The quality control checks performed on the data reviewed and used for making these decisions will also be described in the charter.

Source data verification may not be performed before SRT meetings. Alternative data quality control checks that are performed on data used to make dosing continuation or transition decisions are described in the SRT charter.

3.2. Duration of Dosing

The investigational product will be administered as a single agent or sequential injected doses as shown in Table 8.

Table 8. Investigational Product Dose Timing

Cohort	1	2	3	4	8	5	6	7
Population	**HP**	**HP**	**HP**	**HP**	**HP**	**CHB (Supp)**	**CHB (Supp)**	**CHB (Supp)**
Dose Level	**Low[a]**	**Low[a]**	**Low[a]**	**High[b]**	**High[b]**	**Low[a]**	**High[b]**	**High[b]**
Study Day 1	GS-2829 or PBO IM	GS--6779 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM
Study Day 29			GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM
Study Day 57	GS-2829 or PBO IM	GS-6779 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM	GS-2829 or PBO IM
Study Day 85			GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM	GS-6779 or PBO IM
Study Day 113					GS-2829 or PBO IM			GS-2829 or PBO IM
Study Day 141					GS-6779 or PBO IM			GS-6779 or PBO IM
Total number of doses (injections)	2	2	4	4	6	4	4	6

CHB = chronic hepatitis B; FFU = focus-forming unit; HP = healthy participant; IM = intramuscular; PBO = placebo; Supp = suppressed

a Low dose = 0.5 mL of a 10-fold dilution of high-dose investigational product.

b High dose = 0.5 mL of high-dose investigational product ($\geq 1.0 \times 10^7$ FFU/mL).

All participants will be followed for safety for 6 months after their last dose of investigational product.

3.3. Protocol-Specific Discontinuation Criteria

GS-2829 and GS-6779 have been evaluated in nonclinical studies without any identified dose-limiting toxicity up to the highest proposed dose. In this first in human protocol, the following rules will guide early discontinuations from the study.

3.3.1. Criteria for Early Discontinuation for the Individual Participant From the Investigational Product

Administration of the investigational product should be discontinued in the following instances:

- If a participant experiences a Grade 3 or higher treatment-emergent AE (TEAE; excluding nausea, headache, measured grades of erythema and edema/induration alone) or confirmed Grade 3 or higher laboratory abnormality (except for those with a physiologic explanation for the events [eg, blood in urine occurring in a menstruating female, creatine phosphokinase elevation after strenuous exercise, triglyceride elevation that is nonfasting, etc]) considered clinically significant by the investigator and judged as related to the investigational product
- Any AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Participant request to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study (refer to Appendix11.4)
- Loss to follow-up
- Investigator discretion
- Discontinuation of the study by the sponsor

If a participant refuses to receive the remaining doses of investigational product as the result of an AE that is judged by the investigator as related to investigational product, an early termination (ET) visit should be completed, and every attempt should be made to retain the participant in the study to continue study evaluations. Following the receipt of any abnormal results believed to be related to investigational product at the ET visit, further testing should be repeated weekly or as often as deemed clinically appropriate by the investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

If the participant withdraws consent from the study, the ET evaluations and/or procedures should be performed within 7 days of the decision to discontinue from the study.

3.3.2. Criteria for Early Discontinuation for the Individual Participant From the Study

The participant will be discontinued from the study early in the following instances:

- Withdrawal of consent
- Participant request to discontinue for any reason
- Participant noncompliance
- Death

3.3.3. Criteria for Early Discontinuation of a Cohort (Stopping Rules)

3.3.3.1. Stopping Rules for Cohorts 1 to 4 and 8 (Phase 1a)

Dosing of an individual cohort (ie, 1, 2, 3, 4 or 8) will be suspended when:

- 2 or more participants in each cohort (Cohort 1, 2, or 3) or cohorts with the same high-dose level (Cohorts 4 and 8) experience a treatment-emergent, investigational product-related Grade 3 or higher clinical AE with the same preferred term (with the exception of headache, nausea, measured grades of erythema, or edema/induration)

- 1 or more participants in each cohort (Cohort 1, 2, or 3) or cohorts with the same high-dose level (Cohorts 4 and 8) experience a treatment-emergent, investigational product-related SAE

- 2 or more participants in each cohort (Cohort 1, 2, or 3) or cohorts with the same high-dose level (Cohorts 4 and 8) experience confirmed treatment-emergent, investigational product-related Grade 3 or higher clinically significant laboratory abnormality (as determined by the investigator based on clinical evaluation of the participant) unless there is an obvious physiological explanation for the event

- The number and/or severity of AEs justifies discontinuation of the study

Decisions to reinitiate a study cohort will be made by the sponsor in consultation with the investigators and pending a safety review by the SRT of all safety data generated in participants dosed to date. For individuals already receiving investigational product, the decision whether to complete the full course of study treatment will be made by the sponsor with disclosure of new information to the study participant.

3.3.3.2. Stopping Rules for Cohorts 5 to 7 (Phase 1b)

Dosing of an individual cohort (ie, 5, 6, or 7) will be suspended when:

- 2 or more participants in Cohort 5 or cohorts with the same high-dose level (Cohorts 6 and 7) experience a treatment-emergent, investigational product-related Grade 3 or higher clinical AE with the same preferred term (with the exception of headache, nausea, measured grades of erythema, or edema/induration).

- 2 or more participants in Cohort 5 or cohorts with the same high-dose level (Cohorts 6 and 7) experience confirmed treatment-emergent, investigational product-related Grade 3 or higher clinically significant laboratory abnormality (with the exception of clinically insignificant Grade 3 or 4 cholesterol, triglyceride, or glucose). Alanine aminotransferase (ALT) elevations without any evidence of hepatic injury are excluded and will be managed and followed up based on the guideline provided in Section 7.7.4 and Table 11.

- The number and/or severity of AEs justifies discontinuation of any study cohort.

An SRT review of all safety data generated in participants who have received investigational product will be initiated. No new participants will be enrolled or initiated on investigational product; however, for individuals already receiving the investigational product, the decision whether to complete the full course of investigational product will be made by the sponsor, investigator, and where applicable or required, by review by regulatory agencies with disclosure of new information to the study participants.

3.3.4. Criteria for Early Termination of the Study

The study will be stopped in the following instances:

- On recommendation of the SRT based on review of the available safety data
- Discontinuation of the study at the request of Gilead Sciences (Gilead) or a regulatory agency or an independent ethics committee (IEC)

3.3.5. Reporting a Loss to Follow-Up

Should the participant fail to return to the study site for a scheduled protocol-specified visit, the site will need to make at least 3 attempts by a combination of telephone, email, or mail to contact the participant. The site must document all attempts to contact the participant. If a participant does not respond within 3 months after the initial contact, the participant will be considered lost to follow-up and no additional contact will be required.

3.4. Definitions for Time of Primary Endpoint and End of Study

3.4.1. Primary Endpoint

The date for the last participant last visit for the primary endpoint is the date of the last visit to perform assessments for the final analysis.

3.4.2. End of Study

The end of the study is defined as the last participant’s last observation (or visit).

3.5. Source Data

The source data for this study will be obtained from the participating sites, central laboratory, specialty laboratory, the Interactive Response Technology (IRT), and/or other vendors as designated by the sponsor.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 80 unique participants will be enrolled in the study; study participants will include male and nonpregnant, nonlactating, female participants aged 18 through 60 years in Phase 1a cohorts, and aged 18 through 65 years in Phase 1b cohorts. As described in Section 3.1, participants who will be enrolled in:

- Phase 1a cohorts will be healthy participants
- Phase 1b cohorts will have confirmed CHB and will be virally suppressed

Enrollment of participants of both sexes is encouraged. Participants will be enrolled from several sites across the countries where the study will be conducted. Within these countries, recruitment efforts will be broad enough to capture a fair representation of the population but, due to the small sample size per study cohort, no specific quotas will be provided by race and/or ethnicity.

4.1.1. Participant Replacement

If necessary, replacement participants may be enrolled after discussion and approval from Gilead if a current participant is considered nonevaluable. Replacement participants will not be enrolled for participants who discontinue the study due to investigational product-related AEs. Sites will be encouraged to make efforts to retain all individuals who may wish to discontinue the study due to AEs. Ideally, such participants will receive no further investigational product but will continue all visits on schedule.

The primary outcome of interest in this study is the safety and tolerability of GS-2829 and GS-6779 used in combination, so participants who receive only 1 of the 2 vectors and discontinue the study for non-AE related reasons and participants requiring prolonged systemic steroid therapy may be replaced to ensure the collection of evaluable data but will be encouraged to remain on study for evaluation of safety.

4.2. Phase 1a Healthy Participant Inclusion/Exclusion Criteria

4.2.1. Inclusion Criteria

Phase 1a participants must meet all of the following inclusion criteria at screening (or as stated otherwise) to be eligible for participation in this study:

1) Have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures.

2) Assigned male sex at birth or female sex at birth (and be nonpregnant and nonlactating).

3) Participants assigned male at birth and participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified methods of contraception as described in Appendix 11.4.

4) Be aged 18 through 60 years, inclusive, at enrollment.

5) Have a calculated body mass index (BMI) of ≤ 32.0 kg/m^2.

6) Must, in the opinion of the investigator, be in good health based upon medical history and physical examination, including vital signs.

7) Laboratory evaluations and 12-lead electrocardiogram (ECG) evaluations must be without clinically significant abnormalities as assessed by the investigator.

8) Nondiabetic with a hemoglobin A1c < 6.5%.

9) Must be willing and able to comply with all study requirements.

10) No prior history of HBV infection with a negative HBsAg and hepatitis B core antibody.

11) Have liver biometric tests such as ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin at or below the upper limit of normal (ULN).

12) Have a calculated creatinine clearance (CL_{cr}) of at least 90 mL/min (using the Cockcroft-Gault method {Cockcroft 1976}) based on serum creatinine and actual body weight as measured for:

- Participant assigned **male** at birth: $\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} = CL_{cr}$ (mL/min)

- Participant assigned **female** at birth: $\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]}) \times 0.85}{72 \times (\text{Serum Creatinine [mg/dL]})} = CL_{cr}$ (mL/min)

4.2.2. Exclusion Criteria

Phase 1a participants who meet *any* of the following exclusion criteria at screening will not be enrolled in this study:

1) Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with participant treatment, assessment, or compliance with the protocol. This would include renal, hepatic, cardiac, hematological, pulmonary (including chronic asthma), endocrine (including diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.

2) History or evidence of autoimmune disease or known immunodeficiency of any etiology.

3) Have a history of any of the following:

   a) Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria.

   b) Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity).

   c) Known hypersensitivity to the investigational product, metabolites, or to formulation excipients (see Section 5).

   d) Significant cardiac disease (including history of myocardial infarction based on ECG and/or clinical history, any history of ventricular tachycardia, congestive heart failure, or dilated cardiomyopathy with left ventricular ejection fraction ≤ 40%); or a family history of long QT syndrome, or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years.

   e) Severe peptic ulcer disease, gastroesophageal reflux disease, or other gastric acid hypersecretory conditions requiring prolonged (≥ 6 months) medical treatment.

4) Cancer diagnosis within 5 years prior to study entry, other than squamous or basal cell carcinoma of the skin. Participants under evaluation for possible malignancy are not eligible.

5) Current diagnosis of HIV or hepatitis C virus (HCV). Participants who test positive for HCV antibody will require HCV RNA testing by quantitative polymerase chain reaction (PCR) for confirmation of active disease. Participants who are HCV antibody positive, but have a documented negative HCV RNA are eligible.

6) Use of any systemic antibiotics within 30 days of screening.

7) Receipt of any HBV vaccine within 12 months of screening visit or planning HBV vaccination during the study period.

8) Receipt of any investigational product within 3 months or vaccine within 3 months of screening (with the exception of influenza and SARS-CoV-2 vaccines, which if needed, should be administered at least 14 days before or after an investigational product administration).

9) Receipt of immunoglobulin or other blood products withing 3 months of screening.

10) Have current alcohol or substance abuse history judged by the investigator to potentially interfere with participant compliance.

11) Positive serum pregnancy test at screening or positive urine pregnancy on Day 1 (Appendix 11.4).

12) Male participants unwilling to refrain from sperm donation during and until at least 6 months after the last dose of investigational product.

13) Female participants unwilling to refrain from egg donation and in vitro fertilization during and until at least 6 months after the last dose of investigational product.

14) Have poor venous access that limits phlebotomy.

15) Have taken any prescription medications or over-the-counter medications, including herbal products, within 28 days prior to start of investigational product dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications.

16) Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, other immune or cytokine-based therapies).

17) Requirement for ongoing therapy with or prior use of any prohibited medications listed in Section 5.6.1.

18) Participation in any other clinical study (including observational studies) without prior approval from the sponsor is prohibited while participating in the study.

19) Believed by the investigator to be inappropriate for study participation for any reason not otherwise listed.

4.3. Phase 1b Virally Suppressed CHB Participant Inclusion/Exclusion Criteria

4.3.1. Inclusion Criteria

Phase 1b participants must meet all of the following inclusion criteria at screening (or as stated otherwise) to be eligible for participation in this study:

1) Have the ability to understand and sign a written ICF, which must be obtained prior to initiation of study procedures.

2) Assigned male sex at birth or female sex at birth (and be nonpregnant and nonlactating).

3) Participants assigned male at birth and participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified methods of contraception as described in Appendix11.4

4) Be aged 18 through 65 years, inclusive, at enrollment.

5) Have a calculated BMI of ≤ 32.0 kg/m2.

6) Documented evidence of CHB based on one of the following:

   a) Positive HBsAg or HBV DNA at least 6 months prior to the screening visit; OR

   b) Historical liver biopsy consistent with CHB infection available.

7) Quantitative HBsAg greater than the LLOQ and ≤ 5000 IU/mL at screening.

8) Have no evidence of advanced fibrosis by FibroScan (defined as FibroScan < 9 kPa within 6 months of screening). If a historical FibroScan is not available, this can be done at screening.

9) 12-lead ECG evaluations must be without clinically significant abnormalities as assessed by the investigator.

10) Nondiabetic with a hemoglobin A1c < 6.5%.

11) Must be willing and able to comply with all study requirements.

12) Have a calculated CL_{cr} of at least 60 mL/min (using the Cockcroft-Gault method {Cockcroft 1976}) based on serum creatinine and actual body weight as measured for:

- Participant assigned **male** at birth: $\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} = CL_{cr}$ (mL/min)

- Participant assigned **female** at birth: $\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]}) \times 0.85}{72 \times (\text{Serum Creatinine [mg/dL]})} = CL_{cr}$ (mL/min)

13) Alanine aminotransferase < 3 × ULN; international normalized ratio (INR) ≤ ULN; albumin ≥ 3.5 g/dL; direct bilirubin ≤ 1.5 × ULN; platelets within the normal limit.

14) Must have received an approved HBV-active oral antiviral agent for ≥ 6 months prior to screening with HBV DNA below LLOQ for ≥ 3 months prior to screening and with no plan to stop HBV-active antivirals during the study.

4.3.2. Exclusion Criteria

Phase 1b participants who meet *any* of the following exclusion criteria at screening will not be enrolled in this study:

1) Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with participant treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, pulmonary (including chronic asthma), endocrine (including diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.

2) History or evidence of autoimmune disease or known immunodeficiency of any etiology.

3) Have a history of any of the following:

   a) Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria.

b) Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity).

c) Known hypersensitivity to the investigational product, metabolites, or to formulation excipients (see Section 5).

d) Significant cardiac disease (including history of myocardial infarction based on ECG and/or clinical history, any history of ventricular tachycardia, congestive heart failure, or dilated cardiomyopathy with left ventricular ejection fraction ≤ 40%); or a family history of long QT syndrome, or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years.

4) Cancer diagnosis within 5 years prior to study entry, other than squamous or basal cell carcinoma of the skin. Participants under evaluation for possible malignancy are not eligible.

5) Current diagnosis of HIV, HCV, or hepatitis D virus (HDV). Participants who test positive for HCV antibody will require HCV RNA by quantitative PCR for confirmation of active disease. Participants with a known history of HCV or a positive HCV antibody test will not require an HCV antibody at screening and will only require HCV RNA by quantitative PCR for confirmation of active disease.

6) Use of systemic antibiotics within 30 days of screening.

7) Receipt of any HBV vaccine within 12 months of screening visit or planning HBV vaccination during the study period.

8) Receipt of any investigational product within 3 months or vaccine within 3 months of screening (with the exception of influenza and SARS-CoV-2 vaccines, which if needed, should be administered at least 14 days before or after an investigational product administration).

9) Receipt of solid organ or bone marrow transplant.

10) Receipt of immunoglobulin or other blood products within 3 months of screening.

11) Have current alcohol or substance abuse history judged by the investigator to potentially interfere with participant compliance.

12) Positive serum pregnancy test at screening or positive urine pregnancy on Day 1 (Appendix 11.4).

13) Male participants unwilling to refrain from sperm donation during and until at least 6 months after the last dose of investigational product.

14) Female participants unwilling to refrain from egg donation and in vitro fertilization during and until at least 6 months after the last dose of investigational product.

15) Have poor venous access that limits phlebotomy.

16) Have taken any over-the-counter medications, including herbal products, within 28 days prior to start of investigational product dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications.

17) Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, other immune or cytokine-based therapies).

18) Requirement for ongoing therapy with or prior use of any prohibited medications listed in Section 5.6.1.

19) Participation in any other clinical study (including observational studies) without prior approval from the sponsor is prohibited while participating in the study.

20) Believed by the investigator to be inappropriate for study participation for any reason not otherwise listed.

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Randomization, Blinding, and Treatment Code Access

5.1.1. Randomization

Participants will be assigned a screening number in the IRT system at the time of consent.

Once eligibility has been confirmed, the investigator or designee will randomize the participant using the IRT system. Eligible participants will be randomized in a 4:1 ratio to receive GS-2829 and/or GS-6779, or PBO starting on Day 1. It is the responsibility of the investigator to ensure that the participant is eligible for the study prior to enrollment. Once a participant number has been assigned to a participant, it will not be reassigned to any other participants. The participant number assignment and randomization may be performed up to 3 days prior to the Day 1 visit provided all screening procedures have been completed and participant eligibility has been confirmed.

If necessary, replacement participants may be enrolled after discussion and approval from the sponsor (Section 4.1.1). A new unique participant number will be assigned to the replacement participant.

Participation in any other clinical study (including observational studies) without prior approval from the sponsor is prohibited while participating in this study.

5.1.2. Blinding

This study is designed as a randomized and blinded study, in which Gilead personnel including the medical monitor, Gilead contracted study monitors, and the site pharmacists (or designee), will be unblinded while the investigational site personnel and study participants will remain blinded. To mitigate the risks of inadvertently releasing the treatment information, Gilead personnel will only be provided with the unblinded information when there is a need to access such information based on their function or role for data analysis to support dose determination or safety monitoring. Individuals in Clinical Packaging and Labeling or Clinical Supply Management may have an Unblinded Inventory Manager role in the IRT for purposes of investigational product inventory management. Individuals in Patient Safety (PS) who are responsible for safety signal detection, investigational new drug safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group-level summaries. Should Gilead personnel receive unblinded information, they will maintain the confidentiality of the unblinded information and will not communicate the information to blinded site personnel or participants. The blinding will be preserved at the participant level, the group level summaries without revealing the individual participant treatment assignment may be provided to the investigator without further documentation.

5.1.3. Procedures for Breaking the Blind on Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain the treatment assignment for that participant from the IRT system. The sponsor recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation, along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study. Therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study treatment discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

5.2. Description and Handling of the Investigational Product

5.2.1. Formulation

GS-2829 drug product is formulated as a sterile, preservative-free solution intended for intramuscular administration. The drug product is composed of $\geq 1.0 \times 10^7$ FFU/mL GS-2829 in N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), sodium chloride, glycine, poloxamer 188, and recombinant human serum albumin (rHSA).

GS-6779 drug product is formulated as a sterile, preservative-free solution intended for intramuscular administration. The drug product is composed of $\geq 1.0 \times 10^7$ FFU/mL GS-6779 in HEPES, sodium chloride, glycine, poloxamer 188, and rHSA.

Placebo for GS-2829 and GS-6779 has the same inactive ingredients as GS-2829 and GS-6779.

5.2.2. Packaging and Labeling

The investigational products will be supplied in single-use 2R Type I clear glass vials, with elastomeric stoppers, and capped with aluminum seals with polypropylene flip-off caps.

Investigational products to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), European Union (EU) Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

All investigational products should be stored at ≤ -65 °C and protected from light. Storage conditions are specified on the investigational product labels.

Until dispensed to the participant, all investigational products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure stability and proper identification, the investigational product should be stored in the containers in which it is supplied until preparation for dosing to the participant.

5.3. Dosage and Administration

Following completion of screening assessments, eligible participants will be administered GS-2829 and/or GS-6779 or PBO in the schedule provided in Table 8.

Investigational product or PBO will be administered at 0.5 mL intramuscularly into the deltoid muscle of the arm at the following doses:

- GS-2829 – Low dose will be prepared as a 10-fold dilution of the high-dose investigational product
- GS-6779 – Low dose will be prepared as a 10-fold dilution of the high-dose investigational product
- GS-2829 – High dose will be $\geq 0.5 \times 10^7$ FFU (0.5 mL of the investigational product provided at $\geq 1.0 \times 10^7$ FFU/mL)
- GS-6779 – High dose will be $\geq 0.5 \times 10^7$ FFU (0.5 mL of the investigational product provided at $\geq 1.0 \times 10^7$ FFU/mL)

Investigational product or PBO is to be administered after baseline evaluations are completed, as indicated in Table 1, Table 2, and Table 3. Females of childbearing potential will require a urine pregnancy test performed on the day of administration to confirm nonpregnant status prior to dosing.

Sentinel group participants are to be monitored in the clinic for at least 8 hours following the first administration of investigational product. All subsequent doses for the sentinels and all other Phase 1a participants will be monitored in the clinic for at least 4 hours following each dose of investigational product. Participants in Cohorts 5 to 7 will be monitored in the clinic for at least 2 hours following each dose of investigational product. Participants may be required to remain in the clinic for additional observation at the discretion of the investigator.

Participants in Cohorts 5 through 7 will also receive ongoing treatment with NAs (approved HBV oral antivirals), which are considered AxMPs for this study. Self-administered tenofovir and entecavir-based therapies are allowed at doses used for standard of care.

5.4. Fasting and Meals

No fasting or alteration of diet is required prior to administration of the investigational product.

5.5. Dispensing, Accountability, and Disposal or Return of Investigational Products

The investigator (or designee, eg, study site pharmacist) will acknowledge receipt of the investigational product (after reviewing the shipment's content and condition). The investigator (or designee) will maintain an accurate inventory of all investigational product(s). Each dose of the investigational product(s) administered at the study site will be administered by qualified study site staff. The dose of investigational product(s) administered to participants in the clinic under the supervision of staff will be accurately recorded on the Investigational Product Accountability form provided by Gilead (or on equivalent documentation maintained by the study site), which indicates the date and quantity of each dosage formulation dispensed to individual participants.

Gilead recommends that used and unused investigational products should be destroyed at the site. If the site has an appropriate standard operating procedure for investigational product destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused investigational products in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic Trial Master File. If investigational products are destroyed on site, the investigator must maintain accurate records for all investigational products that are destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the investigational product. Upon study completion, copies of the investigational product accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate procedural document for investigational product destruction, used and unused investigational products are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review investigational product supplies and associated records at periodic intervals.

5.6. Concomitant Medications and Other Protocol Restrictions

5.6.1. Concomitant Medications

Table 9. Prohibited and Cautionary Medications

Medication Class	Medications to Be Used With Caution	Prohibited Medications
Vaccines	Elective standard-of-care vaccines (eg, influenza and SARS-CoV-2) will need to be spaced by at least 14 days before or after an investigational product administration when possible.	Any vaccine within 3 months of screening, hepatitis B vaccine formulations other than the study product within 12 months of screening and during the study period, and live vaccines (including live influenza vaccines) during the study period
Immunosuppressive agents	Topical steroids for skin rash and other relevant conditions are allowed during the study. Short-term systemic steroids for ≤ 14 days are allowed for managing AEs that occur on protocol.	Systemic steroids up to 8 weeks after the last investigational product dose, immunosuppressive therapies, or chemotherapeutic agents prior to screening, immunoglobulins and other immune of cytokine-based therapies, within 3 months of screening and during the study period. Any such use will require sponsor's approval whenever possible.
Immunomodulators and monoclonal antibodies	Any use of SARS-CoV-2 monoclonal antibodies during the course of the study will need to be reported to the sponsor.	Previous use within 12 months of screening or current use of humanized or human monoclonal or polyclonal antibodies, and immunomodulators such as tacrolimus, cyclosporine, methotrexate, sulfasalazine etc.
Antibiotics	During the treatment phase and up to 8 weeks after last dose of the investigational product, treatment of acute infections with systemic antibiotics.	Use of systemic antibiotics within 30 days of screening.
NSAIDs	Encouraged to avoid use of NSAIDs up to 3 days after each investigational product administration.	Not applicable.
Herbal supplements	Not applicable.	All use prohibited up to 8 weeks after last dose of investigational product except with sponsors approval.

NSAIDs = nonsteroidal anti-inflammatory drugs; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

The following agents are excluded while participants are in the study (from screening until the last study visit, as appropriate):

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.
- Recreational or medical cannabinoids or derivatives.

Use of a concomitant medication must be reported on the appropriate electronic case report forms (eCRF).

If a participant requires use of a prohibited medication, a request for such use must be reviewed by the sponsor and if approved, participants may continue to participate in the study. Decisions on the use of cautionary medications will need to follow protocol specifications as documented in Table 9.

There is no substantial safety data regarding the concomitant administration of the SARS-CoV-2 vaccines, influenza vaccines, and GS-2829 and GS-6779. Participants are allowed to receive the SARS-CoV-2 vaccine; however, administering such vaccines within 14 days of investigational product should be avoided. Participants should be encouraged to receive any needed vaccinations prior to enrollment. Study visits should continue as planned if vaccination occurs while the participant is on the study. Investigators should follow local guidelines for concomitant administration of the SARS-CoV-2 vaccines with the investigational product.

5.6.2. Other Protocol Restrictions

Participants will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steam baths, and sunbathing or other prolonged ultraviolet exposure (eg, in a tanning salon) from the screening evaluation until completion of the last study visit, as these activities are known to affect certain clinical laboratory test parameters (eg, creatine kinase [CK]) and will provide false indicators of a potentially treatment-related toxicity.

Upon every visit to the clinic, each participant will be questioned as to their compliance with the above protocol restrictions. If a participant is unable to comply with any of the restrictions described above, the participant's continued participation in the study will be reevaluated by the investigator in consultation with the sponsor.

6. STUDY ASSESSMENTS

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Table 1, Table 2, and Table 3 and are described in the sections below.

Any deviation from protocol procedures should be noted in the participant's clinical chart and appropriate eCRFs. In addition, the sponsor should be promptly notified of any protocol deviations.

The study sites will not initiate dosing until the following have all been met:

- The IEC or other applicable regulatory agencies have reviewed and approved the study and the informed consent document.
- All requested regulatory documents have been submitted to and approved by Gilead.
- A master services agreement and/or study agreement is executed.
- The study initiation meeting has been conducted by Gilead (or designee).

A study initiation meeting will include but is not limited to a review of the protocol, the IB, investigational product, and investigator responsibilities.

Documentation of the personally signed and dated ICF for each participant, using the study-specific, IEC-approved ICF, is required before initiating the screening process.

6.1. Informed Consent

Written informed consent (Section 9.1.4) must be obtained from each participant before initiation of any screening procedure. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study (Section 6.3.2).

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6.2. Participant Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

It is the responsibility of the investigator to ensure that participants are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study.

Once the ICF has been obtained, all screening tests and evaluations have been assessed, and study eligibility has been confirmed, participants will be enrolled to receive investigational product on Day 1. Baseline assessments as well as confirmation of negative urine pregnancy tests in women of childbearing potential will need to be completed prior to dosing.

Participants will receive the study treatment assignments as described in Section 5.3 and Table 8.

6.3. Instructions for Study Procedures

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of investigational product, record all SAEs, as well as any AEs related to protocol-required procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After investigational product administration, report all AEs and SAEs. Evaluation of AEs will occur at the visits shown in Table 1, Table 2, and Table 3. See Section 7 for additional details.

6.3.2. Screening Assessments

A sufficient number of participants will be screened to identify the planned number of participants for randomization.

Screening laboratory assessments may be repeated once within 45 days prior to administration of investigational product for exclusionary laboratory values if, in the investigator's opinion, one of the following are met: there is reason to believe the retest value will be within accepted parameters, if the initial value was deemed to be inaccurate or inconsistent with the participant's previous result(s), if the initial value was generated in error (eg, mishandled sample), or there is another relevant extenuating circumstance. In any instance, the site should obtain approval from Gilead prior to repeating the laboratory assessment.

Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the screening visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

The screening assessment will include a review of the inclusion/exclusion criteria (Sections 4.2 and 4.3) and completion of all screening procedures as outlined in Table 1, Table 2, and Table 3. Eligible participants meeting all of the inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements.

6.3.3. Treatment Assessments

Study procedures and assessments are outlined in Table 1, Table 2, and Table 3.

Sentinel group participants are to be monitored in the clinic for at least 8 hours following the first administration of investigational product. All subsequent doses for the sentinels and all other Phase 1a participants will be monitored in the clinic for at least 4 hours following administration of investigational product. Participants in Cohorts 5 through 7 will be monitored in the clinic for at least 2 hours following the administration of investigational product. Participants may be required to remain in the clinic for additional observation at the discretion of the investigator. At the end of this observation period, participants will need to be assessed for any postinjection reactions and AEs, any reportable events will need to be recorded in the eCRF.

Participants will be contacted by phone on the following days to review protocol restrictions, AEs, any concomitant medication usage, and completion of their participant diaries:

Cohorts 1 and 2: Days 2, 3, 58, and 59.

Cohorts 3, 4, 5, and 6: Days 2, 3, 30, 31, 58, 59, 86, and 87.

Cohorts 7 and 8: Days 2, 3, 30, 31, 58, 59, 86, 87, 114, 115, 142, and 143.

6.3.4. Participant Diaries for Reactogenicity

Participants will be asked to record potential investigational product reactions based on solicited events via a diary for 7 days following each administration of investigational product. Review of participant reactogenicity data will occur at the next visit that is greater than 7 days postdose (Table 1, Table 2, and Table 3). Solicited events will include, but may not be limited to, temperature, local events of injection-site pain, swelling, erythema, induration, and systemic events of fatigue, fever, arthralgia, myalgia, headache, and nausea. Any reactogenicity event that meets the criteria for AEs based on Section 7.1.1 must be reported in the appropriate eCRF.

6.3.5. Clinical Virology

6.3.5.1. Sample Collection for Antivector Antibody Evaluation

The incidence of antivector antibodies against GS-2829 and GS-6779 may be assessed in samples collected at the time points shown in Table 1, Table 2, and Table 3. Samples that are found to be positive for antivector antibodies may be further characterized.

6.3.5.2. HBV Viral Biomarkers

Phase 1b only: HBV viral biomarkers (HBsAg, HBV DNA, HBV RNA, HBcrAg, and HBeAg) will be collected at the time points indicated in Table 2 and Table 3 and evaluated as needed.

6.3.5.3. Sample Collection for Genomic Sequencing

Phase 1b only: Blood samples from virally suppressed participants will be collected for genomic sequencing and genotyping of HBV at the time points indicated in Table 2 and Table 3 and evaluated as needed.

6.3.6. Sample Collection for Biomarker Evaluation

6.3.6.1. Biomarker Samples to Address the Study Objectives

Biological specimens will be collected from all participants who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with investigational product response and dosage selection, and to better understand drug-induced biological pathways and/or HBV biology.

Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to prospectively specify all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state-of-the-art knowledge.

Blood samples will be collected to measure biomarkers that will include, but may not be limited to:

- investigational product-induced T-cell responses by IFN-γ ELISpot
- phenotype and function of HBV-specific T-cell and B-cell responses
- peripheral soluble protein (including cytokines, chemokines, and inflammatory markers)
- HBV-targeted antibody responses

Samples will be collected at the time points outlined in Table 1, Table 2, and Table 3. A more detailed breakdown of the biomarker assays is also provided in Table 4, Table 5, and Table 6.

Samples collected for biomarker assessments will be destroyed no later than 20 years after the end of the study or per country requirements (Section 9.1.4).

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6.4. Safety Assessments

Safety will be evaluated throughout the study. Refer to Table 1, Table 2, and Table 3 for a schedule of safety assessments.

6.4.1. Electrocardiogram Assessment

Recording of the ECG will occur at screening (Table 1, Table 2, and Table 3).

Participants should rest quietly in the supine position for a minimum of 10 minutes prior to each scheduled 12-lead ECG acquisition and should remain in that position until the recording is complete.

The investigator or other qualified individual at the study center will review the ECG for abnormalities.

Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the investigator based on GCP.

6.4.2. Physical Examination

Physical examinations conducted throughout the study will be a complete physical examination or a symptom-driven physical examination, as outlined in Table 1, Table 2, and Table 3. The complete physical examination conducted at screening will also include the following assessments:

- General appearance, and the following body systems: head, neck, thyroid, eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory, cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; neurological. Genitourinary and breast examinations should not be conducted unless clinically indicated.

- Review medical history, including history of allergies, prior and current use of nicotine or nicotine-containing products, alcohol and illegal/illicit drug use, and prior and current (within 30 days) medication use.

6.4.3. Vital Signs

Vital sign measurements include blood pressure, heart rate, and body temperature and should be collected once participants have been seated or are in the supine position. Participant position for measurement should be kept consistent throughout the study. Refer to Table 1, Table 2, and Table 3 for vital signs collection time points.

6.4.4. Body Mass Index

Height (cm) and weight (kg) will be collected at screening for calculation of BMI for inclusion criteria.

6.4.5. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 1, Table 2, and Table 3.

No fasting or alteration of diet is required for this study, with the exception of fasting prior to the collection of laboratory assessments performed for screening. Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the screening visit to ensure an approximate 8 hour fast prior to the fasted blood sample collection the next morning.

Table 10. Laboratory Analytes

Safety Laboratory Measurements			
Chemistry (Serum or Plasma)	**Hematology**	**Urinalysis**	**Other Laboratory Measurements**
ALP AST ALT GGT Total bilirubin Direct and indirect bilirubin Total protein Albumin Lactate dehydrogenase Bicarbonate BUN Calcium Chloride Creatinine Glucose Hemoglobin A1c Phosphorus Magnesium Potassium Sodium Lipase Total cholesterol High-density lipoprotein Low-density lipoprotein Triglycerides CPK/CK Uric acid	CBC with differential, and platelets Coagulation panel, including prothrombin time, aPTT, and INR	Color and clarity Specific gravity pH Glucose Protein Blood and microscopic (reflex if positive) Leukocyte esterase and microscopic (reflex if positive)	Serum pregnancy test Urine pregnancy test Serum FSH Plasma HBV DNA, HBV RNA, HBV surface antigen HBV surface antibody HBV core-related antigen HBeAg HBeAb HIV serology HDV antibody HCV antibody serology reflex to HCV RNA HBV immunogenicity (IFN-γ ELISpot assay) HBV-1-specific T-cell phenotype and function Peripheral soluble proteins (including cytokines, chemokines, and inflammatory markers) Antivector immune responses Autoantibodies: ANA, anti-SMA, AMA, and anti-TPO

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMA = antimitochondrial antibody; ANA = antinuclear antibody; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CK = creatine kinase; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; ELISpot = enzyme-linked immunospot assay; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV = human immunodeficiency virus; IFN = interferon; INR = international normalized ratio; RNA = ribonucleic acid; SMA = smooth muscle antibody; TPO = thyroid peroxidase
Refer to Table 1, Table 2, and Table 3 for collection time points.

6.4.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology: Hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume
- Coagulation panel: prothrombin time, activated partial thromboplastin time, and INR
- Chemistry (fasting at screening only; otherwise nonfasting): ALP, AST, ALT, gamma-glutamyl transferase (GGT), total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, total protein, albumin, lactate dehydrogenase, creatine phosphokinase/CK, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, hemoglobin A1c, phosphorus, magnesium, potassium, sodium, uric acid, and lipase.
- Serum pregnancy test for all women of childbearing potential (Note: participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause)
- Follicle-stimulating hormone testing (screening only) for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure
- HIV-1, HBV, and HCV testing
- HDV testing (Phase 1b only)

6.4.5.2. Urine Samples

Urine samples will be collected for urinalysis and alcohol and drug screen assessments, which may include alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, 3,4-methylenedioxymethamphetamine, methadone, opiates, and phencyclidine at screening and Day 1.

6.4.5.3. Pregnancy Testing

Serum pregnancy testing will be performed at screening and baseline (Day 1). On all dosing days, urine pregnancy testing will be performed in addition to serum testing to confirm pregnancy status for all women of childbearing potential. Pregnancy testing will continue every 28 days posttreatment as shown in Table 1, Table 2, and Table 3 until the end of study follow-up.

For Cohorts 1 to 2, safety follow-up Day 113, Day 169, and Day 197; for Cohorts 3 to 6, safety follow-up Day 141, Day 197, and Day 225; and for Cohorts 7 to 8, safety follow-up Day 169, Day 197, Day 225, Day 253, Day 281, and Day 309 are required only for pregnancy testing for women of childbearing potential. These participants will come to the site and undergo serum pregnancy testing, with the exception of participants who are able to access an at-home urine pregnancy test from the clinical site; these participants may conduct their pregnancy test at home and will be contacted by site staff to confirm the result.

6.4.6. Creatinine Clearance

Weight will be collected at screening to calculate CL_{cr} for inclusion criteria. For all other CL_{cr} calculations, the most current recorded weight will be used.

6.4.7. Concomitant Medications/Protocol Restrictions

Review of concomitant medications, and review of protocol restrictions will occur at the times shown in Table 1, Table 2, and Table 3. See Sections 4.2.2, 4.3.2, and 5.6 for more information about concomitant medications.

6.5. Posttreatment Assessments

The last investigational product administered will be Day 57 for participants in Cohorts 1 and 2, Day 85 for participants in Cohorts 3, 4, 5, and 6, and Day 141 for Cohorts 7 and 8. Safety and biomarker analyses follow-up visits are planned for all participants. Study procedures and assessments are outlined in Table 1, Table 2, and Table 3.

6.6. Assessments for Early Discontinuation From Investigational Product or From the Study

If a participant discontinues dosing with the investigational product (see Section 3.3), for example as a result of an AE, the ET visit evaluation and/or procedures outlined in Table 1, Table 2, and Table 3 should be performed within 7 days of last investigational product dose. If the last investigational product dose was received more than 7 days prior to decision to discontinue future dosing, the ET visit should be completed at the next scheduled study visit. Every attempt should be made to keep the participant on the study and continue to perform study-related follow-up and procedures. Evaluations indicating abnormal results believed to be related to investigational product at the ET visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

If a participant withdraws consent from the study, the ET visit will be their last study visit.

6.6.1. Assessments for End of Study

A participant who completes the study will have an end of study visit for assessments and procedures specified in Table 1, Table 2, and Table 3.

6.7. Sample Storage

Stored biological samples may be used by Gilead or its research partner for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for up to 20 years or per country requirements. CCI

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered an investigational product that does not necessarily have a causal relationship with that investigational product. An AE can, therefore, be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures, or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (see Section 7.1.3).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented medical history.

Preexisting events that increase in severity or change in nature after investigational product initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death.
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction; such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.3. Investigational Products and Gilead Concomitant Therapy Special Situation Reports

Special situations reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an investigational product while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an investigational product by a participant.

Misuse is defined as any intentional and inappropriate use of an investigational product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of an investigational product given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to an investigational product as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, drug/alcohol, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead investigational product.

Counterfeit or falsified medicine is defined as any investigational product with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Investigational Products and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship for each investigational product using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes:** There is reasonable possibility that the AE may have been caused by the investigational product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. For each episode, the highest grade attained should be reported as defined in the toxicity grading scale (Appendix 11.6).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Investigational Product Initiation

After informed consent, but prior to initiation of the investigational product, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study treatment, collect all AEs, regardless of cause or relationship, until the end of study follow-up (24 weeks) after last administration of investigational product and report the AEs on the eCRF as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and PS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 24 weeks of the last dose of investigational product, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if an investigator learns of any SAEs that occur after the protocol defined follow-up period has concluded and the event is deemed relevant to the use of the investigational product, the investigator should promptly document and report the event to PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Investigational Product Special Situations Reports

All investigational product SSRs that occur from investigational product initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.4).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situations reports involving a Gilead concomitant therapy (not considered investigational product), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to PS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situations Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to PS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit the report within 24 hours:

Patient Safety
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Investigational Product

Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information within 24 hours of the investigator's knowledge to PS from investigational product initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record the SSR information electronically, record the SSR on the paper SSR form and transmit the report to:

Patient Safety
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

See Section 7.1.3 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered investigational product must be reported within 24 hours of the investigator's knowledge of the event to PS utilizing the paper SSR form to:

Patient Safety
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study participants and/or female partners of male participants that are identified after initiation of investigational product and throughout the study, including the protocol-required posttreatment follow-up period in participants and/or pregnancies in partners resulting from exposure to sperm from a participant in the study period in which contraceptive measures are needed. Pregnancies should be reported to PS using the paper pregnancy report form within 24 hours of becoming aware of the pregnancy.

Contact details for transmitting the pregnancy report form are as follows:

Patient Safety
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to PS; however, if the SAE occurs in a partner, the pregnancy-related SAE will not be captured in eCRF but should be reported via the paper pregnancy outcome report form.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to PS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to PS. Patient Safety contact information is as follows:

Patient Safety
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

Refer to Appendix 11.4 for Pregnancy Precautions, Definition for Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States (US) FDA CFR, the European Union Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014 and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line-listings, serious adverse drug reactions, or SUSARs. In accordance with the European Union Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014, Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned member states of applicable SUSARs as outlined in current regulations.

The investigator should notify the IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to investigational product interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE, Version 5.0 (Section 7.2.2). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

All treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment-related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix11.5, and as outlined below.

- Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as possible, and preferably within 3 calendar days after receipt of the original test results. The investigational product may be continued without dose interruption for a clinically insignificant Grade 3 and 4 laboratory abnormality (eg, CK elevation after strenuous exercise, triglyceride elevation that is nonfasting or that can be medically managed). Recurrence of laboratory abnormalities considered unrelated to the investigational product may not require permanent discontinuation.
- Grade 3 or 4 clinical events, if considered unrelated to the investigational product, may not require dose interruption and continuation of the investigational product is at the discretion of the investigator.

The Gilead medical monitor should be consulted prior to investigational product discontinuation when medically feasible.

7.7.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- For a Grade 1 or 2 clinical event or clinically significant laboratory abnormality, continue the investigational product at the discretion of the investigator.

7.7.2. Grades 3 Laboratory Abnormality or Clinical Event

- For a Grade 3 clinical event or clinically significant laboratory abnormality confirmed by repeat testing that is considered to be related to the investigational product (with the exception of ALT and AST elevations), the investigational product should be withheld until the toxicity returns to Grade 2 or below.
- If a laboratory abnormality recurs to Grade 3 or higher following rechallenge with the investigational product and this is considered related to the investigational product, then the investigational product should be permanently discontinued, and the participant managed according to local standard of care. Recurrence of laboratory abnormalities considered unrelated to the investigational product may not require permanent discontinuation.
- Detailed information on ALT elevation and flare management is provided in Section 7.7.4.

7.7.3. Grades 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant laboratory abnormality confirmed by repeat testing considered to be related to the investigational product, investigational product should be permanently discontinued, and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.
- Detailed information on ALT elevation and flare management is provided in Section 7.7.4.

7.7.4. Management of ALT Elevation or Flare

For Cohorts 1 to 4 and 8

Participants with a serum ALT and/or AST > 5 × ULN, or ALT > 3 × ULN and total bilirubin > 2 × ULN with or without associated symptoms should be managed according to the guidance below.

Study dosing in an individual participant will be placed on hold and serum ALT or AST meeting the criteria above should be confirmed as soon as possible and ideally within 3 days of receipt of results. A clinical assessment should be performed and should include a history of recent travel and exposures, alcohol consumption, and strenuous exercise. The assessment should also include a physical examination, evaluation of the participant's mental status, and the following laboratory tests:

- Serum ALT and AST, total and direct bilirubin, GGT, INR, serum albumin, alcohol screening and urine drug screen
- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for HIV, plasma HBV DNA, serology for HBV (HBsAg, hepatitis B surface antibody [HBsAb], HBeAg, and hepatitis B e antibody [HBeAb]), anti-HDV immunoglobulin (Ig)M and HDV RNA, hepatitis A virus (HAV) IgM, HCV antibody, HCV RNA, and hepatitis E virus (HEV) IgM

Participants should be monitored weekly or more frequently if clinically indicated until their ALT < 5 × ULN. They should then be monitored every 2 weeks until values return to normal. Investigational product may be restarted based on the recommendations of the SRT or if a self-limited nondrug etiology is identified.

For those with suspected drug-induced liver injury based on Hy's law (ALT or AST > 3 × ULN and total bilirubin > 2 × ULN), liver biopsy may be performed.

For Cohorts 5 to 7

Participants with a serum ALT and/or AST > 5 × ULN, or ALT > 3 × ULN and total bilirubin > 2 × ULN with or without associated symptoms should be managed according to the guidance below.

All on-treatment elevated serum ALT assessments should be confirmed as soon as possible and ideally within 3 days of receipt of results. During the visit, a clinical assessment of the participant should be performed. The assessment should include a physical examination, evaluation of the participant's mental status, and the following laboratory tests:

- Serum ALT and AST, ALP, total and direct bilirubin, GGT, INR, serum albumin, complete blood count, and urine drug screen

- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for HIV, HBV DNA, qualitative HBV serology (HBeAg and HBeAb; HBsAg and HBsAb), HAV IgM, HCV RNA, anti-HDV IgM, HDV RNA, HEV IgM, antinuclear antibody, antimitochondrial antibody, smooth muscle antibody, and liver/kidney microsome

Based on the results of the confirmatory tests, the following study treatment modifications are recommended.

Table 11. ALT Elevation Monitoring and Toxicity Management

Liver Toxicity Criteria	Action
Confirmed, ALT and or AST ≥ 10 × ULN without evidence of hepatic toxicity as defined below	Cohort 5 to 7: Stop investigational product. Evaluate adherence to NA therapy and review recent HBV DNA results. Evaluate for other causes of hepatoxicity. Participant must be monitored weekly or more frequently if clinically indicated until ALT returns to nadir. Investigative product may be restarted when ALT < 5 × ULN upon discussion with medical monitor. Dosing may also be reinitiated upon the recommendations of the SRT.
Persistent ALT and or AST > 2 × baseline and ≥ 5 × ULN without evidence of hepatic toxicity, as defined below	Cohorts 5 to 7: Continue investigative product. ALT should be evaluated every 2 weeks or more frequently as clinically needed, until values return to nadir.
Confirmed ALT and or AST > 2 × nadir, with evidence of hepatic toxicity, defined as any one of the following confirmed laboratory abnormalities: Total bilirubin > 2 × baseline or nadir AND > 2.5 mg/dL in the absence of Gilbert's disease Elevated INR > 0.5 above baseline AND > ULN Abnormal serum albumin > 1 g/dL decrease from baseline	Cohorts 5 to 7: Permanently discontinue investigational product. Evaluate adherence to NA therapy and review recent HBV DNA results. Evaluate for etiology of ALT elevation. Participant should be monitored weekly until ALT < 5 × ULN, and total bilirubin, INR, and albumin values return to normal or baseline levels. Liver biopsy may be performed based on investigator's clinical judgment to determine etiology.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; INR = international normalized ratio; NA = nucleos(t)ide analogue; SRT = Safety Review Team; TAF = tenofovir alafenamide; ULN = upper limit of normal

7.7.5. Potential Immune-mediated Adverse Events on Study

Potential immune-mediated conditions (PIMMC) are AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest, which may or may not have an autoimmune etiology. PIMMCs have been reported in some vaccine studies and in the clinical use of some vaccines {Tavares Da Silva 2013}. For this study, any new onset or worsening of a preexisting PIMMC will need to be reported regardless of grade. A list of PIMMC is provided in Appendix 11.7.

8. STATISTICAL CONSIDERATIONS

Details of the statistical methods will be provided in the statistical analysis plan and the biomarker analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses may be conducted at the discretion of the sponsor and the results from these analyses may be submitted to regulatory agencies to facilitate the overall clinical program development or to scientific meetings or journals to disseminate the findings.

8.2.1.1. Dose-escalation Analysis

For the purpose of making the decision to escalate from the low- to high-dose level or to increase the number of doses (at the high dose) from 2 doses of each investigational product, to 3 doses of each investigational product (see Section 3.1), interim analyses of relevant safety data will be conducted by Gilead. Safety assessments (eg, AEs, ECG, laboratory test results) will be displayed by cohort to facilitate these decisions while preserving the blind at the participant level.

Review of relevant safety data will be conducted by the SRT to facilitate the decision to escalate from the low to high dose; and to increase from 2 doses of each investigational product to 3 doses of each investigational product (high-dose level).

8.2.2. Final Analysis

The unblinded final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoints will be conducted at the time of the final analysis.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Randomized Analysis Set

The All Randomized Analysis Set will include all participants randomized into the study after screening. This is the primary analysis set for safety listings.

8.3.1.2. Safety

The Safety Analysis Set will include all randomized participants who received at least 1 dose of investigational product. Participants who received treatment other than that to which they were assigned will be analyzed according to the treatment received.

The Safety Analysis Set is the primary analysis set for safety analyses. All data collected during the study will be included in the safety summaries.

8.3.1.3. Pharmacodynamics (Immunogenicity)

The Immunogenicity Analysis Set will include all randomized participants who received at least 1 dose of investigational product and have at least 1 nonmissing value for immunogenicity evaluation after administration of the investigational product.

8.3.2. Data Handling Conventions

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantification will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is less than 20, a value of 19 will be assigned; if the result of a continuous laboratory test is less than 20.0, a value of 19.9 will be assigned).

Missing data can have an impact upon the interpretation of the study data. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic Data and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized, and descriptive statistics will be provided. Demographic summaries will include sex, race, ethnicity, and age at baseline. Baseline data will include a summary of body weight, height, BMI, and HBV genotype (for Phase 1b participants only). Additional baseline characteristics may be added, as applicable.

8.5. Safety Analysis

All safety data collected on or after the date that investigational product was first administered up to study completion will be summarized by population and treatment group according to the investigational product received. Data for the pretreatment period and up to study completion will be included in data listings.

8.5.1. Extent of Exposure

A participant’s extent of exposure to investigational product data will be generated from the investigational product administration data. Exposure data will be listed.

8.5.2. Adverse Events

The analysis of data on safety and reactogenicity events will be based on the Safety Analysis Set. Data from participants receiving PBO in different cohorts may be combined within the same population for the final analysis.

Clinical and laboratory AEs will be coded using the current version of the MedDRA. System organ class, high-level group term, high-level term, preferred term (PT), and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as:

- Any AE that begins on or after the date of first dose of investigational product and through the duration of the study; or any AE leading to investigational product discontinuation.

Summaries (number and percentage of participants) of treatment-emergent AEs (by system organ class, high-level term, if applicable, and PT) will be provided by population and treatment group using the current version of MedDRA.

- All TEAEs
- TEAEs of Grade 3 or higher
- TEAEs of Grade 2 or higher
- All treatment-related TEAEs
- Treatment-related TEAEs of Grade 3 or higher
- Treatment-related TEAEs of Grade 2 or higher
- All treatment-emergent SAEs
- All treatment-related treatment-emergent SAEs
- All TEAEs leading to premature discontinuation of any investigational product
- All TEAEs leading to temporary interruption of any investigational product

All AEs collected during the study will be presented in the data listings.

8.5.3. Laboratory Evaluations

Selected laboratory test data will be summarized using only observed data. Change from baseline at all scheduled time points will be summarized. Graded laboratory abnormalities will be defined using the grading scheme in Section 11.6.

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase by at least 1 toxicity grade from baseline levels at any time after baseline evaluation through the duration of the study, will be summarized by population and treatment group.

Laboratory abnormalities that occur before the first dose of investigational product will be included in a data listing.

8.5.4. Other Safety Evaluations

Vital signs and ECG data will be summarized by population, treatment group, and visit.

8.6. Pharmacodynamic Biomarker Analysis (Immunogenicity)

The pharmacodynamic biomarker (immunogenicity) analysis will be based on the proportion of participants with investigational product-induced HBV-specific T-cell response, as determined by the IFN-γ ELISpot assay, and will be summarized by population and treatment group.

The magnitude of the total investigational product-induced HBV-specific T-cell response, as determined by the IFN-γ ELISpot assay, will be summarized by population and treatment group.

The immunoassay result listing will also be included.

8.7. Other Exploratory Biomarker Analyses

Biomarker analyses may include additional measurements of HBV-specific immune response including intracellular cytokine staining, anti-HBsAg antibodies, anti-HBsAg immune complexes, HBV-specific B-cells, and antivector neutralizing antibodies. Further analyses may include gene expression profiling, serum cytokine analysis, T-cell receptor repertoire sequencing, peripheral blood mononuclear cell (PBMC) single cell RNA sequencing, and PBMC cytometry by time of flight immune phenotyping. Data for each assay performed will be summarized by population and/or treatment group and postvaccination changes at defined time points calculated against the baseline. The details for the exploratory biomarker analyses will be described in a separate biomarker analysis plan.

8.8. Sample Size

The sample size in this study is determined based on practical considerations and empirical experience with similar types of studies. No formal power and sample size calculation was performed. Overall, a total sample size of approximately 80 participants (10 participants per cohort, (including 8 active and 2 PBO) is expected to provide a suitable assessment of the safety, tolerability, and immunogenicity of treatment with the investigational product.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the investigational product. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IEC. The investigator will not begin any study participant activities until approval from the IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IEC for any modifications made to the protocol or any accompanying material to be provided to the participant after initial IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IEC-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the participant, the person conducting the consent discussion, and also by an impartial witness if required by the IEC or local requirements.

The ICF will inform participants about genomic testing and/or planned sample retention. [redacted]

CCI [redacted]

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions or in accordance with local regulations. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, investigational product information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IEC, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification (name, date of birth, gender)
- Documentation that participant meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant is not enrolled

- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Start and end dates (including dose regimen) of investigational product, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end dates, dose if relevant, and dose changes)
- Date of study completion and reason for early discontinuation if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the Case Report Form Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification.

System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications IECs in accordance with local requirements and receive documented IEC approval before modifications may be implemented.

9.2.2. Study Reports and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies) when applicable. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Results will be submitted within 1 year (6 months for pediatric studies) of the global last participant last visit date.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator's meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and accuracy of the data recorded in the eCRFs. The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at his or her site. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority(ies), and IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

10. REFERENCES

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11. APPENDICES

11.1. Investigator Signature Page

GILEAD SCIENCES, INC.
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STUDY ACKNOWLEDGEMENT

A Phase 1a/1b Study to Evaluate the Safety and Tolerability of Repeated Doses of Nonreplicating Arenavirus Vector Therapeutic Vaccines GS-2829 and GS-6779 in Healthy Participants and Participants With Chronic Hepatitis B (CHB)

AMENDMENT 2: 20 July 2023

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Investigator Name (Printed)	Signature
Date	Site Number

11.2. Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in at Least 1 Country Following EU Regulation No. 536/2014	To Be Used per Label (Marketed Products Only)
GS-2829	Investigational product/vaccine	NA	NA
GS-6779	Investigational product/vaccine	NA	NA
Placebo	Reference drug/vaccine	NA	NA
Nucleos(t)ide analogues (approved HBV oral antivirals)	AxMPs	Yes	Yes

AxMPs = auxiliary medicinal products; EU = European Union; HBV = hepatitis B virus; NA = not applicable

11.3. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Investigational product supplies to participants and sites:

    a) Participants may be unable to return to the site for a number of visits to get the investigational product, or the site may be unable to accept any participant visits. Without investigational products, the participant would not be able to stay on the investigational product as planned per protocol.

        Mitigation plan: For participants who may be unable to continue the schedule in person, at the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments.

    b) Shipments of investigational product could be delayed because of transportation issues. Without investigational products, the participant would not be able to continue receiving the investigational product as planned per protocol.

        Mitigation plan: The site's investigational product inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in investigational product inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the investigational product depot and investigational sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow-up:

    a) Participants may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

        Mitigation plan: For participants who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

        i) Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

        ii) Review current list of concomitant medications and document any new concomitant medications.

        iii) Confirm if participant diary has been completed.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up visit per protocol. Any changes in the party conducting laboratory assessments for the study due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local independent ethics committee (IEC) and national laws and regulations. Remote consent will be allowed if has been approved by the local IEC. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Study monitors may be unable to carry out source data review or source data verification (SDV), or investigational product accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or underreporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote SDV may be arranged if allowed. The study monitor is to reference the Study Monitoring Plan (or equivalent plan) for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of GS-2829 and GS-6779 in study participants will remain unchanged.

11.4. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

b. Definition of Fertility in a Participant Assigned Male at Birth

For the purposes of this study, a participant assigned male at birth is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Participants Assigned Female at Birth and of Childbearing Potential

a. Investigational Product Effects on Pregnancy and Hormonal Contraception

GS-2829 and GS-6779 are contraindicated in pregnancy as the effect on fetal development is unknown. There are no data on the use of GS-2829 and GS-6779 in pregnant women. Nonclinical toxicology studies of GS-2829 and GS-6779 for evaluating genotoxicity, fertility, or embryo-fetal development have not been performed. There are no available data to indicate that there is no reduction in clinical efficacy of hormonal contraception. Women of childbearing potential should use highly effective contraception for at least 6 months following the last dose of investigational product. Refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential

The inclusion of participants assigned female at birth and of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of less than 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test before vaccination. Pregnancy tests will be performed at monthly intervals thereafter until the end of contraception requirement.

Duration of required contraception for participants assigned female at birth and of childbearing potential in this clinical study should start from the screening visit until 6 months after the last dose of investigational product.

Participants assigned female at birth and of childbearing potential must agree to 1 of the following contraceptive methods:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below:
  - Nonhormonal intrauterine device (IUD)
  - Hormonal IUD (must be used in conjunction with a barrier method)
  - Bilateral tubal occlusion (upon medical assessment of surgical success)
  - Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success)

Or

- Participants assigned female at birth and of childbearing potential who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:
  - Hormonal methods (each method must be used with a barrier method, preferably male condom)
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone

- Subdermal contraceptive implant
- Transdermal contraceptive patch
- Contraceptive vaginal ring

— Barrier methods (each method must be used with a hormonal method)

- Male condom (with or without spermicide)
- Female condom (with or without spermicide)
- Diaphragm with spermicide
- Cervical cap with spermicide
- Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Participants Assigned Male at Birth

It is theoretically possible that a relevant systemic concentration of investigational product may be achieved in a partner assigned female at birth from exposure to the participant's seminal fluid and pose a potential risk to an embryo/fetus. A participant assigned male at birth with a partner assigned female at birth and of childbearing potential must use condoms during treatment and until 6 months after last dose of investigational product. If the partner assigned female at birth and of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Participants assigned male at birth must also refrain from sperm donation during treatment and until the end of contraception requirement.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

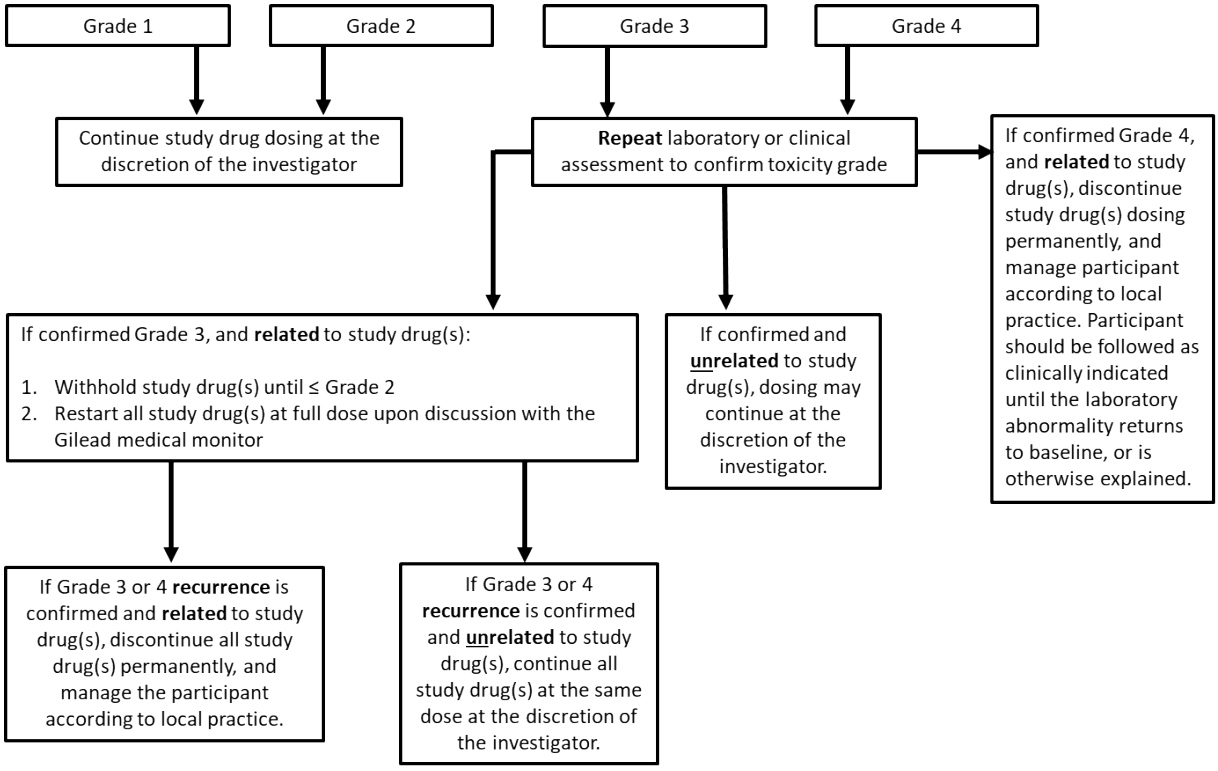
5) Procedures to Be Followed in the Event of Pregnancy

Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to end of study. Investigational product must be discontinued immediately.

Participants assigned male at birth whose partner has become pregnant or suspects they are pregnant from start of study to 6 months after the last investigational product dose must also report the information to the investigator

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

11.5. Management of Clinical and Laboratory Adverse Events



11.6. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

The Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (November 2017) will be used in this study.

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

11.7. Potential Immune-mediated Conditions[a]

This list of potential immune-mediated conditions is not to be considered exhaustive, and investigators may use clinical judgment in applying this list and may consult the medical monitor in situations they believe a new event in a participant may be immune mediated but is not in the list below.

Neuroinflammatory disorders

- Cranial nerve inflammatory disorders, including paralyses/paresis (eg, Bell's palsy)
- Optic neuritis
- Multiple sclerosis
- Transverse myelitis
- Acute disseminated encephalomyelitis, including site-specific variants: encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis, cerebellitis
- Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)
- Immune-mediated peripheral neuropathies and plexopathies (including Guillain-Barré syndrome, Miller Fisher syndrome and other variants, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)
- Narcolepsy

Musculoskeletal disorders

- Systemic lupus erythematosus
- Systemic sclerosis (with limited or diffuse cutaneous involvement)
- Dermatomyositis
- Polymyositis
- Antisynthetase syndrome
- Rheumatoid arthritis
- Juvenile chronic arthritis (including Still's disease)
- Polymyalgia rheumatica

- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's syndrome) and undifferentiated spondyloarthritis
- Psoriatic arthropathy
- Relapsing polychondritis
- Mixed connective tissue disorder

Skin disorders

- Psoriasis
- Vitiligo
- Erythema nodosum
- Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis)
- Cutaneous lupus erythematosus
- Alopecia areata
- Lichen planus
- Sweet's syndrome
- Morphea

Liver disorders

- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Autoimmune cholangitis

Gastrointestinal disorders

- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis
- Celiac disease

Metabolic and Endocrine disorders

- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Grave's or Basedow's disease
- Diabetes mellitus type I
- Addison's disease

Vasculitides

- Large vessels vasculitis including giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and antineutrophil cytoplasmic antibody positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others

- Autoimmune hemolytic anemia
- Autoimmune thrombocytopenia
- Antiphospholipid syndrome
- Pernicious anemia
- Autoimmune glomerulonephritis (including immunoglobulin A nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Uveitis

- Autoimmune myocarditis/cardiomyopathy
- Sarcoidosis
- Stevens-Johnson syndrome
- Sjogren's syndrome
- Idiopathic pulmonary fibrosis
- Goodpasture syndrome
- Raynaud's phenomenon

a Da Silva, Fernanda Tavares, et al. "Optimal approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines." Vaccine 31.14 (2013): 1870-1876.

11.8. Country-Specific Requirements

Not applicable.

11.9. Amendment History

High-level summaries of the history of this study's amendments are provided in tabular form in the subsections below (from most recent amendment to oldest), with changes listed in each table in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing the original protocol to this amendment will be made available upon the publication of this protocol.

11.9.1. Amendment 2 (20 July 2023)

Rationale for Key Changes Included in Amendment 2	Affected Sections
Two cohorts (7 and 8) were added to investigate the addition of a third dose of each vaccine. This brings the number of participants for the study to approximately 80.	Synopsis, Section 1, Section 3, Section 4, Section 6, and Section 7
The previous viremic cohort (Cohort 7) was removed from the study and replaced with virally suppressed CHB participants in order establish the safety and tolerability, and immunogenicity profile of 3 doses in this population. Secondary to establishing the safety profile, will inform on the impact of 3 versus 2 doses on magnitude and durability of vaccine-elicited immune responses.	Throughout, as needed
The upper limit of the age range for Phase 1b participants was increased from 60 to 65 years, inclusive, to increase enrollment	Throughout, as needed
An additional Safety Review Team (SRT) review was added to review data prior to initiating the third dose of the vaccines	Synopsis, Section 3
Select biomarker/safety assessments for Phase 1b have been removed from the assessments to reduce the blood volume draw	Synopsis, Section 6
Safety language as related to reporting toxicity levels has been updated to indicate that participants receiving the same high-dose level (Cohorts 4 and 8 for Phase 1a, and Cohorts 6 and 7 for Phase 1b) will be considered cumulative events for stopping rules.	Section 3.3.3.1
Clarification of use of systemic antibiotics has been added to the concomitant medications.	Section 5.6.1
Minor changes to correct typographic errors and ensure consistency and clarity were made.	Throughout, as needed

11.9.2. Amendment 1 (23 November 2022)

Rationale for Key Changes Included in Amendment 1	Affected Sections
The number of planned Phase 1b study centers was increased for improved enrollment.	Synopsis
Study schemas were updated to include genotyping for Cohorts 5 and 6.	Study Schema
Laboratory requirements were updated, genotyping at screening for Cohorts 5 and 6 was added, hepatitis D virus testing and autoantibody testing for healthy volunteers were removed, and in-clinic postdose monitoring period was extended for all participants.	Table of Assessments, Section 4, and Section 5
Change was made to align stopping rules to European Medicines Agency requirements.	Section 3
Change was made to align early discontinuation rules to United States Food and Drug Administration requirements.	Section 3
Inclusion criteria for Cohorts 5 and 6 were updated to aide with enrollment.	Section 4
Inclusion criteria for Cohort 7 were updated to remove “genotype identifiable” simplifying the screening process.	Section 4
Change was made to add follow-up telephone calls after each dose of investigational product	Figures 2 and 3, Table of Assessments, and Section 6
Appendices were added for country-specific requirements and amendment history.	Appendices 11.8 and 11.9
Minor changes to correct typographic errors and ensure consistency and clarity were made.	Throughout, as needed

11.10. Sponsor Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404 USA

A Phase 1a/1b Study to Evaluate the Safety and Tolerability of Repeated Doses of Nonreplicating Arenavirus Vector Therapeutic Vaccines GS-2829 and GS-6779 in Healthy Participants and Participants With Chronic Hepatitis B (CHB)

AMENDMENT 2: 20 July 2023

APPROVAL OF CLINICAL STUDY PROTOCOL

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Senior Associate Clinical Development Director

[See appended electronic signature]

Signature

[See appended electronic signature]

Date

protocol GS-US-642-5670 amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	20-Jul-2023 16:52:32