CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2a, Open-Label Study to Evaluate the Safety and Efficacy of Selgantolimod (SLGN)-Containing Combination Therapies for the Treatment of Chronic Hepatitis B (CHB)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	This is a non-IND study
ANZCTR Trial ID:	Not Available
EudraCT Number:	2021-000672-11
ClinicalTrials.gov Identifier:	NCT04891770
Indication:	Chronic Hepatitis B
Protocol ID:	GS-US-465-4439
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 04 March 2021 Amendment 1: 20 April 2022 Amendment 2: 12 April 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.

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PROTOCOL SYNOPSIS

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Study Title:	A Phase 2a, Open-Label Study to Evaluate the Safety and Efficacy of Selgantolimod (SLGN)-Containing Combination Therapies for the Treatment of Chronic Hepatitis B (CHB)
IND Number: **ANZCTR Trial ID:** **Clinical Trials.gov Identifier:**	This is a non-IND study Not Available NCT04891770
EudraCT Number:	2021-000672-11
Study Centers Planned:	Approximately 30 centers globally
Objectives:	The primary objectives of this study are as follows: • To evaluate the safety and tolerability of study treatment(s) • To evaluate the efficacy of study treatment(s) as measured by the proportion of participants who achieve functional cure, defined as negative qualitative hepatitis B surface antigen (HBsAg loss) and hepatitis B virus (HBV) DNA < lower limit of quantitation (LLOQ) at Follow-up (FU) Week 24 The secondary objectives of this study are as follows: • To evaluate the proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study • To evaluate in participants with CHB who are hepatitis B e antigen (HBeAg) positive at baseline the proportion of participants who achieve HBeAg loss with and without anti-HBeAg seroconversion during the study • To evaluate the proportion of participants who remain off nucleos(t)ide(s) (NUC) treatment during FU • To evaluate the proportion of participants experiencing HBV virologic breakthrough (defined as confirmed HBV DNA ≥ LLOQ after 2 consecutive HBV DNA < LLOQ in participants who are complying with NUC therapy OR confirmed HBV DNA ≥ 1 $\log_{10}$ IU/mL increase from nadir on treatment) during study treatment(s) CCI [redacted]

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Study Design:	This is a Phase 2, open-label study to evaluate the safety and efficacy of SLGN-containing combination therapies in CHB participants. The study will consist of 2 cohorts (Cohorts 1, and 2). Approximately 40 NUC-suppressed and 60 viremic CHB-infected participants, may be enrolled and assigned into a cohort below. Each cohort will enroll a minimum of 20% HBeAg-positive participants, and up to 20% of participants can have HBsAg ≤ 100 IU/mL. **NUC-suppressed Cohort** **Cohort 1 (n = 40)**: • Tenofovir alafenamide (TAF) 25-mg tablet administered orally once daily for 36 weeks • VIR-2218 200 mg administered as subcutaneous (SC) injection once every 4 weeks for 24 weeks (total 6 doses) At Week 12, add-on and initiate the below treatment: • SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for 24 weeks (total 24 doses) • Nivolumab 0.3 mg/kg administered intravenously (IV) once every 4 weeks for up to 24 weeks (up to 6 doses) **Viremic Cohort (Cohort 2)** **Cohort 2 (n = 60):** Participants will be randomized 2:1 into Cohort 2 Groups A and B and stratified by HBsAg > or ≤ 3 $\log_{10}$ IU/mL. **Group A (n = 40):** • VIR-2218 200 mg administered as SC injection once every 4 weeks for 24 weeks (total 6 doses) At Week 12, add-on and initiate the below treatment: • SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for 24 weeks (total 24 doses) • Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses) **Group B (n = 20):** • SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for up to 24 weeks (up to 24 doses) • Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses)

	NOTE: Nivolumab dosing was stopped in this study. This was a sponsor decision based on a benefit risk assessment of the use of nivolumab in HBV cure. As the study had completed enrollment and all participants were in treatment when the decision was made to stop nivolumab administration, the following amendments to the protocol were implemented: • Stop further nivolumab administration for all study participants across all cohorts • Continue treatment with VIR-2218 and SLGN through Week 36 for Cohorts 1 and 2 (Group A) • Discontinue all study treatment for Cohort 2 Group B participants with next follow up visit being EOT for those still in treatment period • Stop all sample collections related to nivolumab • NUC therapy cessation is no longer required for our NUC treated patients (Cohort 1) **Follow-up Period:** At the end of treatment, all participants will enter a FU period • All participants not on TAF treatment at end of treatment (EOT) will enter a treatment-free follow-up (TFFU) period • Participants who are on TAF treatment will continue TAF treatment over the duration of the follow up period Participants who initiated TFFU prior to the approval of this amendment and stopped NUC treatment may continue off NUCs after discussion between participant and investigator on the benefits and risks of continuing off NUCs in TFFU. Those who decide to restart NUCs would initiate commercial NUC treatment. **Pharmacokinetic assessments** **Sparse Pharmacokinetic Collection** Sparse (timed) plasma/serum PK samples will be obtained at specific in-clinic treatment visits at any time between 1 to 5 hours postdose relative to SLGN and/or VIR-2218 administration unless otherwise indicated. CCI [redacted]

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Alanine Aminotransferase (ALT) Elevation or Flare Management

On-Treatment ALT Management

Participants with on-treatment serum ALT elevation > 2 × nadir or > 2 × baseline value and ≥ 5 × ULN, with or without associated symptoms should be managed according to the guidance below.

All elevated serum ALT 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:

- Laboratory parameters: serum ALT and aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR), serum albumin, and alcohol screening.
- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg, HBsAb, HBeAg, and HBeAb), hepatitis D virus (HDV), hepatitis A virus (HAV) immunoglobulin M (IgM), hepatitis C virus (HCV), and hepatitis E virus (HEV).
- Liver biopsy may be collected for participants meeting Hy's law (ALT > 3 × ULN and Total Bilirubin > 2 × ULN; AST > 3 × ULN and Total Bilirubin > 2 × ULN) with suspected drug-induced-liver-injury (DILI)

Based on the results of the confirmatory tests, the following study treatment modifications are recommended (Table 1):

Table 1. Dose Modification and Monitoring

Liver Toxicity Parameters	Action
Confirmed, ALT ≥ 10 × ULN without evidence of hepatic toxicity as defined below	**Cohort 1**: Hold VIR-2218 and SLGN treatment. Participant should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting study treatment (VIR-2218, SLGN) may be considered when ALT < 5 × ULN in discussion with the medical monitor. Study treatment should be restarted in line with the original assigned administration schedule. **Cohort 2**: Initiate TAF 25 mg once daily and hold SLGN, and/or VIR-2218 dose. Participant should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting study treatment (VIR-2218, and SLGN) may be considered when ALT < 5 × ULN in discussion with the medical monitor. Study treatment should be restarted in line with the original assigned administration schedule.
Persistent ALT > 2 × baseline and ≥ 5 × ULN without evidence of hepatic toxicity, as defined below	Continue study treatment(s), ALT should be evaluated every 2 weeks or more frequently as clinically needed, until ALT < 5 × ULN

Confirmed ALT > 2 × nadir, with evidence of hepatic toxicity, defined as any one of the following confirmed laboratory abnormalities: • Total bilirubin > 2 × ULN • Elevated INR > 0.5 above baseline AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	**Cohort 1:** Permanently discontinue study treatment(s) except TAF 25 mg once daily. Participant should be monitored weekly until ALT < 5 × ULN, and total bilirubin, INR, and albumin values return to normal or baseline levels. **Cohort 2:** Initiate commercially approved NUC treatment once daily and permanently discontinue study treatment(s). Participant should be monitored weekly until ALT < 5 × ULN, and total bilirubin, albumin, and/or INR values return to normal or baseline levels

ALT = alanine aminotransferase; INR = international normalized ratio; NUC = nucleos(t)ide(s); SLGN = selgantolimod; TAF = tenofovir alafenamide; ULN = upper limit of normal

Treatment-Free Follow-up ALT Management

All eligible participants will enter a TFFU period after completion of study treatment, in which they will undergo close safety monitoring. The proportion of participants who achieve HBsAg loss or are able to remain off NUC therapy during TFFU period will be assessed. Table 2 provides guidance for initiating commercially approved NUC treatment, in participants who experience rebound of HBV DNA and ALT levels. Any deviation from Table 2 should be discussed in advance with the medical monitor.

If unscheduled visits are required for ALT monitoring, 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:

- Laboratory parameters: serum ALT and AST, total and direct bilirubin, GGT, INR, serum albumin, plasma HBV DNA, quantitative HBsAg, peripheral blood mononuclear cells (PBMC) for immune profiling, and alcohol screen.
- At the initial confirmatory visit, collect serology for HDV, HAV IgM, HCV, and HEV.

Participants with HBV DNA < LLOQ and ALT elevation/flare meeting any of the below table criteria, should be evaluated for alternative liver disease etiologies by the investigator and in discussion with the medical monitor. Liver biopsy may be collected at the investigator's discretion.

Participants with HBV DNA > LLOQ and ALT elevation/flare should be managed according to the following table:

Table 2. Starting Commercial NUC Treatment Criteria

Liver Toxicity Parameters	Action

Confirmed ALT ≥ 10 × ULN with no evidence of hepatic toxicity, as defined below.	Initiate NUC treatment and monitor weekly until ALT < 5 × ULN, and every 2 weeks until ALT < 2 × ULN, or more frequently if clinically indicated.
ALT ≥ 5 × ULN without evidence of hepatic toxicity, as defined below	ALT should be evaluated every 2 weeks or more frequently as clinically needed, until ALT < 2 × ULN.
Confirmed ALT > ULN with evidence of hepatic toxicity, defined as any one of the following confirmed laboratory abnormalities: • Total bilirubin > 2 × nadir AND > 2.5 mg/dL in the absence of Gilbert's disease • Elevated INR > 0.5 above nadir AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	Initiate NUC treatment and monitor weekly or more frequently if clinically indicated until return to baseline levels or within normal reference range. Liver biopsy may be considered if appropriate for participant management.
Confirmed, HBV DNA > 20,000 IU/mL (HBeAg positive) or > 2,000 IU/mL (HBeAg negative) and persistent ALT > ULN without evidence of hepatic toxicity, as defined above, for > 8 weeks	Initiating NUC treatment may be considered in discussion with medical monitor.

ALT = alanine aminotransferase; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; INR = international normalized ratio; NUC = nucleos(t)ide(s); ULN = upper limit of normal

Individual Treatment Modification Criteria

Study treatment(s) that are considered related by the investigator to any of the following event(s) will be held in a participant until resolution of the event:

- Any study drug–related adverse event (AE) ≥ Grade 3
- A confirmed, clinically significant laboratory test abnormality (other than ALT) ≥ Grade 3 considered study drug(s) related by the investigator.

Study treatment(s) may be reinitiated following resolution of the above event(s) after discussion with the medical monitor. Study treatment(s) should be restarted in line with their preassigned schedules.

Individual Treatment Discontinuation Criteria

	Study treatment(s) that are considered related by the investigator to any of the below events will be permanently discontinued: • Any on treatment uveitis confirmed by ophthalmologic evaluation • Any confirmed recurrence of study drug–related Grade 3 or 4 (excluding laboratory abnormalities) AE following dose interruption mandates permanent discontinuation of study drug(s) • Any study drug–related ≥ Grade 3 AE not able to be medically managed (eg, nausea with antiemetics) • Any study drug–related Grade 4 AE (excluding laboratory abnormalities) • Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study specific procedures or is considered not to be in the participant's best interest • Any confirmed study drug–related laboratory abnormality ≥ Grade 3 following rechallenge • A clinically significant Grade 4 laboratory abnormality • Virological breakthrough as defined in Section 2 Additional criteria for permanent discontinuation of study treatment(s): • Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree • Hepatic disease progression or lack of efficacy defined as participants in Cohorts 1 or 2 (Group A), who do not achieve HBsAg decline ≥ 0.2 $\log_{10}$ IU/mL at Week 12 • Participant requests to discontinue for any reason • Participant noncompliance • Pregnancy during the study • At the discretion of the investigator, Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)
Number of Participants Planned:	Approximately 100 participants

Target Population:	Adult, noncirrhotic, participants with CHB infection who are viremic or virally suppressed on a commercially approved HBV NUC treatment.
Duration of Treatment:	TAF 25-mg tablet will be administered orally once daily for up to 84 weeks, as applicable, in Cohort 1 VIR-2218 200 mg SC will be administered once every 4 weeks for 24 weeks (6 doses) Nivolumab 0.3 mg/kg IV was administered once every 4 weeks for up to 24 weeks (up to 6 doses) SLGN 3 mg (2 × 1.5-mg tablets) will be administered orally while fasting once a week on the same day for up to 24 weeks (up to 24 doses) NOTE: Nivolumab dosing was stopped in this study. This was a sponor decision based on a benefit risk assessment on the use of nivolumab in HBV cure. SLGN was discontinued for Cohort 2 Group B.
Diagnosis and Main Eligibility Criteria:	Male and nonpregnant female participants, ages 18 to 65 years, inclusive, with chronic HBV infection without the presence of cirrhosis, and who are viremic or virally suppressed on NUC treatment for at least 6 months may be eligible for the study. Refer to Section 4 of the protocol for detailed Inclusion and Exclusion criteria.
Study Procedures/ Frequency:	This study includes prescreening (optional), screening, treatment, and follow-up assessments. After consent is obtained, screening assessments will be completed within 45 days prior to the Baseline/Day 1 treatment. All participants will complete the study treatments described below. **Cohort 1:** • Screening Visit • Treatment Period Visits: Baseline/Day 1, Weeks 4, 8, 12, 13, 14, 16, 20, 24, 28, 32, and 36 • FU Visits: Weeks 1, 4, 8, 12, 16 (for women of childbearing potential), 24 (Primary), 36, and 48 **Cohort 2:** • Screening Visit • **Group A**: — Treatment Period Visits: Baseline/Day 1, Weeks 4, 8, 12, 13, 14, 16, 20, 24, 28, 32, and 36

	— FU Visits: Weeks 1, 4, 8, 12, 16 (for women of childbearing potential), 24 (Primary), 36, and 48 • **Group B:** — Treatment Period Visits: Baseline/Day 1, Weeks 1, 2, 4, 8, 12, , 14, 16, 20, and 24 — FU Visits: Weeks 1, 4, 8, 12, 16 (for women of childbearing potential), 24 (Primary), 36, and 48 **Screening assessments include:** • Obtain informed consent • Review of inclusion/exclusion criteria • Obtain medical history (including HBV disease and treatment history) • Review concomitant medications • Complete physical examination • Vital signs • Body weight and height • 12-Lead electrocardiogram (ECG) (Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording) • Chest x-ray • Ophthalmologic examination • FibroScan (where available and as necessary for liver disease staging) • Sample collection for: — Safety laboratory tests (hematology, chemistry, and coagulation) — AST to platelet ratio index (APRI), FibroTest, α-fetoprotein (computed tomography [CT] scan with contrast for participants with α-fetoprotein ≥ 50 ng/mL at screening) — Serology testing to exclude HCV, HDV, and HIV infection — Quantitative plasma HBV DNA — Quantitative HBV serum HBsAg, HBcrAg, HBeAg, and HBV RNA — Qualitative HBV serology HBeAg, HBeAb, and HBsAg, HBsAb — Estimated CL_{cr} (using the Cockcroft-Gault method) — Other screening laboratory tests: urinalysis, urine drug screen, alcohol screen, autoantibodies, quantification of

	thyroid-stimulating hormone (TSH) levels, and serum β human chorionic gonadotropin (β-hCG) (females of childbearing potential only), follicle-stimulating hormone (FSH) (for female participants who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure) — Serum sample for HBV viral sequencing, genotyping sample, and ddPCR • Record any serious adverse events (SAEs) and all AEs related to protocol mandated procedures occurring after signing of the consent form. **<u>Treatment assessments include</u>:** • Vital signs • Weight • Review AEs • Review concomitant medications • Complete Physical Examination • Symptom-directed physical examination • 12-Lead ECG (Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording) • Symptoms-directed ophthalmologic examination • Sample collection for: — Safety laboratory tests (hematology and chemistry; coagulation) — APRI and FibroTest — Quantitative plasma HBV DNA — Quantitative serum HBsAg, HBcrAg, HBeAg, and HBV RNA — Qualitative HBV serology HBeAg, HBeAb, and HBsAg, HBsAb — Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis — Sparse PK samples — Urine pregnancy test (females of childbearing potential only) — Urinalysis — Estimated CL_{cr} (using Cockcroft-Gault method)

	— Serum sample for HBV viral sequencing, genotyping sample, and ddPCR • CCI [redacted] • CCI [redacted] • Perform study drug accountability, dispensation, and administration (TAF, as needed, nivolumab IV, SLGN, and VIR-2218 SC) CCI [redacted]

	• CCI [redacted]
Test Product, Dose, and Mode of Administration:	Selgantolimod will be supplied as tablets in strengths of 1.5 mg. SLGN 3 mg (2 × 1.5-mg tablets) will be administered while fasting, once a week, on the same day. Participants must be fasting for at least 8 hours overnight (no food or drinks, except water) and continue through the morning, with no food or drinks, including water, 1 hour before to 2 hours after dosing. After 2 hours postdose, water is allowed and after 4 hours postdose, participants are allowed food and drinks. Participants should take their other prescribed medications, including NUC treatment, no earlier than 2 hours after SLGN dosing or, if medications require dosing with food, no earlier than 4 hours after SLGN dosing. VIR-2218, 200 mg/mL, solution for injection will be supplied as 0.5 mL single dose vials. VIR-2218 200 mg (2 × 0.5 mL solution) will be administered SC. Nivolumab (Opdivo®) 40 mg/4 mL solution for injection was supplied as single dose vials. Nivolumab 0.3 mg/kg was administered as IV infusion over 45-60 minutes. TAF 25-mg tablet orally once daily with food.
Reference Therapy, Dose, and Mode of Administration:	None

Criteria for Evaluation:	
Safety:	Safety will be evaluated by assessment of clinical laboratory tests and AEs collected through FU Week 48. The primary safety analysis will be evaluated through 30 days posttreatment of SLGN ± nivolumab ± VIR-2218. Posttreatment is defined as the following: • For VIR-2218 and nivolumab, posttreatment will start 4 weeks after last dose. • For SLGN, posttreatment will start 1 week after last dose. Posttreatment for each cohort will be based on the last study drug(s) end of the treatment window duration that is the longest. The safety analysis will also be conducted through FU Week 24 as a secondary safety analysis.
Efficacy:	**Primary efficacy endpoint:** • The proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < LLOQ at FU Week 24 **Secondary efficacy endpoints:** • The proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study • The proportion of participants with HBeAg loss with and without anti-HBeAg seroconversion during the study in participants with CHB who are HBeAg positive at baseline • The proportion of participants who remain off NUC treatment during FU • The proportion of participants experiencing HBV virologic breakthrough during study treatment(s)

Pharmacokinetics:	Sparse PK blood samples will be collected at specific in-clinic treatment visits for all participants at the time points specified in the protocol. CCI [redacted] Plasma concentrations of SLGN and VIR-2218, and serum concentrations of nivolumab may be analyzed (as applicable, from existing samples).
Statistical Methods:	The primary analysis will be conducted after all participants within each cohort have completed FU Week 24 or early terminated from the study prior to FU Week 24. The primary efficacy endpoint is the proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < LLOQ at FU Week 24. The primary efficacy analysis will summarize the primary efficacy endpoint for each treatment cohort. A point-estimate with 2-sided 95% exact CI will be constructed for the proportions using the binomial distribution (Clopper-Pearson method). The secondary efficacy endpoints will be summarized by treatment cohort. Continuous secondary endpoints will be summarized using conventional descriptive statistics (n, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) by treatment cohort. Categorical secondary endpoints will be summarized by number and percentage of participants who meet the endpoint by treatment cohort. Safety will be evaluated by treatment cohort. It will be summarized by the number and percentage of participants with AEs or laboratory abnormalities for categorical values or by the conventional descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data. **Sample Size** CCI [redacted] The number of participants in each treatment cohort was decided based on clinical experience.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
Ab	antibody
ABW	actual body weight
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AMA	antimitochondrial antibodies
ANA	antinuclear antibodies
APRI	AST to Platelet Ratio Index
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{0-24}	partial area under the concentration versus time curve from time "0" to time "24"
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
β-hCG	β human chorionic gonadotropin
cccDNA	covalently closed circular DNA
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHB	chronic hepatitis B
CI	confidence interval
CK	creatine kinase
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
CL/F	apparent oral clearance
C_{max}	maximum observed concentration of drug
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 19
CRF	case report form
CRO	contract (or clinical) research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
ddPCR	digital droplet polymerase chain reaction

DILI	drug-induced-liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
ELIspot	enzyme-linked immunospot assay
EOT	end of treatment
ESC+	Enhanced Stabilization Chemistry Plus
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
FU	follow-up
GalNAc	N-acetyl-galactosamine ligand
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
Gilead	Gilead Sciences, Inc.
GSI	Gilead Sciences, Inc.
HAV	hepatitis A virus
HBV	hepatitis B 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
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV, HIV-1	human immunodeficiency virus, type 1
HLA	human leukocyte antigen
HLGT	high-level group term
HLT	high-level term
IB	investigator’s brochure

ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	independent ethics committee
IFN	interferon
Ig	immunoglobulin
IgM	immunoglobulin M
IL	interleukin
IND	investigational new drug (application)
INR	international normalized ratio
irAE	immune-related AE
IRB	institutional review board
IRR	infusion-related reaction
ISR	injection site reaction
IV	intravenous
LDH	lactic acid dehydrogenase
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
LLT	lower-level term
mAb	monoclonal antibody
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NK	natural killer cells
NOAEL	no-observed-adverse-effect-level
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NUC	nucleos(t)ide(s)
OAV	oral antiviral
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PD-1	programmed cell death protein 1
PEG	polyethylene glycol
PG	pharmacogenomic
PgRNA	pregenomic RNA
PHH	primary human hepatocytes
PI	principal investigator
PK	pharmacokinetic(s)
PS	Patient Safety
PT	preferred term

QT	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
QTcF	QT interval corrected for heart rate using the Fridericia formulation
Q1	first quartile
Q3	third quartile
RBC	red blood cell
RNA	ribonucleic acid
RT	reverse transcriptase
SADR	serious adverse drug reaction
SAE	serious adverse event
SC	subcutaneous(ly)
S_{cr}	serum creatinine
SD	standard deviation
SDV	source data verification
siRNA	short interfering RNA
SLGN	selgantolimod
SMA	smooth muscle antibodies
SMQ	Standardised MedDRA Query
SNP	single-nucleotide polymorphism
SOC	system organ class
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TE	treatment emergent
TFFU	treatment-free follow-up
TFV	tenofovir
T_{last}	time (observed time point) of C_{last}
TLR	toll-like receptor
T_{max}	the time (observed time point) of C_{max}
TNF	tumor necrosis factor
TPO	thyroid peroxidase
TSH	thyroid-stimulating hormone
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
ULN	upper limit of normal
US, USA	United States, United States of America
WBC	white blood cell

WHV	woodchuck hepatitis virus
WHsAg	woodchuck hepatitis virus surface antigen

1. INTRODUCTION

1.1. Background

Chronic hepatitis B (CHB) is a major public health care issue worldwide and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The hepatitis B virus (HBV) is easily transmissible through perinatal, percutaneous, and sexual exposure {World Health Organization (WHO) 2015b}. Following acute HBV infection, 5% to 10% of adults and up to 90% of children fail to produce an immune response adequate to clear the infection; these individuals become chronic carriers of the virus {Zuckerman 1996}. Individuals who develop CHB are at substantial risk of cirrhosis, hepatic decompensation, and HCC, which will afflict 15% to 40% of patients with CHB in the absence of effective treatment {Ratnam 2006, World Health Organization (WHO) 2015a}. Liver cancer is the third leading cause of cancer deaths globally, with the highest burden of disease found in regions where HBV is endemic {Global Burden of Disease Cancer Collaboration 2015}. Recent reports estimated that 250 to 350 million individuals were living with HBV (ie, are hepatitis B surface antigen [HBsAg]-positive) in 2010, representing a worldwide prevalence of 3.6%, with considerable geographic variability {Schweitzer 2015, World Health Organization (WHO) 2015c}. In 2015, an estimated 654,000 deaths were due to HBV infection and associated complications, placing it among the top 20 causes of mortality worldwide {G. B. D. Mortality Causes of Death Collaborators 2016}.

The loss of HBsAg, accompanied by seroconversion to anti-HBsAg, is the accepted endpoint for anti-HBV therapy endorsed by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver allowing for cessation of therapy {European Association for the Study of the Liver (EASL) 2012, European Association for the Study of the Liver (EASL) 2017, Lok 2009}, {Sarin 2015, Terrault 2016}. Clearance of HBsAg has been associated with improvements in liver histology, including the reversal of cirrhosis, a decreased risk of HCC, and prolonged survival, and is considered evidence of a functional cure {Benias 2011, Fattovich 1998, Kim 2013}. Nucleos(t)ide (NUC) analogs are the standard-of-care for CHB treatment, providing durable suppression of viral replication that results in long-term clinical benefits with a reduced risk of liver complications {Dienstag 2003, Liaw 2011, Lok 2013}. However, treatment with NUCs rarely results in clearance of HBsAg {Kwon 2011}. Thus, new treatment options that enhance rates of HBsAg clearance are needed; such treatments will allow patients to discontinue life-long oral antiviral (OAV) therapy and provide a finite-duration treatment option for a functional cure. A finite therapy is expected to be applicable to a broader population of those chronically infected with HBV, including immunotolerant patients who are currently untreated.

The host immune response to HBV infection plays a pivotal role in whether acute infection is resolved or becomes chronic. Individuals who are able to clear HBV infection spontaneously following an acute infection display a vigorous, polyclonal, HBV-specific cluster of differentiation (CD)8+ and CD4+ T-cell response {Rehermann 2005}. In contrast, CHB is associated with a limited and dysfunctional CD8+ T-cell response, as well as impaired natural

killer (NK) cell antiviral function {Peppa 2010, Rehermann 2005}. Suppression of HBV DNA with NUC analogs has been associated with overall improvements in the ability of the immune system to respond to HBV antigens {Evans 2008, Mizukoshi 2004, Sherman 2013}. The suppression of HBV DNA also results in the reduction of regulatory T cells, an increase in HBV-specific CD8+ T cells and reduction in exhaustion markers (such as programmed cell death protein 1 [PD-1]) on CD8+ T cells {Evans 2008, Sherman 2013}. These improvements, however, are modest and do not result in durable immune control with loss of HBsAg in the majority of treated participants. However, further control of HBV viral antigens with HBV DNA suppression and the enhancement of virus-specific immune responses, may theoretically enhance rates of durable control of HBV.

1.2. General Information About Study Drugs

1.2.1. General Information About Selgantolimod

Selgantolimod (SLGN, also GS-9688) is a Toll-like receptor 8 (TLR8) agonist that induces the cellular immune mediator interleukin (IL)-12 and the antiviral cytokines tumor necrosis factor (TNF)-α and interferon (IFN)- γ in vitro in peripheral blood mononuclear cells (PBMCs). Cytokine induction by SLGN is comparable in PBMCs from patients with CHB and from healthy donors. Selgantolimod induces little to no IFN-α (a cytokine induced by TLR7 agonists) in human PBMCs in vitro, indicating that SLGN is a potent and selective TLR8 agonist in primary human immune cells. Selgantolimod activates monocytes and professional antigen-presenting cells (pAPCs) in vitro in PBMCs from healthy donors. It also activates NK cells and total CD8+ T cells in vitro in PBMCs isolated from both healthy donors and patients with CHB. Additionally, SLGN increases IFN-γ production and reduces expression of the inhibitory receptor PD-1 by HBV-specific CD8+ T cells. Cytokines induced by SLGN in healthy human donor PBMCs in vitro reduce the levels of HBV DNA, HBV RNA, HBsAg, and hepatitis B e antigen (HBeAg) in HBV-infected primary human hepatocytes (PHH). Prophylactic treatment with cytokines induced by SLGN prevents establishment of HBV covalently-closed circular DNA (cccDNA) in PHH in vitro.

In cynomolgus monkeys, dose-dependent induction of serum IL-12p40, IL-1RA, and other cytokines was observed following oral administration of SLGN at doses ≥ 0.3 mg/kg. These pharmacodynamic (PD) markers are consistent with TLR8 activation. In woodchucks chronically infected with the woodchuck hepatitis virus (WHV), once-weekly oral administration of 3 mg/kg SLGN for 8 weeks resulted in > 2 $\log_{10}$ IU/mL reduction of serum woodchuck hepatitis virus surface antigen (WHsAg) and WHV DNA in 4 of 6 woodchucks. This antiviral response was sustained in 3 of 6 woodchucks until the end of study. Moreover, these 3 animals developed detectable anti-WHsAg and had > 95% reduction in intrahepatic WHV cccDNA at the end of study.

Selgantolimod shows low systemic concentrations across multiple species (rat, dog, and cynomolgus monkey), indicating low potential for immune activation in the periphery. Mouse and cynomolgus monkey toxicology studies of ≥ 13 weeks (≥ 14 doses) demonstrated that SLGN was well tolerated and nonadverse at doses up to 10 mg/kg/week in the mouse and 30 mg/kg/week in the monkey. At the highest observed exposure in a clinical study (GS-US-389-2022) with a clinical dose of 3 mg, the exposure margins at the no observed adverse

effect level (NOAEL) based on the AUC are approximately 192-fold and 37-fold for mouse and cynomolgus monkey, respectively.

A first-in-human (FIH) pharmacokinetic (PK) and food-effect study (GS-US-389-2021) was completed in healthy participants. For the 48 participants who received a single dose of 0.5, 1.5, 3, or 5 mg of SLGN, the dose was generally safe and resulted in dose-dependent increases in serum IL-12p40 and IL-1RA. For the 12 participants who received a single dose of 1.5 mg in both the fed and fasted states, SLGN plasma concentrations were similar between the 2 states, whereas serum IL-12p40 and IL-1RA were strongly reduced when SLGN was dosed with food. Based on these data, subsequent clinical evaluations are conducted under fasted conditions.

A drug-drug interaction (DDI) study (GS-US-389-5545) to evaluate the PK and pharmacodynamics (PD) of SLGN upon coadministration with a representative proton pump inhibitor (omeprazole) or histamine 2 receptor antagonist (famotidine) was completed in healthy participants. Statistical comparisons of SLGN AUC between SLGN administered alone versus in combination with either omeprazole or famotidine were within the predefined no-effect DDI boundary of 70% to 143%, indicating a lack of significant effect on SLGN PK. There was no clinically significant impact of omeprazole or famotidine on relevant PD markers of SLGN. These data demonstrate that SLGN may be administered without regard to acid-reducing agents such as omeprazole or famotidine thereby not warranting any dosing adjustments.

Limited dosing of SLGN has been evaluated in participants with CHB (Studies GS-US-389-2022, GS-US-389-2024, and GS-US-389-2025) and was shown to be generally safe and well tolerated. In the GS-US-389-2022 study, doses of 1.5 mg and 3 mg resulted in dose-dependent induction of IL-12p40 and IL-1RA, with no evidence of tachyphylaxis with up to 4 doses of SLGN. Pharmacokinetic data show similar exposures in participants with CHB compared with healthy participants in the FIH study, with no accumulation over time. At the interim Week 48 analysis for Study GS-US-389-2024, 1 participant (HBeAg negative in the SLGN 1.5-mg dose group) met the primary endpoint of ≥ 1 $\log_{10}$ IU/mL decline from baseline in HBsAg at Week 24. Based on the interim safety data from Studies GS-US-389-2024 and GS-US-389-2025, nausea, vomiting, and iridocyclitis were added as adverse drug reactions (ADRs) for SLGN at the current stage of development.

For further information on SLGN, refer to the investigator's brochure (IB) for SLGN.

1.2.1.1. Ongoing Studies

There is an ongoing Phase 1b study assessing safety, tolerability, and efficacy of once-weekly administration of SLGN 3 mg in special populations with CHB (GS-US-389-5458). This study is evaluating SLGN in 3 populations with CHB: (1) immune tolerant HBV with HBV DNA $\geq 1 \times 10^7$ IU/mL, (2) patients with inactive HBV (HBV DNA ≤ 2000 IU/mL) at screening, and (3) HBV/hepatitis D virus (HDV) coinfected participants on suppressive NUC therapy. Based on the interim safety data at Week 24, no new safety issues for SLGN have been observed.

1.2.2. General Information About Nivolumab

Nivolumab (Opdivo®, BMS), an anti-PD-1 immunoglobulin (Ig)G4 monoclonal antibody (mAb), is approved for the treatment of metastatic melanoma and is under development for other malignancies including lung cancer and HCC. The clinical dose of nivolumab is 3 mg/kg intravenously (IV) every 2 weeks, though initial dose ranging studies in melanoma demonstrated equivalent receptor occupancy of peripheral lymphocyte PD-1 at doses as low as 0.1 mg/kg {Topalian 2012}. In those studies, clinical effect for melanoma was observed at all doses tested. The lowest doses of 0.1 mg/kg and 0.3 mg/kg were not associated with Grade 3 or 4 serious adverse events (SAEs) or Grade 3 or 4 adverse events (AEs) of special interest (including autoimmune AEs) and had lower rates of treatment-related Grade 3 or 4 AEs compared with higher dose groups.

Nivolumab has also been studied in a single dose study in hepatitis C virus (HCV) (N = 45) with dose ranges of 0.03 mg/kg to 10 mg/kg {Gardiner 2013}. The majority of AEs were Grade 1 or 2 with a single Grade 4 alanine aminotransferase (ALT) elevation in the highest dose evaluated. All immune-related AEs (irAE) were mild to moderate and resolved without intervention. Reductions in HCV RNA were modest and seen in 5/45 (11%) of treated participants at doses as low as 0.1 mg/kg, although the highest dose of 10 mg/kg induced a > 4 $\log_{10}$ IU/mL reduction in HCV RNA in 3 participants (n = 20 total at this dose).

Nivolumab has also been evaluated for HCC (related to HCV, HBV or neither), where a subpopulation of 66 HBV-infected participants with HCC were dosed with nivolumab at doses of 0.1 mg/kg to 3.0 mg/kg IV every 2 weeks. No participants with HBV in either the dose escalation phase or in the expansion phase discontinued treatment due to study drug toxicity. Among the HBV-infected participants with HCC who received nivolumab at 3.0 mg/kg IV every 2 weeks (n = 51), no participants experienced Grade 3 or 4 ALT/aspartate aminotransferase (AST) increases and 6% (n = 3) experienced a Grade 3 or 4 treatment-related AE {El-Khoueiry 2017}.

For further information on nivolumab, refer to the current approved product label for nivolumab.

1.2.2.1. Ongoing Studies

There are no other ongoing Gilead-sponsored studies with nivolumab.

1.2.3. General Information About Tenofovir Alafenamide (TAF)

Vemlidy® (TAF, GS-7340) is a novel oral prodrug of tenofovir (TFV), a NUC analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, tenofovir diphosphate, a competitive inhibitor of HIV-1 reverse transcriptase (RT) and HBV RT that terminates the elongation of the viral DNA chain.

For further information on TAF, please refer to the approved product label for TAF.

1.2.4. General Information About VIR-2218

VIR-2218 is a short interfering RNA (siRNA) that targets a region of the HBV genome that is common to all HBV viral transcripts. The siRNA is chemically modified using Enhanced Stabilization Chemistry Plus (ESC+) consisting of 2'-fluoro (2'F), 2'-O-methoxy (2'OMe) ribose sugar modifications, phosphorothioate backbone modifications, glycol nucleic acid modification, and conjugation to a triantennary N-acetyl-galactosamine ligand (GalNAc) at the 3' end of the sense strand, to facilitate delivery to hepatocytes through the asialoglycoprotein receptor. The drug product, VIR-2218, is the drug substance of VIR-2218 formulated in water for subcutaneous (SC) injection. VIR-2218 is pharmacologically active against HBV genotypes A through J; see the current IB for additional information on VIR-2218. The use of siRNA offers a novel strategy for the treatment of chronic HBV infection. The siRNAs are 19-21 base-pair RNA duplexes that exploit the endogenous RNA-interference pathway to enable sequence-specific RNA cleavage and degradation. One siRNA can have multiple antiviral effects, including degradation of the pregenomic RNA (pgRNA), thus inhibiting viral replication, and degradation of all viral messenger RNA transcripts, thereby preventing expression of viral proteins. This may result in the return of a functional immune response directed against HBV, especially if combined with other therapies, in particular, immune modulatory agents.

By contrast, nucleoside reverse transcriptase inhibitors (NRTIs) act at a distinct part of the viral life cycle and have a different mechanism of action than VIR-2218. NRTIs inhibit the action of HBV RNA polymerase, blocking the reverse transcription of the viral pgRNA to viral DNA and preventing the production of infectious virions. NRTIs, however, do not directly impact the production of viral proteins such as HBsAg. Reduction of HBsAg-containing noninfectious subviral particles by VIR-2218 is considered an important differentiator from current treatments.

For further information, refer to the IB for VIR-2218.

1.3. Rationale for the Current Study

1.3.1. Rationale for Modifications to Study Design

Nivolumab was chosen in the initial study design, as an immunomodulator, in order to reverse HBV mediated T-cell exhaustion to induce an HBV-specific immune response to subsequently achieve an HBV functional cure.

Nivolumab dosing was stopped for all participants in this study. This was a sponsor decision based on a benefit risk assessment of the use of nivolumab in HBV cure. For Cohort 2 Group B, where participants were originally designed to be treated with SLGN and nivolumab, Gilead made the decision to stop all treatment in this cohort on account of low likelihood of efficacy with SLGN alone, based on results from previous studies {Gane 2023, Janssen 2021}. Study participants in Cohorts 1 and 2 (Group A) will continue all other treatments (SLGN and VIR-2218) up to Week 36.

1.3.2. Rationale for This Study as Originally Designed

Given the low rate of HBsAg loss with currently available therapies and the treatment burden associated with life-long treatment to maintain viral suppression, there is a need to identify new therapies that may provide durable HBsAg loss with a finite treatment duration. The host immune response to HBV infection plays a pivotal role in whether acute infection is resolved or becomes chronic. Individuals who are able to clear HBV infection spontaneously following an acute infection display a vigorous, polyclonal, HBV-specific CD8+ and CD4+ T-cell response {Rehermann 2005}. In contrast, CHB is associated with a limited and dysfunctional CD8+ T-cell response, as well as impaired NK-cell antiviral function {Peppa 2010, Rehermann 2005}. The primary objective of this Phase 2 study is to evaluate the safety, tolerability, and efficacy of novel HBV immunomodulatory containing combination regimens in association with or without a HBV targeted siRNA for the treatment of participants with CHB.

This Phase 2 study was originally intended to evaluate the safety and efficacy of combination treatment with 2 immunomodulatory agents, a toll-like receptor 8 (TLR8) agonist, SLGN, and a PD-1 checkpoint inhibitor, nivolumab, with and/or without siRNA, VIR-2218, in both virally suppressed and viremic participants with CHB. The aim of the virally suppressed cohort was to evaluate the hypothesis that maximum viral and antigen reduction before immunomodulation therapy will improve HBV-specific immune response to combination treatment. In contrast, the aim of the viremic cohorts is to evaluate the hypothesis that immune modulation in the presence of active liver inflammation caused by HBV infection will improve HBV-specific immune response to treatment. Immune active, viremic patients have been well characterized by a pro-inflammatory state with the presence of high viral burden and active liver inflammation. The effectiveness of immunomodulatory agents targeting functional improvement of exhausted HBV-specific CD8+ T cell in immune active patients with and without an siRNA has not yet been evaluated.

Multiple studies have recently demonstrated that NUCs can be safely stopped with a close safety monitoring plan in a noncirrhotic patient population {Buti 2019}. Therefore, participants who are virally suppressed, HBeAg negative and have HBsAg < 100 IU/mL at end of treatment (EOT), will enter a treatment-free follow-up (TFFU) period after completion of study treatment, where they will be closely followed with safety visits every 4 weeks in the first 3 months and then every 8 weeks for a total of 48 weeks. Criteria for initiation of NUC treatment during follow-up (FU) period have been defined to guide investigators and allow for evaluation of predictors of response. The aim of the TFFU period will be to evaluate the continued off-treatment response to siRNA and/or SLGN plus nivolumab, which have all demonstrated prolonged/sustained activity beyond the dosing period {Gane 2020}.

1.4. Rationale for Dose Selection of Study Drugs

1.4.1. Rationale for Dose Selection of Selgantolimod

The safety, PD, and PK of SLGN have been evaluated in healthy volunteers and participants with CHB. Selgantolimod has demonstrated dose-dependent induction of IL-12p40 and IL-1RA, PD markers of SLGN pharmacological activity, and comparable PK in both populations

(GS-US-389-2021 and GS-US-389-2022). Food effect evaluation on SLGN disposition in the FIH study (GS-US-389-2021) showed comparable SLGN plasma exposures in the fed and fasted state, however, the PD markers markedly reduced in the presence of food which led to dosing of SLGN in fasted conditions in subsequent clinical evaluations.

The safety and efficacy of SLGN 1.5 mg and 3 mg weekly for 24 weeks in combination with NUC therapy has been evaluated in 2 ongoing Phase 2 studies in virally suppressed and viremic participants with CHB (GS-US-389-2024 and GS-US-389-2025, respectively) and in the Phase 1b study assessing safety and efficacy of once-weekly administration of SLGN 3 mg coadministered with nivolumab (dosed IV every 4 weeks) in virally suppressed participants (GS-US-493-5342). Safety data from these studies indicate that SLGN treatment (at doses of 1.5 mg and/or 3 mg, once weekly) was generally safe and well tolerated.

Based on the collective clinical data available to date, in this study, once-weekly dosing of SLGN 3 mg (the higher of the 2 evaluated doses) for 24 weeks in fasted state was proposed for administration with nivolumab ± VIR-2218.

For further information, refer to the current IB for SLGN.

1.4.2. Rationale for Dose Selection of Nivolumab

In a Phase 1 study, GS-US-330-1938, the safety and efficacy of a single IV dose of nivolumab 0.3 mg/kg was evaluated in virally suppressed participants with CHB. After the single IV administration, 3 out of 22 (14%) participants had > 0.5 $\log_{10}$ IU/mL reduction in HBsAg with 1 participant achieving > 1 $\log_{10}$ IU/mL reduction. This participant achieved HBsAg loss and anti-HBs seroconversion 10 weeks after completing the study, as reported by the investigator {Gane 2019}. Overall, single IV administration of nivolumab 0.3 mg/kg was safe and well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, or laboratory abnormalities, except for the 1 participant who achieved HBsAg loss and had a Grade 3 ALT flare, were reported. The only nivolumab-related AEs as determined by the investigator were fatigue, headache, and cough which were reported in only 1 participant each. Additionally, in Study GS-US-493-5342, nivolumab 0.3 mg/kg once every 4 weeks (dosed IV for 12 weeks), alone or in combination with SLGN in virally suppressed participants with CHB, was shown to be generally safe.

Based on these data, this study will evaluate the safety and efficacy of 0.3 mg/kg nivolumab dosed IV once every 4 weeks for 24 weeks in combination with: SLGN and VIR-2218 in virally suppressed participants with CHB, and SLGN ± VIR-2218 in viremic participants with CHB.

1.4.3. Rationale for Dose Selection of TAF

TAF 25 mg administered orally once daily with food is the approved dose for the treatment of CHB virus infection in adults (≥ 18 years of age) with compensated liver disease {VEMLIDY 2020}.

1.4.4. Rationale for Dose Selection of VIR-2218

Available safety, tolerability, antiviral activity, and PK/PD data from Parts A-C of Study VIR-2218-1001 were considered when selecting dose levels for VIR-2218 in combination with VIR-3434. In Part A of the VIR-2218-1001 study, a single SC dose of VIR-2218 was administered to healthy participants over the dose range of 50 to 900 mg. In Parts B and C of the study, 2 doses of VIR-2218 given 4 weeks apart, ranging from 20 to 200 mg were administered to participants with chronic HBV infection. VIR-2218 was well tolerated across all dose levels evaluated, with no significant safety signals observed.

In healthy adult participants, VIR-2218 was absorbed after SC injection with median T_{max} of 4 to 7 hours in plasma. Consistent with rapid GalNAc-mediated liver uptake {Nair 2017}, VIR-2218 was not measurable in plasma beyond 48 hours for any participant. PK data following a single SC dose suggest that VIR-2218 AUC_{0-12} and C_{max} exposures increase with dose and were slightly greater than dose-proportional across the dose range evaluated. Available PK data from HBV participants were similar to that observed in healthy participants. No accumulation of VIR-2218 in plasma was evident following a second dose of VIR-2218 administered 4 weeks apart in participants with chronic HBV infection.

Despite rapid elimination of VIR-2218 from plasma, prolonged presence is anticipated in the liver, based on tissue PK of VIR-2218 in nonclinical species and data from other GalNAc-conjugated siRNA molecules {Janas 2018}. Since no direct measurement of liver PK was available from human participants in the study, liver PK data from nonclinical studies were initially used to predict human liver PK based on allometric scaling. Using a model describing the onset, peak, and durability of PD response for a chemically similar ESC-GalNAc-siRNA {Attarwala 2017} and available rat tissue PK data for VIR-2218, the human liver half-life of VIR-2218 was previously estimated to be approximately 40 days. An updated analysis was conducted using measured HBsAg following VIR-2218 treatment in participants with chronic HBV infection (from Study VIR-2218-1001 Parts B and C). A sequential PK-PD modeling approach was applied to estimate PK parameters of VIR-2218 in plasma, then an effect compartment representing the site of drug action in liver was used to link the plasma PK and HBsAg reduction observed over time in an indirect response PK-PD model. The PK-PD model described the observed VIR-2218 plasma PK and HBsAg data well and predicted a half-life of approximately 80 days in the liver.

The liver half-life of VIR-2218 of 80 days was used to estimate VIR-2218 liver tissue exposure in humans (Table 3). The median liver exposures for the proposed VIR-2218 doses (6 doses of 200 mg given every 4 weeks) are estimated to not exceed the projected liver exposure of the highest dose at which the safety and tolerability of VIR-2218 has been demonstrated (ie, 900 mg single dose).

Table 3. Estimated Median VIR-2218 Liver Tissue Exposure in Humans Based on PK-PD Model

Simulated Dosing Regimen	C_{max} (µg/g)	AUC (h*µg/g)
900 mg single dose	61.1	34,300 (135,000) [a]
200 mg Q4W × 6	52.9	34,100 [b]

PD = pharmacodynamics; PK = pharmacokinetics; Q4W = once every 4 weeks

a For single dose regimens, partial AUC_{last} up to Day 29 is presented; AUC_{inf} is also presented in parenthesis.
b For multiple dose regimens, AUC refers to AUC_{last} during the 28-day dosing interval following 2 or 6 doses of VIR-2218.

Taken together, the observed safety and tolerability of VIR-2218, in conjunction with estimations of VIR-2218 liver exposure, support the VIR-2218 regimen selected for this study

1.5. Benefit/Risk Assessment for the Study

Chronic hepatitis B remains a global health concern with significant morbidity worldwide. The loss of HBsAg with seroconversion is the gold standard endpoint for anti- HBV therapy and allows for cessation of treatment {European Association for the Study of the Liver (EASL) 2012, Liaw 2012, Lok 2009}. Loss of serum HBsAg is associated with improvement in both the rates of liver cirrhosis and the development of HCC in patients with CHB, and in increased survival rate {Idilman 2012, Kim 2013, Moucari 2009, Simonetti 2010}. While HBsAg loss is the ultimate goal of treatment, it occurs at a very low rate and over several years: less than 1% of patients treated with NUC analogs achieve clearance of HBsAg. Thus, new treatment options that enhance rates of HBsAg loss with seroconversion are needed.

Selgantolimod

Selgantolimod treatment alone have been evaluated in multiple Phase 1 and Phase 2 studies in both healthy volunteers and participants with CHB. The longest durations of treatment were evaluated in 2 Phase 2 studies, GS-US-389-2024 (NUC-suppressed participants with CHB) and GS-US-389-2025 (treatment-naive participants with CHB), that administered placebo, SLGN 1.5 mg, or 3 mg once weekly with a NUC for 24 weeks to 93 participants with CHB. Selgantolimod up to 3 mg once weekly was safe and well tolerated in 102 participants with CHB (48 participants in Study GS-US-389-2024 and 54 participants in Study GS-US-389-2025). Based on pooled safety review of the SLGN studies, 3 potential ADRs related to SLGN of nausea, vomiting, and iridocyclitis were identified. Majority of these ADRs reported have been mild or moderate in severity. To mitigate the impact of ADR of nausea and vomiting for SLGN, the use of antiemetic (eg, ondansetron) is allowed in the study. A Grade 2 iridocyclitis (in the SLGN 1.5-mg dose group) was the only SAE reported that was considered related to SLGN by the investigator and led to early study drug discontinuation. This occurred in a participant who tested positive for the human leukocyte antigen (HLA)-B27 haplotype, a genetic risk factor associated with various immune disorders including anterior uveitis. No Grade 3 or 4 AEs considered related to SLGN treatment have been reported in the studies, except for 1 Grade 3 AE of rhinorrhea considered possibly related by the investigator that was reported in Study GS-US-389-2025. Additional safety results can be found in the IB for SLGN.

Nivolumab

In oncology, nivolumab treatment alone has been well characterized and the risks of irAEs are listed in the approved product label for nivolumab {OPDIVO 2022}.

The risk of irAEs has been observed upon administration of nivolumab and other anti PD-1 mAbs in the oncology setting {Friedman 2016}. These events are a class effect of all immune checkpoint inhibitors including nivolumab.

The use of nivolumab in HBV cure was based on the hypothesis that lower doses of the product with less frequent dosing would result in a reduced risk of irAEs. In Gilead studies, including Study GS-US-465-4439, nivolumab has been dosed at approximately 1/10th of the clinically approved oncology dose and is administered as only 1 infusion every 4 weeks for up to 6 doses. In prior Gilead studies involving patients with HBV, the use of nivolumab alone, or in combination with SLGN for up to 3 doses every 4 weeks, was well tolerated {Gane 2019}. However, irAEs have been observed at low doses of other anti-PD1 mAbs in non-oncology indications {Gubser 2022}. Therefore, the sponsor decision was to stop further dosing of nivolumab based on a benefit-risk assessment of the use of nivolumab in HBV cure.

VIR-2218

VIR-2218 is an siRNA that targets a specific sequence in the HBV virus. The safety and tolerability of VIR-2218 has been evaluated in an ongoing Phase 1/2 study, VIR-2218-1001 that evaluated single doses of VIR-2218 up to 900 mg administered SC in healthy participants (Part A) and a regimen of 2 doses administered 4 weeks apart at doses up to 200 mg in participants with CHB (Part B/C). In Part A, 59.5% of VIR-2218 participants (22 of 37) and 50% of placebo participants (6 of 12) had at least 1 AE, each of which was Grade 1 or 2 in severity with the exception of a single Grade 3 AE of respiratory tract infection (considered not related to study drug). The most common AEs in VIR-2218 participants were headache (24.3%; 9 of 37 participants), and upper respiratory tract infection, contact dermatitis, injection site bruising, and injection site pain (8.1% each; 3 of 37 participants). Three VIR-2218 participants (8.1%) had AEs considered related to study drug by the investigator, including headache, injection site pain, and abdominal pain, each of which was Grade 1 in severity. Seven VIR-2218 participants (18.9%) had injection site reactions (ISRs). All ISRs were Grade 1 in severity and resolved within 12 days of onset.

In Part B/C, 54.2% of VIR-2218 participants (13 of 24) and 25% of placebo participants (2 of 8) had at least 1 AE, each of which was Grade 1 or 2 in severity with the exception of 1 Grade 3 nonserious AE of hypophosphatemia (considered not related to study drug), a known ADR of tenofovir disoproxil fumarate (TDF) with which the participant was receiving treatment. The most common AEs in VIR-2218 participants were headache (25.0%; 6 of 24 participants), and dizziness, fatigue, and myalgia (8.3% each; 2 of 24 participants). Five participants (20.8%) had AEs considered related to study drug by the investigator, including headache, injection site pain, and pyrexia, each of which was Grade 1 or 2 in severity. Two VIR-2218 participants (8.3%) each had 1 ISR. All ISRs were Grade 1 in severity and resolved within 3 days of onset. Injection site reactions were reported in the 50-mg and 100-mg dose cohorts. One treatment-emergent (TE)

SAE was reported in Study VIR-2218-1001 in a participant administered 100 mg VIR-2218. The SAE of headache was Grade 2 in severity and considered related to study drug by the investigator, but the Gilead determined that the constellation of concurrent symptoms (fever, headache, nausea, vomiting, and dehydration) was more consistent with a viral syndrome than a drug reaction and assessed the event as not related to study drug. Two participants had a non-TE SAE considered not related to study drug by the investigator; 1 participant had depression and 1 participant committed suicide (outcome of death). The death (suicide) occurred approximately 9 months after last study drug administration.

Selgantolimod + Nivolumab

In the Phase 1b study, GS-US-493-5342, the combination of SLGN 3 mg oral once weekly plus nivolumab 0.3 mg/kg IV every 4 weeks for 12 weeks was evaluated in 14 participants with CHB. The combination treatment for 12 weeks was generally safe and well tolerated. The most common (> 1 participant) AEs considered related to study drugs by the investigator were nausea (n = 6), vomiting (n = 5), headache (n = 2), diarrhea (n = 2), and fatigue (n = 2). To mitigate the risk of nausea and vomiting, the use of antiemetics (eg, ondansetron) was allowed during the study. No Grade 3 or 4 AEs or SAEs were reported, and no Grade 3 laboratory abnormalities were observed. A single Grade 4 laboratory abnormality of elevated lipase was reported in 1 asymptomatic participant at posttreatment Week 4 that resolved to below upper limit of normal (ULN) 12 weeks later.

Selgantolimod + Nivolumab + VIR-2218

The risk of SLGN plus nivolumab with VIR-2218 is unknown. In nonclinical studies, the primary finding for both SLGN and nivolumab was inflammatory cell infiltrates of various organs and tissues; an anticipated pharmacological effect of each of the single agents. With SLGN at ≥ 3 mg/kg/week in the mouse, nonadverse findings included mononuclear cell infiltrates in multiple tissues. Effects became adverse at 30 mg/kg in the kidney, esophagus, thymus, spleen, mesenteric lymph node, mandibular salivary gland, Harderian gland, and/or lacrimal gland. These findings were partially reversed and/or not observed following the 4-week recovery period. In the monkey, SLGN-related nonadverse microscopic findings of inflammatory cellular infiltrates were observed in the liver and stomach; All effects exhibited reversibility at the end of the recovery phase. The NOAEL in mice and monkeys for SLGN was 10 mg/kg and 30 mg/kg orally once weekly for 26 weeks and 13 weeks, respectively, and for nivolumab was 50 mg/kg IV twice weekly for 13 weeks. These doses were associated with exposures (AUC) that were 192×, 37× and 21× higher, respectively, than the human exposure after a single oral 3 mg dose of SLGN (selgantolimod IB) and 3 mg/kg dose every 2 weeks IV of nivolumab (Food and Drug Administration [FDA] Pharmacology Review 4 Dec 2014). For VIR-2218, the liver (rats), kidney (rats), and injection site (rats and monkeys) were identified as potential target tissues in the pivotal 6-month (rat), and 9-month (monkey) repeat-dose toxicity studies, typical findings of the siRNA class. In rats, nonadverse microscopic liver findings included hepatocellular hypertrophy, vacuolation, increased mitoses, single cell necrosis, and basophilic granules in Kupffer cells. Basophilic granules were also observed in renal tubular epithelial cells. These changes were accompanied by minimal increases in bilirubin (female rats at high dose in

4-week study) or minimal to mild increases in ALT and AST (male rats at mid-dose in 6-month study). The microscopic changes were partially reversible and the clinical pathology changes were fully reversible at the end of the 13-week recovery period. In rats and monkeys, nonadverse microscopic findings at the injection sites and draining lymph nodes were noted at all dose levels in both sexes and were only partially reversible at the end of the recovery period. The NOAELs were 150 mg/kg (rats) and 300 mg/kg (monkeys); the highest doses tested. At the proposed clinical dose of 200 mg in this study, the estimated AUC_{last} in humans is approximately 48-fold lower compared to the NOAEL in the 6-month rat study, and 187-fold lower compared to the NOAEL in the 9-month monkey study.

Based on the large exposure margins in the toxicology studies for the single agents, the risk for an exaggerated inflammatory response from the combination of these agents at the proposed doses in this Phase 2 clinical study is considered low. The potential for unpredicted off-target effects with the combination is considered negligible since nivolumab as an mAb is specific for its intended target and off-target activity has not been observed with SLGN even at very high exposure margins. While the liver and kidney were identified as target organs for VIR-2218, effects were observed at high exposure margins and exaggerated toxicity with SLGN at clinically relevant doses is low. Combination toxicity study of the 3 agents were not conducted since the potential risks of combining the 3 agents are predictable with low probability of occurrence at the proposed doses in this study. Therefore, the nonclinical studies of the single agents are considered sufficient for supporting this Phase 2 proof-of-concept study of the combination of 3 mg SLGN orally once weekly and 0.3 mg/kg nivolumab IV once every 4 weeks and VIR-2218 every 4 weeks.

Overall Benefit/Risk

Based on emerging safety data from the study, the sponsor decision was to 1) stop further dosing of nivolumab across all cohorts based on a benefit-risk assessment of the use of nivolumab in HBV cure, and to 2) stop all treatment in Cohort 2 Group B on account of low likelihood of efficacy of continuing with SLGN alone {Gane 2023, Janssen 2021}. Cohort 1 and Cohort 2 (Group A) will continue receiving all study treatment without nivolumab administration.

Gilead has determined that all participants will complete the protocol-specified follow-up period through posttreatment Week 48, including those who have completed treatment or have stopped study treatment, and that the benefit-risk profile of this study is considered to remain positive following amendments to the protocol described above.

All participants enrolled in Cohort 1 were switched from their prescribed antiviral to TAF (25 mg) in order to ensure consistency of treatment. Additional risk mitigation strategies that have been incorporated into the protocol from the beginning of the study include a requirement for participants enrolled in this study to have adequate hematologic function at study entry and sufficient hepatic reserve (F0-F2). The protocol will follow participants closely with frequent virtual or in-clinic visits to routinely monitor AEs, laboratory abnormalities, ophthalmologic examinations, and vital sign changes. The study also allows for more frequent monitoring visits based on investigator's discretion for safety monitoring. In addition, specific parameters that would lead to dose modification, interruption, or discontinuation are included in Section 6.9.1

and toxicity management of irAEs are included in Section 7.7.4. Based on historical enrollment rates (internal data), participants with CHB in this study will be enrolled in a staggered fashion over the course of at least 8 to 12 months. Enrollment in Cohorts 1 and 2 will be enrolled in parallel. In summary, potential risks of the novel HBV treatment regimens evaluated in this study have been minimized by dose selection, study design, and inclusion criteria.

An infectious disease pandemic may pose additional risks to study drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.2 further details on the pandemic risk assessment and mitigation plan.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of study treatment(s)
- To evaluate the efficacy of study treatm'ent(s) as measured by the proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < lower limit of quantitation (LLOQ) at FU Week 24

The secondary objectives of this study are as follows:

- To evaluate the proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study
- To evaluate in participants with CHB who are HBeAg positive at baseline, the proportion of participants who achieve HBeAg loss with and without anti-HBeAg seroconversion during the study
- To evaluate the proportion of participants who remain off NUC treatment during FU
- To evaluate the proportion of participants experiencing HBV virologic breakthrough (defined as confirmed HBV DNA ≥ LLOQ after 2 consecutive HBV DNA < LLOQ in participants who are complying with NUC therapy OR confirmed HBV DNA ≥ 1 $\log_{10}$ IU/mL increase from nadir on treatment) during study treatment(s)

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is as follows:

- The proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < LLOQ at FU Week 24

The secondary endpoints of this study are as follows:

- The proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study
- The proportion of participants with HBeAg loss with and without anti-HBeAg seroconversion during the study in participants with CHB who are HBeAg positive at baseline
- The proportion of participants who remain off NUC treatment during FU
- The proportion of participants experiencing HBV virologic breakthrough during study treatment(s) as defined in Section 2

3.2. Study Design

This is an open-label study to evaluate the safety and efficacy of SLGN-containing combination therapies in participants with CHB.

Approximately 40 NUC-suppressed and 60 viremic CHB-infected participants, may be enrolled and assigned into a cohort below (Section 3.3). Each cohort will enroll a minimum of 20% of HBeAg-positive participants, and up to 20% of participants can have HBsAg ≤ 100 IU/mL.

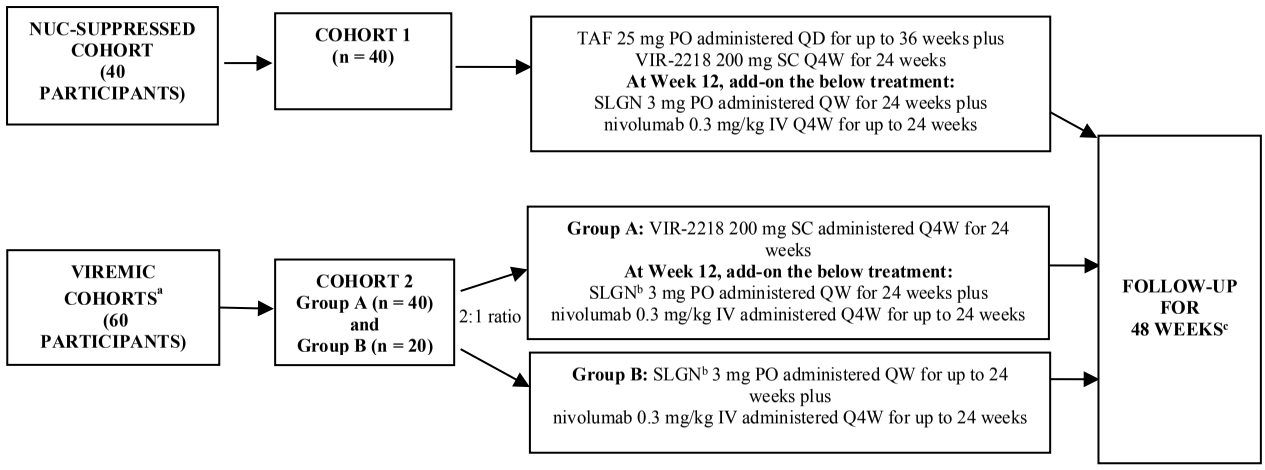
3.2.1. Changes to Study Design

Nivolumab dosing was stopped by Gilead based on emerging safety data from this study, other studies, and pertinent patient and prescriber insights {Cohen C. 2020}. As the study had completed enrollment and all participants were in treatment when the decision was made to stop nivolumab administration, the following measures were implemented:

- Stop further nivolumab administration for all study participants across all cohorts.
- Continue treatment with VIR-2218 and SLGN through Week 36 for Cohorts 1 and 2 (Group A).

- Discontinue all study treatment for Cohort 2 Group B participants with next follow-up visit being EOT for those still in treatment period.
- Stop all sample collections related to nivolumab.
- NUC therapy cessation is no longer required for our NUC treated patients (Cohort 1).

Figure 1. GS-US-465-4439: Study Design Schema*



IV = intravenous; NUC = nucleos(t)ide(s); PO = oral; Q4W = every 4 weeks; QD = once daily; QW = every week; SLGN = selgantolimod; SC = subcutaneous; TAF = tenofovir alafenamide

a Viremic participants who meet criteria to initiate NUC treatment will receive TAF 25 mg once daily for up to 36 weeks during the study.
b SLGN dosed while fasting once a week, on the same day, for 24 weeks.
c Participants will continue to receive TAF per Section 3.5.
* NOTE: Nivolumab dosing was stopped in this study and all treatments in Cohort 2 Group B were discontinued. This was a sponor decision based on a benefit risk assessment on the use of nivolumab in HBV cure. Rationale is provided in Section 1.3.1.

3.3. Study Treatments

NUC-suppressed Cohort

Cohort 1 (n = 40):

- TAF 25-mg tablet administered orally once daily for 36 weeks
- VIR-2218 200 mg administered via SC injection once every 4 weeks for 24 weeks (total 6 doses)

At Week 12, add-on and initiate the below treatment:

- SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for 24 weeks (total 24 doses)
- Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses)

Viremic Cohort

Cohort 2 (n = 60)

Participants will be randomized 2:1 into Cohort 2 (Groups A and B) and stratified by HBsAg > or ≤ 3 $\log_{10}$ IU/mL.

Group A (n = 40):

- VIR-2218 200 mg administered via SC injection once every 4 weeks for 24 weeks (total 6 doses)

At Week 12, add-on and initiate the below treatment:

- SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for 24 weeks (total 24 doses)

- Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses)

Group B (n = 20):

- SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for up to 24 weeks (up to 24 doses)

- Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses)

3.4. Duration of Treatment

The duration of study treatment are as follows:

- TAF 25-mg tablet will be administered orally once daily up to 84 weeks (inclusive of 48 Week FU), as applicable, in Cohort 1.

- VIR-2218 200 mg SC will be administered once every 4 weeks for 24 weeks (6 doses).

- Nivolumab 0.3 mg/kg IV will be administered once every 4 weeks for up to 24 weeks (up to 6 doses).

- SLGN 3 mg (2 × 1.5-mg tablets) will be administered orally while fasting once a week on the same day for up to 24 weeks (up to 24 doses).

After completing study treatments all participants will undergo 48 weeks of FU.

NOTE: Nivolumab dosing was stopped in this study and all treatments in Cohort 2 Group B were discontinued. Rationale is provided in Section 1.3.1.

3.5. Follow-up Period

At the end of treatment, all participants will enter the FU period.

- All participants not on TAF treatment at EOT will enter a TFFU period.
- Participants who are on TAF treatment will continue TAF treatment over the duration of study follow-up.
- Participants who initiated TFFU prior to the approval of this amendment and stopped NUC treatment may continue off NUCs after discussion between participant and investigator on the benefits and risks of continuing off NUCs in TFFU. Those who decide to restart NUCs would initiate commercial NUC treatment.

3.6. Treatment Discontinuation Criteria

Refer to Section 6.9 for detailed individual and treatment discontinuation criteria.

3.7. End of Study

The end of this study will be last participant's last observation.

3.8. Poststudy Care

Once a participant has completed study participation, the long-term care of the participant will be the responsibility of their primary treating physicians.

3.9. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory, specialty laboratory (for PK and/or PD data).

3.9.1. Biomarker Samples to Address the Study Objectives

CCI [redacted] The specific analyses may include, but will not be limited to, the biomarkers and assays listed below. Because biomarker science is a rapidly evolving area of investigation, and AEs are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. 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 the growing state of the art knowledge.

- Evaluation of HBV-specific T-cells response to hepatitis B antigen peptides by enzyme-linked immunospot assay (ELIspot)
- Evaluation of T-cell, NK-cell, and B-cell subsets by flow cytometry
- Evaluation of peripheral gene expression
- Evaluation of peripheral T-cell and B-cell receptor repertoire
- Evaluation of serum and plasma cytokine levels
- Evaluation of TLR8 single-nucleotide polymorphism (SNP)
- Evaluation of HLA genotypes
- Evaluation of whole blood transcriptome profiling

[redacted]

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of the study or per country requirements.

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

3.9.4. Pharmacokinetic Assessments

3.9.4.1. Sparse Pharmacokinetic Collection

Sparse (timed) blood PK samples will be obtained at specific in-clinic treatment visits at any time between 1 to 5 hours postdose relative to SLGN and/or VIR-2218 administration unless otherwise indicated.

See Section 6.1.10 for sparse PK sampling collection visit details.

CCI [redacted]


CCI

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Cohorts 1 and 2 will enroll approximately 100 male and nonpregnant female participants, ages 18 to 65 years, inclusive, with CHB infection without the presence of cirrhosis, and who are viremic or virally suppressed on NUC treatment for at least 6 months.

4.1.1. Participant Replacement

Participants who discontinue before the end of study will not be replaced.

4.2. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

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

2) Adult male and nonpregnant, nonlactating female participants, 18 to 65 years (19-65 years of age in Republic of Korea) of age inclusive based on the date of the screening visit

3) Documented evidence of chronic HBV infection (eg, HBsAg positive for more than 6 months) with detectable HBsAg levels (> 1.5 $\log_{10}$ IU/mL) at screening

4) Screening electrocardiogram (ECG) without clinically significant abnormalities and with QTcF interval (QT corrected using Fridericia's formula) ≤ 450 msec for males and ≤ 470 msec for females.

5) Females of childbearing potential (as defined in Appendix 11.4) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline prior to enrollment

6) Male and female participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 11.4. Must be willing and able to comply with all study requirements.

Participants in Cohort 1 should meet the following additional criteria to be eligible to participate in this study:

7) Have been on a commercially available HBV NUC treatment(s) (ie, TAF, TDF, entecavir, adefovir, lamivudine, telbivudine, either as single agents or in combination) with no change in regimen for 3 months prior to screening and willing to initiate TAF 25 mg.

8) Have a historical HBV DNA < LLOQ, measured at least once at local laboratory, 6 or more months prior to screening.

9) HBV DNA < LLOQ by central laboratory at screening

Participants in Cohort 2 should meet the following additional criterion at screening to be eligible to participate in this study:

10) HBV DNA > 2000 IU/mL (HBeAg negative) and HBV DNA > 20,000 IU/mL (HBeAg positive)

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) Extensive bridging fibrosis or cirrhosis as defined clinically by any 1 of the following:

   a) Metavir ≥ 3 or Ishak fibrosis score ≥ 4 by a liver biopsy within 1 year of screening, or, in the absence of an appropriate liver biopsy, either:

   b) Screening FibroTest score of > 0.48 and AST to platelet ratio index (APRI) > 1 by central laboratory, or

   c) Historical (within ≤ 6 months of screening) or current FibroScan with a result > 9 kPa

If liver biopsy is available, the liver biopsy result supersedes (b) and/or (c, if available)

If an appropriate liver biopsy is not available, fibrosis will be evaluated by (b) and/or (c, if available). In the event of discordance between (b) and (c), the FibroScan results will take precedence.

2) Participants meeting any of the following laboratory parameters at screening:

   a) Hemoglobin < 12 g/dL (for males) or < 11 g/dL (for females)

   b) White blood cell (WBC) count < 2500 cells/mm^3

   c) Neutrophil count < 1500 cell/mm^3 (or < 1000 cell/mm^3 if considered a physiological variant in a participant of African descent)

   d) ALT ≥ 2 × ULN (Cohort 1 only), ALT > 5 × ULN (Cohort 2)

   e) International normalized ratio (INR) > ULN unless the participant is stable on an anticoagulant regimen affecting INR

   f) Albumin < 3.5 g/dL

g) Direct bilirubin > 1.5 × ULN

h) Platelet Count < 100,000/μL

i) Positive autoantibodies, defined as any one or more of the following:

i) Antinuclear antibodies (ANA) > 1:80

ii) Smooth muscle antibodies (anti-SMA) > 1:80

iii) Antimitochondrial antibodies (AMA) > 1:40

iv) Anti-thyroid peroxidase (anti-TPO) > 35 IU/mL

j) Estimated creatinine clearance (CL_{cr}) < 60 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the screening evaluation, ie,

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

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

3) Participants in Cohort 2: Received OAV treatment for HBV within 6 months of screening. Participants who meet criteria for initiation of NUC treatment as judged by the principal investigator (PI) during screening should be excluded from Cohort 2.

4) Coinfection with HIV, HCV, or HDV. Participants who are HCV antibody (Ab) or HDV Ab positive, but have a documented negative HCV RNA or HDV RNA, respectively, are eligible.

5) Current or prior history of HCC (eg, as evidenced by prior imaging) or screening α-fetoprotein ≥ 50 ng/mL without imaging to rule out HCC

6) Current or prior history of clinical hepatic decompensation (eg, ascites, encephalopathy, or variceal hemorrhage).

7) Malignancy within 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (eg, basal cell skin cancer). Participants under evaluation for possible malignancy are not eligible

8) Significant cardiovascular, ophthalmological, pulmonary, or neurological disease in the opinion of the investigator

9) Diagnosis of any autoimmune disease (eg, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, pneumonitis, autoimmune hepatitis, sarcoidosis, psoriasis of greater than mild severity, autoimmune uveitis, autoimmune nephritis, thyroiditis), poorly controlled diabetes mellitus, significant psychiatric illness, severe chronic obstructive pulmonary disease (COPD), hemoglobinopathy, retinal disease, or are immunosuppressed

10) Chronic liver disease of a non-HBV etiology (eg, Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, cholangitis), except for nonalcoholic fatty liver disease

11) Received solid organ or bone marrow transplant

12) Received prolonged therapy with immunomodulators (eg, corticosteroids) or biologics (eg, mAb, IFN, nivolumab) within 6 months of screening

13) Have received inactivated vaccinations (eg, injectable influenza or pneumococcal) within 4 weeks prior to randomization or received live vaccinations within 4 weeks prior to screening

14) Use of another investigational agent within 90 days of screening, unless allowed by the sponsor

15) Current alcohol or substance abuse judged by the investigator to potentially interfere with participant compliance

16) Known hypersensitivity to study drug or formulation excipients

17) Women who are breastfeeding, pregnant, or who wish to become pregnant during the course of the study

18) Female participants unwilling to refrain from egg donation and in vitro fertilization during and until at least 5 months after last study drug dose.

19) Male participants unwilling to refrain from sperm donation during and until at least 5 months after the last study drug dose

20) Use of any prohibited concomitant medications as described in Section 5.4

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Treatment Assignment

5.1.1. Randomization/Enrollment

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.

Screening and enrollment may be placed on hold based on investigator's discretion, or in accordance with local regulation due to COVID-19 impact.

Cohort 1 and 2 will enroll in parallel.

Cohort 2 (Group A and B): In the viremic cohorts, participants will be randomized 2:1 into Cohort 2 Groups A and B and stratified by HBsAg > or ≤ 3 $\log_{10}$ IU/mL.

5.1.2. Blinding

Blinding of treatment response is critical to the integrity of this clinical study and therefore, quantitative HBsAg will be blinded to the investigative sites for the duration of the study. The sponsor or designee may unblind investigators to individual participant results as needed for safety reasons.

5.2. Description and Handling of SLGN, TAF, and VIR-2218, and Nivolumab

5.2.1. Formulation

5.2.1.1. Selgantolimod

Selgantolimod tablets, 1.5 mg, have been formulated with microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. Tablets are round, plain-faced, film-coated, and white. The white tablet film-coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol (PEG) 3350, and talc.

5.2.1.2. Nivolumab

Commercially available product of nivolumab injection will be used for this study. Further information regarding formulation is available in the current approved product label for nivolumab.

NOTE: Nivolumab dosing was stopped by Gilead based on a sponsor benefit risk assessment. Rationale is provided in Section 1.3.1.

5.2.1.3. Tenofovir Alafenamide

Each film-coated tablet contains tenofovir alafenamide fumarate equivalent to 25 mg of TAF and have been formulated with croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are yellow, round, film-coated, and debossed with "GSI" on one side of the tablet and "25" on the other side of the tablet.

5.2.1.4. VIR-2218

VIR-2218 is a clear, colorless to pale yellow solution, which will be supplied by Gilead as a sterile solution for SC injection at a free acid concentration of 200 mg/mL.

5.2.2. Packaging and Labeling

5.2.2.1. Selgantolimod

Selgantolimod, 1.5 mg, tablets are packaged in clear polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE) film blister strips and sealed with aluminum foil lidding material. Each blister strip contains 4 round tablets sealed with an aluminum push through lidding material. Selgantolimod blister strips in the quantity needed for a 4-week supply of SLGN (ie, 2 strips/8 tablets) are placed into a paperboard child-resistant wallet system in accordance with the dosage strategy.

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

5.2.2.2. Nivolumab

Commercially available product of nivolumab injection will be used for the study. Study drug(s) to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice -Annex 13 (Investigational Medicinal Products), and/or other local regulations (See Section 1.3.1).

5.2.2.3. Tenofovir Alafenamide

TAF tablets are packaged in white, high-density polyethylene (HDPE) bottles and enclosed with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminum foil liner. Each bottle contains 30 tablets, silica gel desiccant, and polyester coil. Study drug(s) to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice -Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.2.4. VIR-2218

VIR-2218 Solution for Injection, 200 mg/mL, are packaged in 2R vials. Each vial is filled with 0.5 mL solution. Study drug(s) to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice -Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

5.2.3.1. Selgantolimod

The SLGN tablets are packaged in blister strips/wallet system should be stored below 30 °C. Storage conditions are specified on the label.

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling. Any unused study drug should be disposed of in accordance with local requirements.

5.2.3.2. Nivolumab

Nivolumab vials must be stored in a secure area at 2-8 °C. Commercial product of nivolumab injection will be used for the study. Further information regarding storage and handling are available in the current approved product label for nivolumab (See Section 1.3.1).

5.2.3.3. Tenofovir Alafenamide

TAF bottles should be stored at 25 °C (77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F). Storage conditions are specified on the label. All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling. Any unused study drug should be disposed of in accordance with local requirements.

5.2.3.4. VIR-2218

VIR-2218 solution for injection should be stored upright, at 2°C to 8°C. Storage conditions are specified on the label. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling. Any unused study drug should be disposed of in accordance with local requirements.

5.3. Dosage and Administration of SLGN, TAF, VIR-2218, and Nivolumab

5.3.1. Selgantolimod

Selgantolimod will be supplied as tablets in strengths of 1.5 mg. SLGN 3 mg (2 × 1.5-mg tablets) will be administered while fasting once a week, on the same day. Participants must be fasting for at least 8 hours overnight (no food or drinks, except water) and continue through the morning, with no food or drinks, including water, 1 hour before to 2 hours after dosing. After 2 hours postdose, water is allowed; and after 4 hours postdose, participants are allowed food and drinks. Participants should take their other prescribed medications, including NUC treatment, no earlier than 2 hours after SLGN dosing or, if medications require dosing with food, no earlier than 4 hours after SLGN dosing.

5.3.2. Nivolumab

Nivolumab 40 mg/4 mL solution for injection will be supplied as single dose vials. Nivolumab 0.3 mg/kg will be administered as IV infusion over 45-60 minutes. This slower rate of infusion was shown in a PK study of nivolumab to lower the risk of infusion-related reactions (IRRs) compared with a rapid rate of infusion over 30 minutes {OPDIVO 2022} (See Section 1.3.1).

5.3.3. Tenofovir Alafenamide

TAF 25-mg tablet orally once daily with food.

5.3.4. VIR-2218

VIR-2218, 200 mg/mL, solution for injection will be supplied as 0.5 mL single dose vials. VIR-2218 200 mg (2 × 0.5 mL solution) will be administered SC.

5.4. Prior and Concomitant Medications

Concomitant/previous medications including over-the-counter medications, vitamins, and supplements that have been taken up to 30 days prior to screening, and the ones taken up to 4 weeks after discontinuation of study treatment need to be recorded in the source documents and electronic case report forms (eCRFs).

For participants requiring treatment with a concomitant medication (including treatment of an AE) after starting study drug(s), the participant's continued participation in the study should be re-evaluated by the investigator, in consultation with the medical monitor (or designee) on an ongoing, case-by-case basis. The investigator is authorized to administer acetaminophen or ibuprofen for the treatment of minor ailments occurring on study without prior consultation with the medical monitor. Acetaminophen is the preferred agent, followed by ibuprofen. The medical monitor should be consulted before administering acetaminophen at doses ≥ 2 g/day and ibuprofen as a single dose of > 200 mg or > 400 mg/day. Where an alternative to acetaminophen is needed, ibuprofen may be administered with milk or a light snack to minimize the chance of gastrointestinal side effects. Coadministration of an antiemetic (eg, ondansetron) at the discretion of the investigators is allowed in this study. Antiemetics will be administered following local guidelines and regulations.

There are no substantial safety data regarding the concomitant administration of the COVID-19 vaccines and SLGN, TAF, VIR-2218, and nivolumab. Participants are allowed to receive the COVID-19 vaccine, and 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 COVID-19 vaccines with the study drugs.

The following medications, not including protocol-specified study treatment(s), are prohibited in all cohorts for the entirety of the screening period through the end of study treatment due to interaction with study treatment(s) or the underlying HBV infection:

- Systemic chemotherapeutic agents, systemic corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks, except short-term use of prednisone as a steroid burst [< 1 week of use] and treatment of irAEs in this study), immunosuppressants (eg, azathioprine), mAbs (eg, infliximab), or immunomodulating agents

- Investigational agents or devices for any indication (unless approved by Gilead)

- Hematologic-stimulating agents (eg, erythropoiesis-stimulating agents, granulocyte colony stimulating factor, thrombopoietin mimetics)

Additional Concomitant Medication Restrictions:

For Cohorts 1 and 2 (Group A)

During treatment with SLGN, use of the medications listed below and in Table 3 are prohibited for a minimum of 21 days prior to the first dose of SLGN through the last dose of SLGN plus 7 days.

For Cohort 2 (Group B)

During treatment with SLGN, use of the medications listed below and in Table 4 are prohibited during the screening period and for a minimum of 21 days prior to the baseline/Day 1 visit through the last dose of SLGN plus 7 days.

Data from the DDI study indicates that cytochrome P450 (CYP)3A plays a major role in SLGN metabolism and therefore the administration of potent CYP3A inhibitors/inducers is not permitted in this study. Additionally, participants will be required to refrain from consumption of grapefruit juice, grapefruits, Seville oranges and Seville orange juice 72 hours prior to the first dose of SLGN and through the last dose of study treatment(s) plus 7 days.

The following list of medications and nutritional products are prohibited (as indicated above) due to potential interaction with SLGN. This is not an exhaustive list of agents. Any medications not in Table 4 should be reviewed with Gilead prior to dosing during the specified period.

Table 4. List of Agents Disallowed Due to Potential Interaction With SLGN

Drug Class	Agents Disallowed
Antibiotics	Clarithromycin, rifabutin, rifampin, rifapentine, telithromycin, troleandomycin
Anticonvulsants	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	Rifapentine, rifabutin, rifampin
Antidepressants	Nefazodone
Antifungals	Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
Antiviral	VIEKIRA PAK (ombitasvir/paritaprevir/ritonavir & dasabuvir), telaprevir, danoprevir, boceprevir
Cardiac Medications	Mibefradil
Diuretics	Conivaptan
GI Motility Agents[a]	Cisapride, metoclopramide, domperidone, mosapride citrate, pruclopride, itopride hydrochloride, levosulpride
Hematologic-stimulating agents	Erythropoiesis-stimulating agents; granulocyte colony stimulating factor (GCSF); and thrombopoietin (TPO) mimetics
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Other	Apalutamide, avasimive, enzalutamide, idelalisib, lumacaftor, nitotane

GI = gastrointestinal; SLGN = selgantolimod

a GI motility agents are prohibited starting 2 days prior to SLGN dosing and for the 24 hours postdose.

There are no DDIs or contraindications mentioned in the product information for nivolumab {OPDIVO 2022}.

Additionally, given the safety profile of multiple doses of VIR-2218 has not been well characterized and the use of VIR-2218 in combination with IFN has not previously been assessed, the administration of any potentially hepatotoxic medications during the study should be considered only if no therapeutic alternative can be identified and after a careful consideration of the potential risks and benefits for the participant. Medications that are potentially hepatotoxic or associated with drug-induced liver injury (DILI) include, but are not limited to, the following {Bjornsson 2016}:

- Aspirin > 3 g/day or ibuprofen ≥ 1.2 g/day
- Tricyclic antidepressants
- Valproate
- Phenytoin
- Amiodarone

- Anabolic steroids
- Allopurinol
- Amoxicillin-clavulanate
- Minocycline
- Nitrofurantoin
- Sulfamethoxazole/trimethoprim
- Erythromycin
- Rifampin
- Azole antifungals
- Herbal or natural remedies

During treatment with TAF, use of the following medications listed below and in Table 5 are prohibited for a minimum of 21 days prior to the baseline/Day 1 visit through the end of study:

- Investigational agents or devices for any indication
- Agents that reduce renal function or compete for active tubular secretion with TFV (eg, cidofovir, acyclovir, valacyclovir, ganciclovir, famciclovir, valganciclovir, high dose or multiple nonsteroidal anti-inflammatory drugs [NSAIDs], probenecid)
- Nephrotoxic agents (eg, aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Systemic chemotherapeutic agents, systemic corticosteroids (except short-term use of prednisone as a steroid burst [≤ 1 week of use] and treatment of irAEs in this study), immunosuppressant, or immunomodulating agents

Concomitant use of certain medications or herbal/natural supplements (inducers of drug transporters such as, P-glycoprotein) with study drug(s) may result in PK interactions. Any medications not on the list above should be reviewed with Gilead prior to randomization and during the study treatment.

Table 5. Disallowed Concomitant Medications While on TAF

Medication Class	Prohibited Medications
Anticonvulsants	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: may lower concentration of TAF and/or TFV
Antimycobacterials	Rifapentine, rifabutin, rifampin
Herbal/Natural Supplements	St. John's Wort, echinacea, milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)

TAF = Tenofovir alafenamide; TFV = tenofovir

5.5. Accountability for Investigational Medicinal Product: SLGN, TAF, VIR-2218, and Nivolumab

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to participants must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug
- The date, participant number, and the study drug kit number dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.5.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

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

6. STUDY PROCEDURES

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Appendix 11.3 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract (or clinical) research organization (CRO).

6.1. Study Procedure Details

6.1.1. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing; history of prior and current use of nicotine or nicotine-containing products, alcohol, and illegal drugs; and history of current and prior (within previous 30 days) medication; and all prior medication administered to treat HBV infection

6.1.2. Complete Physical Examination

A complete physical examination must include source documentation of general appearance, and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological.

6.1.3. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and oral, ear or forehead temperature.

Blood pressure will be measured using the following standardized process:

- Participant should sit for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery
- Measure and record the blood pressure to the nearest 2 mm Hg mark on the manometer or to the nearest whole number on an automatic device

6.1.4. 12-Lead Electrocardiograms

Participants will be required to rest in a supine position for 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities. On-treatment ECGs should be compared with the participant's Day 1 as part of routine safety monitoring.

QTc interval will be reported using Fridericia's correction: $QTcF = QT/RR^{1/3}$.

6.1.5. Clinical Laboratory Tests/Assessments for Safety Evaluations

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Appendix 11.3.

- Hematology: hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, WBC count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume (MCV)

- Chemistry: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total protein, albumin, lactic acid dehydrogenase (LDH), creatine kinase (CK), bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (see below), glucose, phosphorus, magnesium, potassium, sodium, uric acid, and lipase (reflex amylase testing is performed in participants with total lipase > 1.5 × ULN)

- Coagulation panel: prothrombin time, activated partial thromboplastin time, and INR

- Qualitative HBV serology (HBeAg and hepatitis B e antibody [HBeAb]; and HBsAg [reflex HBsAb if HBsAg is negative])

- Quantitative HBV serology (HBsAg, HBcrAg, HBeAg [if applicable], and HBV RNA)

- Serum sample for HBV viral sequencing, genotyping sample, and ddPCR

- Quantitative plasma HBV DNA

- Thyroid-stimulating hormone (TSH) levels

- Pregnancy test: serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test (if positive, requires immediate confirmation with serum β-hCG)

  — Follicle-stimulating hormone (FSH) testing (FSH test is required for female participants who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)

- Urinalysis: appearance, blood, color, glucose, leukocyte esterase, pH, protein, urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

- Urine drug (amphetamines, cocaine, methadone, opiates) and alcohol screen

- Autoantibodies: ANA, anti-SMA, AMA, and anti-TPO

6.1.6. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft 1976} using actual body weight (ABW).

Male: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times ABW(kg)}{72 \times Scr}$$

Female: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times ABW(kg) \times 0.85}{72 \times Scr}$$

Scr = serum creatinine (mg/dL)
ABW = actual body weight

6.1.7. Ophthalmologic Examination

Ophthalmologic examinations will be performed as applicable for Cohorts 1 and 2 during screening, at Week 12, 24, 36, and early discontinuation (ED) to assess ophthalmologic findings, including slit lamp and fundoscopic examination (both eyes). An examination of the full retinal field should be conducted noting changes or abnormalities.

Additional symptoms-directed ophthalmologic examinations may be conducted at investigator's discretion during the study for all participants in Cohorts 1 and 2.

See Section 6.6 and Schedule of Assessments in Appendix 11.3 for more details on time points for examination in specific cohorts.

6.1.8. HBV Sequence Analysis

Sequence analysis of the HBV full genome may be performed (if applicable) to assess if the presence of mutations at baseline and/or enrichment at posttreatment time points are associated with treatment response. As it may not be known at the time of the visit whether a participant is viremic or if it will be their last study visit, a separate virology sample for potential sequence analyses will be collected at each study visit.

6.1.9. Digital Droplet Polymerase Chain Reaction

If participant has HBV DNA ≤ LLOQ, ddPCR will be conducted.

6.1.10. Sparse PK Sampling

Sparse (timed) blood PK samples will be obtained at specific in-clinic treatment visits at any time between 1 to 5 hours postdose relative to SLGN and/or VIR-2218 administration unless otherwise indicated.

Plasma concentrations of SLGN and VIR-2218 may be analyzed. Serum concentrations of nivolumab may be analyzed (as applicable, from existing samples).

- Sparse PK collection visits for VIR-2218 in Cohort 1 and Cohort 2 Group A: Baseline/Day 1 (predose and postdose), Weeks 12 and 20
- Sparse PK collection visits for SLGN in Cohort 1 and Cohort 2 Group A: Weeks 12, 20, and 32
- Sparse PK collection visits for SLGN in Cohort 2 Group B: Baseline/Day 1, Weeks 12 and 20

6.1.12. Biomarker Samples

Whole blood, serum, and plasma samples will be collected as detailed in Appendix 11.3 for biomarker analysis. Additional whole blood samples will be collected for PBMC isolation and gene expression (PaxGene RNA).

Reference Section 3.9 for additional information on Biomarker Samples.

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6.1.15. Management of Participants Impacted by the COVID-19 Pandemic

Local regulation and guidance should be followed in the management of participants impacted by the COVID-19 pandemic. Study-specific guidance provided by Gilead regarding crisis management communications should also be referenced.

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.

Screening and enrollment may be placed on hold based on investigator's discretion, or in accordance with local regulation due to COVID-19 impact.

6.3. Pretreatment Assessments

6.3.1. Prescreening Visit

At the investigator's discretion, participants may be asked to consent to HBeAg testing prior to screening procedures in order to ensure the required minimum of 20% HBeAg-positive participants for each cohort. Once a participant's HBeAg status has been confirmed, the participant may then be able to complete the screening procedures.

6.3.2. Screening Visit

Participants will be screened within 45 days prior to baseline Day 1 visit.

With Gilead's approval, candidates who fail to meet eligibility criteria by screening evaluations may be re-screened if there is a reasonable expectation that the candidate will be eligible after repeat screening. Gilead must approve all re-screening requests.

Retests of screening laboratory parameters are permitted once only if there is reason to believe the retest value will be within accepted parameters, if the initial value was either due to a sample processing error, inconsistent with a recent local laboratory result, or due to an extenuating circumstance (eg, intercurrent infection).

The following will be performed and documented at screening:

- Written informed consent
- Review of inclusion/exclusion criteria
- Obtain medical history (including HBV disease, treatment history, and historical HBV genotype [if available] for cohort 1 only)
- Review concomitant medications
- Complete physical examination
- Vital signs
- Body weight and height
- 12-Lead ECG (participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Chest x-ray
- Ophthalmologic examination
- FibroScan (where available and as necessary for liver disease staging)
- Sample collection for:
  - Safety laboratory tests (hematology, chemistry, and coagulation)
  - APRI, FibroTest, α-fetoprotein (computed tomography [CT] scan with contrast for participants with α-fetoprotein ≥ 50 ng/mL at screening)
  - Serology testing to exclude HCV, HDV, and HIV infection
  - Quantitative plasma HBV DNA
  - Serum sample for HBV viral sequencing (resistance surveillance) and ddPCR
  - Quantitative HBV serum HBsAg, HBcrAg, HBeAg (if not performed during prescreening), and HBV RNA

— Qualitative HBV serology HBeAg, HBeAb (if not performed during prescreening), and HBsAg, HBsAb

— Estimated CL_{cr} (using the Cockcroft-Gault method)

— Other screening laboratory tests: urinalysis, urine drug screen, alcohol screen, autoantibodies, quantification of TSH levels and serum β-hCG (females of childbearing potential only), FSH (test is required for female participants who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)

- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the ICF.

Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 45 days after screening for randomization into the study.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated 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. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.3.3. Baseline/Day 1 Assessments

All baseline tests and procedures must be completed prior to the receipt of the first dose of study drug(s). Participants screened within 45 days before baseline will be eligible to participate in the study.

Initiation of treatment with study drug(s) should take place on the day of the baseline visit (Day 1).

Cohorts 1 and 2

- Vital signs
- Weight
- Review AEs
- Review concomitant medications
- Complete physical examination
- 12-Lead ECG (Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)

- Symptoms-directed ophthalmologic examination
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry; coagulation)
  - APRI and FibroTest
  - Quantitative plasma HBV DNA
  - Quantitative HBV serum HBsAg, HBcrAg, HBeAg, and HBV RNA
  - Qualitative HBV serology HBeAg, HBeAb, HBsAg, and HBsAb
  - Serum sample for HBV viral sequencing and genotyping sample (baseline)
  - Sparse PK (sparse PK for SLGN not required for Cohorts 1 and 2 [Group A])
  - Urine pregnancy test (females of childbearing potential only)
  - Urinalysis
  - Estimated CL_{cr} (using Cockcroft-Gault method)
- CCI [redacted]
- Perform study drug dispensation, and administration (TAF, as needed, VIR-2218 SC, and SLGN)
- Biomarker Samples: collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis

6.4. Randomization

Viremic Cohort 2 (Group A and B) Only

Participants will be randomized 2:1 into Cohort 2 Group A and B and stratified by HBsAg > or ≤ 3 $\log_{10}$ IU/mL.

6.5. Treatment Schedule

Cohort 1:

- Baseline/Day 1, Week 4, and Week 8 - SC VIR-2218
- Week 12, 16, and 20 - SC VIR-2218; add-on IV nivolumab
- Week 24, 28, and 32 - IV nivolumab
- Oral TAF dose daily for 36 weeks
- Oral SLGN dose weekly for 24 weeks, starting Week 12 through Week 35

Cohort 2:

Group A:

- Baseline/Day 1, Weeks 4 and 8 - SC VIR-2218
- Weeks 12, 16, and 20 - SC VIR-2218; add-on IV nivolumab
- Weeks 24, 28, and 32 - IV nivolumab
- Oral SLGN dose weekly for 24 weeks, starting Week 12 through Week 35

Group B:

- Baseline/Day 1, Weeks 4, 8, 12, 16, and 20 - IV nivolumab
- Oral SLGN dose weekly for 24 weeks, starting Day 1 through Week 23

6.6. Post-Day 1 Treatment Assessments

The post-Day 1 treatment assessments have a visit window of ± 2 days (except for Weeks 13 and 14 in Cohort 1 and Weeks 1, 2, 13, 14 in Cohort 2), and EOT will have a window of −5 days. Posttreatment assessments include the following, performed in a fasted state at all visits from baseline/Day 1 through EOT or in event of ED, unless specifically noted:

All participants will complete the following post-Day 1 study visits:

Cohort 1: Weeks 4, 8, 12, 13*, 14, 16, 20, 24, 28, 32, and 36 (EOT)

Cohort 2 Group A: Weeks 4, 8, 12, 13*, 14, 16, 20, 24, 28, 32, and 36 (EOT)

Cohort 2 Group B: Weeks 1*, 2, 4, 8, 12, 14, 16, 20, and 24 (EOT)

- Vital signs
- Symptom-directed physical examination (at Weeks 4, 8, 14 to 32, if applicable)
- Complete physical examination (at Weeks 12 and EOT)
- Weight (at Week 12, and EOT)
- Review AEs and concomitant medications (at Weeks 1*, 2, 4, 8, 12, 13*, and 14 to EOT)
- 12-lead ECG (Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording) (at Weeks 12 and EOT)
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry; coagulation) (at Weeks 4, 8, 12, 14 to EOT)
  - APRI and FibroTest (at Weeks 12, and EOT)
  - Quantitative plasma HBV DNA (at Weeks 4, 8, 12, 14 to EOT)
  - Quantitative HBV serum HBsAg, HBcrAg, HBeAg, and HBV RNA (at Weeks 4, 8, 12, 14 to EOT)
  - Qualitative HBV serology HBeAg, HBeAb, HBsAg, and HBsAb (at Weeks 4, 8, 12, 14 to EOT)
  - Sparse PK samples (Cohorts 1 and 2 [Group A] at Day 1, Weeks 12, 20, and 32; Cohort 2 [Group B] at Weeks 12 and 20)
  - Serum sample for HBV viral sequencing and genotyping sample (at Weeks 4, 8, 12, 14 to EOT)
  - Urinalysis (4, 8, 12, 16 to EOT)
  - Urine pregnancy test (females of childbearing potential only; at Weeks 4, 8, 12, 16, 20, and EOT; and at Weeks 24, 28, and 32, if applicable)
  - Estimated CL_{cr} (using Cockcroft-Gault method) (at Weeks 12 and EOT)
  - Quantification of TSH levels at EOT (Cohort 1 and 2 [Group A], Weeks 24 and 36; Cohort 2 [Group B], Weeks 12 and 24)
- CCI [redacted]

- CCI [redacted]
- Ophthalmologic Examination (−4 to +10 days of visit)
  - — Cohort 1 and 2 [Group A]: Week 24 and 36
  - — Cohort 2 [Group B]: Week 12 and 24 and EOT for participants who stop dosing before Week 24.
  - — Symptom-directed ophthalmologic examination (at Weeks 4, 8, 14 to 32, if applicable)
- Study treatment
  - — Study drug accountability and review dosing diary
  - — Study drug dispensation
  - — Study drug administration (Oral TAF, as needed, SC VIR-2218, and oral SLGN)

* Treatment Assessments on Week 1 and Week 13 (Phone Call/Virtual Visit)

The following evaluations are to be completed at phone call or virtual visit:

- Review of AEs and concomitant medications
- Review of dosing diary and treatment compliance

6.7. Follow-up Assessments

The FU assessments have the following visit windows: Cohort 1: Week 1 (+ 3 days), Weeks 4 to 16 (± 5 days), and Weeks 24 to 48 (± 14 days); Cohort 2: Weeks 1 (± 2 days), and Weeks 4 to 16 (± 5 days), and Weeks 24 to 48 (± 14 days). FU assessments include the following:

- All participants will complete following FU visits: Weeks 1*, 4, 8*, 12, 16* (for women of childbearing potential), 24 (Primary), 36, and 48
- Vital signs (at Weeks 4 to 48)
- Symptom-directed physical examination (at Weeks 4 to 48)
- Symptom-directed ophthalmologic examination (at Weeks 4 to 48)

- Weight (At Week 48 only)
- 12-lead ECG (At Week 48 only)
- Review AEs and concomitant medications (At Week 1*, 8*, 16*, at Weeks 4 to 48)
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry; coagulation) (at Weeks 4 to 48)
  - APRI and FibroTest (at Weeks 12 and 48)
  - Quantitative plasma HBV DNA (at Weeks 4 to 48)
  - Quantitative HBV serum HBsAg, HBcrAg, HBeAg, and HBV RNA (at Weeks 4 to 48)
  - Qualitative HBV serology HBeAg, HBeAb, HBsAg, and HBsAb (at Weeks 4 to 48)
- Urine pregnancy test (females of childbearing potential only, every 4 weeks through Week 48; Week 8 and Week 16 collection will be a virtual/telephonic visit)
- Serum sample for HBV viral sequencing and genotyping sample (baseline) (at Weeks 4 to 48)
- Estimated CL_{cr} (using Cockcroft-Gault method) (at Week 48 only)

*FU Visit Week 1, Week 8, and Week 16 (Phone Call/Virtual Visit)

The following evaluations are to be completed at the FU Week 1 phone call or virtual visit:

- Review of AEs and concomitant medications
- Review of laboratory results from EOT visit to determine entry into TFFU

Participants who discontinue the study treatment(s) prematurely will be followed for the reminder of the study according to the defined study visits and procedures.

6.8. Immunologic Testing

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6.8.1. Biomarker Sample Collection During Treatment Period

Cohort 1

Baseline/Day 1 (predose), Week 12 (pre-SLGN dose, 4 and 24-72 hours postdose), Week 14 (predose), Week 32 (pre-SLGN dose, 4 and 24-72 hours postdose).

Cohort 2

Group A:

Baseline/Day 1 (predose), Week 12 (pre-SLGN dose, 4 and 24-72 hours postdose), Week 14 (predose), Week 32 (pre-SLGN dose, 4 and 24-72 hours postdose)

Group B*:*

Baseline/Day 1 (pre-SLGN dose, 4, and 24-72 hours postdose), Week 2 (predose), Week 20 (pre-SLGN dose, 4, and 24-72 hours postdose)

6.8.2. Biomarker Sample Collection During Follow-up

Biomarker samples will be collected at FU Week 24 for Cohorts 1 and 2.

6.9. Assessments for Early Discontinuation of Study Treatment

6.9.1. Criteria for Discontinuation of Study Treatment

Study treatment(s) that are considered related by the investigator to any of the below event(s) will be held in a participant until resolution of the event:

- Any study drug–related AE ≥ Grade 3
- A confirmed, clinically significant laboratory test abnormality (other than ALT) ≥ Grade 3 considered study drug(s) related by the investigator

Study treatment(s) may be reinitiated following resolution of the above event(s) after discussion with the medical monitor. Study treatment(s) should be restarted in line with their preassigned schedules.

Study treatment(s) that are considered related by the investigator to any of the below events will be permanently discontinued:

- Any on-treatment uveitis, confirmed by ophthalmologic evaluation
- Any confirmed recurrence of study drug–related Grade 3 or 4 (excluding laboratory abnormalities) AE following dose interruption mandates permanent discontinuation of study drug(s)
- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the participant's best interest
- Any study drug–related Grade 4 AE (excluding laboratory abnormalities)
- Any study drug–related ≥ Grade 3 AE not able to be medically managed (eg, nausea with antiemetics)
- Any confirmed study drug–related laboratory abnormality ≥ Grade 3 following rechallenge
- A clinically significant Grade 4 laboratory abnormality
- Virological breakthrough: as defined in Section 2

Additional criteria for permanent discontinuation of study treatment(s):

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Hepatic disease progression or lack of efficacy defined as participants in Cohorts 1 and 2 (Group A) who do not achieve HBsAg decline ≥ 0.2 $\log_{10}$ IU/mL at Week 12
- Participant requests to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study
- At the discretion of the investigator, Gilead, a regulatory agency or an institutional review board (IRB), or independent ethics committee (IEC).

If a participant discontinues study dosing (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related FU and procedures.

6.9.2. Criteria for Individual Dose Modification

Dose modification and discontinuation criteria for participants with ALT elevations or flare by treatment and cohort are provided in Section 7.7 Toxicity Management

6.9.3. Study and/or Cohort Discontinuation Criteria

Study treatment(s) that is considered related by the investigator(s) to the graded toxicities in a cohort will be held in all participants if ≥ 3 participants experience a Grade 3 AE or ≥ 2 participants experience a Grade 4 or SAE (excluding ALT), in the same system organ class (SOC). Decisions to reinitiate continuation of dosing will be made by the medical monitor upon review of all safety data generated by participants dosed to date.

Study and/or cohort may be discontinued at the request of Gilead, a regulatory agency, or an IRB or IEC.

6.9.4. Premature Study Discontinuation

A primary goal of this study is to assess the safety of a combination of products in participants with CHB. Therefore, every effort should be made to retain participants on study to assess safety outcomes. Participants who stop study treatments must therefore be maintained on study and continue study evaluations.

If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study and an early study discontinuation visit should be performed. The early study discontinuation visit should be performed within 14 days from determination by participant or investigator of study discontinuation.

Other reasons for study discontinuation:

- Request by participant to withdraw from study
- Request by study investigator or participant's primary physician/provider

The following assessments will be performed at the study discontinuation visit:

- Perform complete physical examination
- Ophthalmologic examination and chest x-ray, as needed
- Collect vital signs and body weight

- 12-lead ECG (Participant must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Review AEs and concomitant medications
- Obtain blood samples for laboratory assessments as follows:
  - Safety laboratory tests (hematology and chemistry and coagulation)
  - Urinalysis
  - Qualitative and quantitative HBV serology (HBsAg, HBcrAg, HBeAg, and HBV RNA)
  - Quantitative plasma HBV DNA
  - Serum sample for HBV viral sequencing
  - Serum pregnancy test (females of childbearing potential only)
  - Estimated CL_{cr} (using Cockcroft-Gault method)
  - APRI and FibroTest
  - TSH

6.10. End of Study

The end of this study will be last participant's last observation.

6.11. Poststudy Care

Once a participant has completed their study participation, the long-term care of the participant will return to the responsibility of their primary treating physicians.

6.12. Sample Storage

The 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 a period up to 15 years. CCI [redacted]

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 a study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. 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 (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 as medical history.

Preexisting events that increase in severity or change in nature after study drug 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.)
- In-patient 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 one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is 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. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation 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 a study drug 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 a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug 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 a study drug given per administration or cumulatively which 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 a study drug as a result of one’s professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, 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 study drug.

Counterfeit or falsified medicine: Any study drug 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 Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

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

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 Gilead Sciences Inc. (GSI) Toxicity Grading Scale, Version 01 April 2015, with the exception of IRRs. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 11.5).

Grading of IRRs will be done according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 found on the National Cancer Institute (NCI) website:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

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

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until the end of the study including the posttreatment FU visit and report them on the eCRFs as instructed.

All AEs 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 FU period.

7.3.3. Serious Adverse Events

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

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

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment FU visit, must be reported to Gilead 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 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the ICF) and

throughout the duration of the study, including the posttreatment FU visit, must be reported to Gilead 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 does 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 Situation 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 Gilead 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 FU period. Detailed instructions can be found in the eCRF completion guidelines.

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

  Gilead PS
  Email: Safety_fc@gilead.com
  or
  Fax: 1-650-522-5477

- As soon as it is possible to do so, any SAE reported via paper must be transcribed on the applicable eCRFs according to instructions and within the timelines outlined in the eCRF completion guidelines.

- 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.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted 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.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

- All SSRs will be recorded on the SSR form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment FU period.

  Gilead PS
  Email: Safety_fc@gilead.com
  or
  Fax: 1-650-522-5477

7.4.2.2. Reporting Process for Gilead Concomitant Medications

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

  Gilead PS
  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 who are identified after initiation of study drug and throughout the study, including the posttreatment FU period, to Gilead PS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

  Gilead PS
  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 after study completion must be reported to the Gilead PS.

- 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 Gilead 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 Gilead PS. Gilead PS contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

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

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA CFR, the EU Clinical Trials Directive (2001/20/EC) 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 (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), 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.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive either a safety letter or quarterly SUSAR line listing (applicable for United Kingdom and European Economic Area sites) notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or 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 study drug 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. 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 GSI Grading Scale (see reference table in Appendix 11.5: Toxicity Grading Scale, Version 01 April 2015). 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 clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 11.6.

- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before study drug discontinuation, unless such a delay is not consistent with good medical practice
- Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 11.5)
- When restarting study drug following resolution of the AE, the study drug should be restarted at full dose or modified dose that is dependent upon discussion with the medical monitor
- Any recurrence of the study drug–related Grade 3 or 4 clinical or clinically significant laboratory AE following dose interruption mandates permanent discontinuation of study drug
- Administration of study drug(s) may be discontinued due to a clinical or laboratory event. The medical monitor should be consulted prior to dose discontinuation of study drug(s) unless the investigator believes that immediate action is warranted to ensure the continued safety of the participant
- Any questions regarding toxicity management should be directed to the medical monitor.

7.7.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.7.2. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug
- For any study drug–related, Grade 3 AE, study drug should be held
- For any study drug–related ≥ Grade 3 AE not able to be medically managed (eg, nausea with antiemetics), study drug should be permanently discontinued
- For a confirmed laboratory abnormality, study drug–related Grade 3, study drug would be held until toxicity returns to ≤ Grade 2. If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge, study drug should be permanently discontinued, and the participant managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing within 3 calendar days that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2

7.7.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing within 3 calendar days, the study drug 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 Day 1 of treatment 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.

- A Grade 4 laboratory abnormality or clinical event that is not considered clinically significant by the investigator may also be tested for confirmation and study drug continued at the discretion of the investigator.

- The study drug may be continued without dose interruption for a clinically nonsignificant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed).

7.7.4. Toxicity Management of Immune-Related Adverse Events Observed With Nivolumab

Adverse events related to the use of immunomodulatory therapies such as nivolumab are immunologic in etiology. They may occur at any time from shortly after first dose **to many months after the last dose** and can affect multiple organs simultaneously. Most irAEs observed with anti-PD-1/programmed cell death ligand 1 (PD-L1) mAbs are reversible with early detection and treatment discontinuation or treatment with immunomodulating agents such as corticosteroids. Investigators should exercise clinical judgment regarding best clinical management, based on the symptoms and condition of the individual participant.

General instructions:

- Monitor all participants closely for signs and symptoms of irAEs, including signs related to gastrointestinal, endocrine, hepatic, ophthalmologic, or cardiac irAEs.

- Early evaluations with radiographic imaging, relevant laboratory testing, procedures and speciality consultation should be considered.

- Initiate high dose steroid (prednisone 1-2 mg/kg) when indicated for appropriate Grade 3-4 irAEs.

- The investigator must notify the Gilead medical monitor in a timely manner upon identification of any potential irAE regardless of grade or seriousness.

- Report all irAEs that meet serious criteria in accordance with Sections 7.3.3 and 7.4.

According to the approved product label for nivolumab, patients should be monitored continuously (at least up to 5 months after the last dose) as an ADR with nivolumab may occur at any time during or after discontinuation of therapy.

For more detailed management guidance, refer to the current approved product label for nivolumab {OPDIVO 2022}.

7.7.5. ALT Elevation or Flare Management on Treatment and Treatment-Free Follow-up

On-Treatment ALT Management

Participants with on-treatment serum ALT elevation > 2 × nadir or > 2 × baseline value and ≥ 5 × ULN, with or without associated symptoms should be managed according to the guidance below.

All elevated serum ALT 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:

- Laboratory parameters: serum ALT and AST, total bilirubin, GGT, INR, and serum albumin, alcohol screening
- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg, HBsAb, HBeAg and HBeAb), HDV, hepatitis A virus (HAV) IgM, HCV, and HEV
- Liver biopsy may be collected for participants meeting Hy's law (ALT > 3 × ULN and Total Bilirubin > 2 × ULN; AST > 3 × ULN and Total Bilirubin > 2 × ULN) with suspected DILI

Additional confirmatory tests such as HDV RNA, HDV IgM, and HEV RNA may be performed locally as per local regulations after further discussion with the Gilead's Medical Monitor.

Based on the results of the confirmatory tests, the following study treatment modifications are recommended (Table 6).

Table 6. Dose Modification and Monitoring

Liver Toxicity Parameters	Action
Confirmed, ALT ≥ 10 × ULN without evidence of hepatic toxicity as defined below	**Cohort 1**: Hold VIR-2218 and SLGN treatment. Participant should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting VIR-2218 and/or SLGN treatment may be considered when ALT < 5 × ULN in discussion with the medical monitor. Study treatment should be restarted in line with the original assigned administration schedule. **Cohort 2**: Initiate TAF 25 mg once daily and hold VIR-2218 and SLGN dose. Participant should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting VIR-2218 and/or SLGN treatment may be considered when ALT < 5 × ULN in discussion with the medical monitor. Study treatment should be restarted in line with the original assigned administration schedule.
Persistent ALT > 2 × baseline and ≥ 5 × ULN without evidence of hepatic toxicity, as defined below	Continue study treatment(s), ALT should be evaluated every 2 weeks or more frequently as clinically needed, until ALT < 5 × ULN
Confirmed ALT > 2 × nadir, with evidence of hepatic toxicity, defined as any one of the following confirmed laboratory abnormalities: • Total bilirubin > 2 × ULN • Elevated INR > 0.5 above baseline AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	**Cohort 1:** Permanently discontinue study treatment(s) except TAF 25 mg once daily. Participant should be monitored weekly until ALT < 5 × ULN, and total bilirubin, INR, and albumin values return to normal or baseline levels. **Cohort 2:** Initiate commercially approved NUC treatment once daily and permanently discontinue study treatment(s). Participant should be monitored weekly until ALT < 5 × ULN, and total bilirubin, albumin, and/or INR values return to normal or baseline levels

ALT = alanine aminotransferase; INR = international normalized ratio; NUC = nucleos(t)ide(s); SLGN = selgantolimod; TAF = tenofovir alafenamide; ULN = upper limit of normal

Treatment-Free Follow-up ALT Management

All participants not on NUC treatment will enter TFFU period after completion of study treatment, in which they will undergo close safety monitoring. The proportion of participants who achieve HBsAg loss or are able to remain off NUC therapy during TFFU period will be assessed. Table 7 provides guidance for initiating commercially approved NUC treatment, in participants who experience rebound of HBV DNA and ALT levels. Any deviation from the table should be discussed in advance with medical monitor.

If unscheduled visits are required for ALT monitoring, 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:

- Laboratory parameters: serum ALT and AST, total and direct bilirubin, GGT, INR, serum albumin, plasma HBV DNA, quantitative HBsAg, PBMC for immune profiling, and alcohol screen.
- At the initial confirmatory visit, collect serology for HDV, HAV IgM, HCV, and HEV.

Participants with HBV DNA ≤ LLOQ and ALT elevation/flare meeting any of the below table criteria should be evaluated for alternative liver disease etiologies by the investigator and in discussion with the medical monitor. Liver biopsy may be collected at the investigator's discretion.

Participants with HBV DNA > LLOQ and ALT elevation/flare should be managed according to the table below:

Table 7. Starting Commercial NUC Treatment Criteria

Liver Toxicity Parameters	Action
Confirmed ALT ≥ 10 × ULN with no evidence of hepatic toxicity, as defined below.	Initiate NUC treatment and monitor weekly until ALT < 5 × ULN, and every 2 weeks until ALT < 2 × ULN, or more frequently if clinically indicated.
ALT ≥ 5 × ULN without evidence of hepatic toxicity, as defined below	ALT should be evaluated every 2 weeks or more frequently as clinically needed, until ALT < 2 × ULN.
Confirmed ALT > ULN with evidence of hepatic toxicity, defined as any one of the following confirmed laboratory abnormalities: • Total bilirubin > 2 × nadir AND > 2.5 mg/dL in the absence of Gilbert's disease • Elevated INR > 0.5 above nadir AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	Initiate NUC treatment and monitor weekly or more frequently if clinically indicated until return to baseline levels or within normal reference range. Liver biopsy may be considered if appropriate for participant management.
Confirmed, HBV DNA > 20,000 IU/mL (HBeAg positive) or > 2,000 IU/mL (HBeAg negative) and persistent ALT > ULN without evidence of hepatic toxicity, as defined above, for > 8 weeks	Initiating NUC treatment may be considered in discussion with the medical monitor.

ALT = alanine aminotransferase; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; NUC = nucleos(t)ide(s); ULN = upper limit of normal

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of study treatment(s)
- To evaluate the efficacy of study treatment(s) as measured by the proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < LLOQ at FU Week 24

The secondary objectives of this study are as follows:

- To evaluate the proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study
- To evaluate in participants with CHB who are HBeAg positive at baseline, the proportion of participants who achieve HBeAg loss with and without anti-HBeAg seroconversion during the study
- To evaluate the proportion of participants who remain off NUC treatment during FU
- To evaluate the proportion of participants experiencing HBV virologic breakthrough during study treatment(s)

CCI

8.1.2. Primary Endpoint

The primary efficacy endpoint is the proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < LLOQ at FU Week 24.

8.1.3. Secondary Endpoint

Secondary efficacy endpoints of this study are as follows:

- The proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study
- The proportion of participants with HBeAg loss with and without anti-HBeAg seroconversion during the study in participants with CHB who are HBeAg positive at baseline
- The proportion of participants who remain off NUC treatment during FU
- The proportion of participants experiencing HBV virologic breakthrough during study treatment(s)

8.2. Planned Analyses

8.2.1. Primary Analysis

The primary analysis will be conducted after all participants within each cohort have completed FU Week 24 or early terminated from the study prior to FU Week 24.

8.2.2. Final Analysis

The final analysis will be performed at the end of the study, after all participants have completed the study or early terminated from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS), defined as all participants who are enrolled and have received at least 1 dose of study drug. Participants will be analyzed according to the treatment(s) to which they were assigned.

8.3.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set, defined as all participants who have received at least 1 dose of study drug. Participants will be analyzed according to the treatment(s) they actually received.

8.3.1.3. Pharmacokinetics

The PK Analysis Set will include all enrolled participants who took at least 1 dose of study drug and have at least 1 nonmissing concentration value reported by the PK laboratory.

CCI [redacted]

8.3.1.4. Biomarkers

The Biomarker Analysis Set will include all enrolled participants who took at least 1 dose of the study drug and have at least 1 nonmissing biomarker value for each respective biomarker.

8.3.1.5. Data Handling Conventions

For the primary efficacy endpoint and the categorical secondary efficacy endpoints, missing data will be handled using a missing = failure approach. For continuous secondary endpoints, a missing = excluded approach will be employed.

For selected analyses, HBsAg and HBV DNA data (IU/mL) will be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and one-half of the LLOQ for postdose time points.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized by cohort using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, randomization stratification group (if applicable), and age.

Baseline data will include a summary of body weight, height, body mass index, HBsAg ($\log_{10}$ IU/mL), HBV DNA ($\log_{10}$ IU/mL), HBeAg/HBeAb status, HBV genotype, ALT, and additional endpoints as necessary.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary analysis will be performed separately for each cohort when the last participant in each cohort reaches FU Week 24.

The proportion of participants who achieve functional cure at FU Week 24 will be analyzed for each treatment cohort. A point estimate with a 2-sided 95% exact CI will be constructed for the proportion using the binomial distribution (Clopper-Pearson method).

8.5.2. Secondary Analyses

The secondary efficacy endpoints will be summarized by treatment cohort.

Continuous secondary endpoints will be summarized using conventional descriptive statistics (n, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) by treatment cohort.

Categorical secondary endpoints will be summarized by number and percentage of participants who meet the endpoint by treatment cohort.

8.5.3. Analysis of Other Endpoints of Interest

Continuous endpoints will be summarized using conventional descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment cohort.

Categorical endpoints will be summarized by number and percentage of participants who meet the endpoint by treatment cohort.

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests and AEs. The primary safety analysis will be evaluated through 30 days posttreatment.

Posttreatment is defined as the following:

- For VIR-2218 and nivolumab, posttreatment will start 4 weeks after last dose.
- For SLGN, posttreatment will start 1 week after last dose.

Posttreatment for each cohort will be based on the last study drug(s) end of the treatment window duration that is the longest.

The safety analysis will also be conducted through FU Week 24 as a secondary safety analysis.

All safety data collected during the study will be included in data listings.

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by treatment cohort.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System organ class, high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) 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 (TEAE) will be defined as:

- Any AE that begins on or after the date of first dose of any study drug and no later than 30 days posttreatment of SLGN + nivolumab ± VIR-2218
- Any AE leading to premature discontinuation of any study drug

Summaries (number and percentage of participants) of TEAEs (by SOC and PT) will be provided by treatment group:

- All TEAEs
- TEAEs of Grade 3 or higher
- All TE treatment-related AEs
- TE treatment-related AEs of Grade 3 or higher
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to premature discontinuation of any study drug
- All TEAEs leading to temporary interruption of any study drug
- AEs of special interest (eg, uveitis)

Summaries (number and percentage of participants) of all on-treatment and posttreatment potential irAEs (by SOC and PT), as defined by relevant MedDRA Standardised MedDRA Queries (SMQs), will be provided by treatment group.

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

8.6.3. Laboratory Evaluations

Selected laboratory data (using units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 11.5.

Incidence of TE laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time postbaseline up to 30 days posttreatment of SLGN + nivolumab ± VIR-2218, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered TE.

This analysis will also be provided through FU Week 24.

All laboratory abnormalities will be included in the listings of laboratory data.

8.6.4. Other Safety Evaluations

Individual data for ECG and vital signs measurements will be listed by participant and summarized for each treatment group by visit by incidence of events/abnormalities or descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate.

8.7. Pharmacokinetic Analysis

Plasma concentrations of SLGN and VIR-2218 may be analyzed. Serum concentrations of nivolumab may be analyzed (as applicable, from existing samples).

CCI

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Concentration data from all sparse and intensive blood PK samples may be pooled with data from other studies and may be used for estimation of population PK parameters.

CCI


CCI


CCI

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (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 Gilead or proprietary interests in the study drug during the course of a clinical study. 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. Institutional Review Board/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 IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/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 IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/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 IRB- or IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform participants about PG testing and/or planned sample retention. 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 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.

NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. 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, case report forms (CRFs)/eCRFs, study drug 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 study 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, CRFs/eCRFs, governmental approval with correspondence, the ICF(s), 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
- Documentation that participant meets eligibility criteria, ie, medical 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
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, 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 (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for ED, 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 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 CRF Completion Guidelines provided by Gilead. Subsequent to data entry, a study monitor may perform source data verification (SDV). 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 IRBs/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 to IRB/IEC and regulatory authorities in accordance with local requirements and receive documented IRB/IEC and regulatory authority approvals before modifications may be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. 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. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.7).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

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 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, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF 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 monitor should have access to any participant records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, 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 medical 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. Premature Study Termination

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority, and IRB/IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

11.1. Investigator Signature Page

GILEAD SCIENCES, INC.
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STUDY ACKNOWLEDGMENT

A Phase 2a, Open-Label Study to Evaluate the Safety and Efficacy of Selgantolimod (SLGN)-Containing Combination Therapies for the Treatment of Chronic Hepatitis B (CHB)

GS-US-465-4439, Amendment 2 12 April 2023

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

PPD Medical Monitor	*[See appended electronic signature]* Signature
[See appended electronic signature] Date	

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.

Principal Investigator Name (Printed)	Signature
Date	Site Number

11.2. 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) Study drug supplies to participants and sites:

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

Mitigation plan: Study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on study drug as determined by the principal investigator (PI). A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study participants if permitted by local ethic committee (EC)/institutional review boards (IRB)/Regulatory Authority as applicable and with sponsor's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug participant would not be able to stay on the study drug as planned per protocol.

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

2) Participant safety monitoring and FU:

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

Mitigation plan: For participants who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI 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 virtual 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 FU on any unresolved AE/SAEs.

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

iii) If applicable, confirm participants study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (1).

iv) If applicable, remind participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

d) 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 lab analyses.

Mitigation plan: Local labs may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular FU per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local lab pregnancy testing is not feasible.

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

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

3) Protocol and monitoring compliance:

f) 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.

g) Monitors may be unable to carry out source data review (SDR) or (SDV), or study drug accountability or assess protocol and Good Clinical Practice (GCP) compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. In compliance with Gilead policy, a remote SDV should not be arranged). The study monitor is to reference the Study Monitoring 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:

    h) 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 selgantolimod (SLGN), VIR-2218, and TAF in study participants remains unchanged.

11.3. Study Procedures Tables

Appendix Table 1. Study Procedures Table for NUC-Suppressed Cohort 1

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days)[a]										EOT (−5 days)		Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT	ED[d]	1[c]	4	8[c]	12	16[c]	24	36	48
Written Informed Consent[e]	X																					
Review of Inclusion/Exclusion Criteria	X																					
Medical History	X																					
AEs & Concomitant Medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X	X			X								X	X								
Symptom-directed physical examination			X	X			X	X	X	X	X	X				X		X		X	X	X
Vital signs	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Height	X																					
Body weight	X	X			X			X	X	X	X	X	X	X								X
12-lead ECG[g]	X	X			X								X	X								X
Chest x-ray	X													X[h]								
Ophthalmologic examination[i]	X									X			X	X[h]								
Symptom-directed ophthalmologic examination		X	X	X			X	X	X		X	X				X		X		X	X	X
Safety laboratory tests (hematology & chemistry; coagulation)	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
APRI	X	X			X								X	X				X				X
FibroTest	X	X			X								X	X				X				X

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days)[a]										EOT (−5 days)		Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT	ED[d]	1[c]	4	8[c]	12	16[c]	24	36	48
FibroScan[j]	X																					
α-fetoprotein (HCC imaging [eg, CT scan] is required for participants with α-fetoprotein ≥ 50 ng/mL at screening)	X																					
Serology testing to exclude HCV, HDV, and HIV infection[k]	X																					
Quantitative plasma HBV DNA	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Serum sample for HBV viral sequencing (resistance surveillance) and ddPCR	X																					
Serum sample for HBV viral sequencing (resistance surveillance) and genotyping sample		X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Quantitative HBV Serum HBsAg, HBcrAg, HBeAg, and HBV RNA	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Qualitative HBV serology HBeAg, HBeAb, and HBsAg, HBsAb	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days)[a]										EOT (−5 days)	ED[d]	Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT		1[c]	4	8[c]	12	16[c]	24	36	48
Biomarker Samples: Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis[l, m]		X			X[l]		X					X[m]								X		
Sparse PK for VIR-2218[n]		X			X				X													
Sparse PK for SLGN[n]					X				X			X										
Estimated creatinine clearance (using the Cockcroft-Gault method)	X	X			X								X	X								X
Urinalysis	X	X	X	X	X			X	X	X	X	X	X	X								
Urine Drug and Alcohol Screen	X																					
Autoantibodies	X																					
TSH	X									X			X	X								
FSH[o]	X																					
Serum Pregnancy Test[p]	X													X								
Urine Pregnancy Test[p]		X	X	X	X			X	X	X	X	X	X			X	X[p]	X	X[p]	X	X	X
Enrollment		X																				
Dispense and Administer TAF as appropriate		Tenofovir alafenamide (TAF) 25-mg tablet administered orally daily for up to 84 weeks																				
Dispense & Administer VIR-2218 SC as appropriate		X	X	X	X			X	X													
Dispense & Administer SLGN[q] as appropriate					X	X	X	X	X	X	X	X										

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days)[a]										EOT (−5 days)		Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT	ED[d]	1[c]	4	8[c]	12	16[c]	24	36	48
Study Drug Accountability			X	X	X		X	X	X	X	X	X	X									
CCI																						
CCI																						
CCI																						

AE = adverse event; APRI = AST to Platelet Ratio Index; CT = computed tomography; ddPCR = digital droplet polymerase chain reaction; ECG = electrocardiogram; ED = early discontinuation; EOT = end of treatment; FSH = follicle-stimulating hormone; FU = follow-up; 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; IV = intravenous; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; SLGN = selgantolimod; TAF = tenofovir alafenamide; TSH = thyroid-stimulating hormone

a All study visits except for Weeks 13 and 14.
b FU Week 1 will have a visit window of + 3 days, FU Weeks 4 through FU Week 16 will have a visit window of ± 5 days, and FU Weeks 24 through FU Week 48 will have a visit window of ± 14 days.
c Week 13, FU Week 1, FU Week 8, and FU Week 16 will be conducted as a virtual/telephonic visit to review AEs, concomitant medications, and overall health of the participant by investigator.
d The ED visit should be performed within 14 days from notification of study discontinuation. If ED is done in FU period, all of these procedures should be performed.
CCI
f Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the informed consent form. After drug administration, report all AEs and SAEs.
g Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording.
h At ED visit, these procedures are optional and to be done as needed.
i Ophthalmologic examination at screening should be performed during the screening window, ie, within 45 days of randomization. Ophthalmologic examinations post-Day 1 should occur within −4 to +10 days of visit.
j FibroScan testing where applicable for liver disease staging.
k In the event of a positive result for serology and/or antigen testing for HIV, HDV, or HCV, reflex tests will be performed as necessary.
l Collect pre-SLGN dose administration on Week 12, 4 hours and 24-72 hours postdose.
m Collect pre-SLGN dose administration on Week 32, 4 hours, and 24-72 hours postdose.
n The sparse PK collection for VIR-2218 at baseline/Day 1 should occur predose and postdose. Postdose sparse PK collection should occur any time between 1 and 5 hours postdose relative to VIR-2218, and/or SLGN administration.
o FSH test is required for female participants who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
p For female participants of childbearing potential, the serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at all other visits as indicated. Positive urine pregnancy test will be confirmed with serum pregnancy test. Pregnancy testing should include prevention counseling. FU Week 8 and Week 16 urine pregnancy test will be a virtual/telephonic visit for females participants of childbearing potential.
q SLGN tablets will be administered while fasting once a week, on the same day.

CCI

s Intensive PK sample to be drawn at any one visit at Week 20, 24, 28 or 32 **relative to SLGN** dosing in clinic on the morning of the intensive PK visit. Collection will occur at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12 and 24 hours postdose (8, 10, 12 hour collections are optional).

t Intensive PK sample to be drawn on Baseline/Day 1 and at Week 20 **relative to VIR-2218** dosing in clinic on the morning of the intensive PK visit. Collection will occur at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12 and 24 hours postdose (8, 10, 12 hour collections are optional).

Appendix Table 2. Study Procedures Table for Viremic Cohort 2

	Screening (45 days)	BL Day 1	Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only			24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)	ED[e]								
			1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32			1[b,c]	4	8[c]	12	16	24	36	48
Written Informed consent[f]	X																							
Review of Inclusion/ Exclusion Criteria	X																							
Medical History	X																							
AEs & Concomitant Medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X	X					X								X	X								
Symptom-directed physical examination					X	X			X	X	X	X	X	X		X		X	X	X		X	X	X
Vital signs	X	X		X (Cohort 2 Group B)	X	X	X		X	X	X	X	X	X	X	X		X	X	X		X	X	X
Height	X																							
Body weight	X	X			X (Cohort 2 Group B)	X (Cohort 2 Group B)	X			X	X	X	X	X	X	X								X
12-lead ECG[h]	X	X					X								X	X								X
Chest x-ray	X															X[i]								

	Screening (45 days)	BL Day 1	Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only			24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)	ED[e]								
			1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32			1[b,c]	4	8[c]	12	16	24	36	48
Ophthalmologic examination[j]	X						X (Cohort 2 Group B)					X			X	X[i]								
Symptom-directed ophthalmologic examination		X			X	X			X	X	X		X	X				X		X		X	X	X
Safety laboratory tests (hematology & chemistry; coagulation)	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
APRI	X	X					X								X	X				X				X
FibroTest	X	X					X								X	X				X				X
FibroScan[k]	X																							
α-fetoprotein (HCC imaging [eg, CT scan] is required for participants with α-fetoprotein ≥ 50 ng/mL at screening)	X																							
Serology testing to exclude HCV, HDV, and HIV infection[l]	X																							
Quantitative plasma HBV DNA	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X

	Screening (45 days)	BL Day 1	Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only			24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)	ED[e]								
			1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32			1[b,c]	4	8[c]	12	16	24	36	48
Serum sample for HBV viral sequencing (resistance surveillance) and ddPCR	X																							
Serum sample for HBV viral sequencing (resistance surveillance) and genotyping sample		X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Quantitative HBV Serum HBsAg, HBcrAg, HBeAg, and HBV RNA	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Qualitative HBV serology HBeAg, HBeAb, and HBsAg, HBsAb	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Biomarker Samples: Collection of PBMC, whole blood, serum and plasma samples for biomarker analysis[m,n]		X[m,n]		X[n]			X[m]		X[m]		X[n]			X[m]								X		
Sparse PK for VIR-2218[o]		X					X				X													
Sparse PK for SLGN[p]		X[p]					X				X			X[p]										

	Screening (45 days)	BL Day 1	Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only			24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)	ED[e]								
			1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32			1[b,c]	4	8[c]	12	16	24	36	48
Estimated creatinine clearance (using the Cockcroft-Gault method)	X	X					X								X	X								X
Urinalysis	X	X			X	X	X			X	X	X	X	X	X	X								
Urine Drug and Alcohol Screen	X																							
Autoantibodies	X																							
TSH	X						X (Cohort 2 Group B)					X			X	X								
FSH[q]	X																							
Serum Pregnancy Test[r]	X															X								
Urine Pregnancy Test[r]		X			X	X	X			X	X	X	X	X	X			X	X[r]	X	X[r]	X	X	X
Enrollment		X																						
Dispense & Administer VIR-2218 SC as appropriate (Group A only)		X			X	X	X			X	X													
Dispense & Administer SLGN[s] as appropriate (Group A only)							X	X	X	X	X	X	X	X										

	Screening (45 days)	BL Day 1	Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only			24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)									
			1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32		ED[e]	1[b,c]	4	8[c]	12	16	24	36	48
Dispense & Administer SLGN[s] as appropriate (Group B only)		X	X	X	X	X	X	X	X	X	X													
Study Drug Accountability					X	X	X		X	X	X	X	X	X	X	X								
CCI																								
CCI																								
CCI																								

AE = adverse event; APRI = AST to Platelet Ratio Index; BL = baseline; CT = computed tomography; ddPCR = digital droplet polymerase chain reaction; ECG = electrocardiogram; ED = early discontinuation; EOT = end of treatment; FSH = follicle-stimulating hormone; FU = follow-up; 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; IV = intravenous; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; SLGN = selgantolimod; TAF = tenofovir alafenamide; TSH = thyroid-stimulating hormone

a All study visits (± 2 days), except for Weeks 1, 2, 13, and 14.
b FU Week 1 will have a visit window of ± 2 days, FU Weeks 4 through FU Week 16 will have a visit window of ± 5 days, and FU Weeks 24 through FU Week 48 will have a visit window of ± 14 days.
c Week 1 (Cohort 2 Group B only), Week 13 (Cohort 2 Group A only), and FU Week 1, Week 8, and Week 16 will be conducted as a virtual/telephonic visit to review AEs, concomitant medications, and overall health of the participant by investigator.
d Week 2 visit is only applicable for Cohort 2 Group B.
e The ED visit should be performed within 14 days from notification of study discontinuation.
CCI
g Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form. After drug administration, report all AEs and SAEs.

h Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording.
i At ED visit, these procedures are optional and to be done as needed.
j Ophthalmologic examination at screening should be performed during the screening window, ie, within 45 days of randomization. Ophthalmologic examinations post-Day 1 should occur within −4 to +10 days of visit.
k FibroScan testing where applicable for liver disease staging.
l In the event of a positive result for serology and/or antigen testing for HIV, HDV, or HCV, reflex tests will be performed as necessary.
m Cohort 2 Group A biomarker collection. Collect pre-SLGN dose administration at Baseline/Day 1, Week 12, 4 hours and 24-72 hours postdose. Collect at Week 14, predose. Collect pre-SLGN dose administration at Week 32, 4 hours and 24-72 hours postdose.
n Cohort 2 Group B biomarker collection. Collect pre-SLGN dose administration on Baseline/Day 1, 4 hours and 24-72 hours postdose. Collect at Week 2, pre-dose. Collect pre-SLGN dose administration at Week 20, 4 hours and 24-72 hours postdose.
o The sparse PK collection for VIR-2218 at baseline/Day 1 should occur predose and postdose. Postdose sparse PK collection for VIR-2218 should occur any time between 1 and 5 hours postdose relative to VIR-2218 administration.
p Sparse PK collection for SLGN should occur any time between 1 and 5 hours postdose relative to SLGN administration. The collection at Baseline/Day 1 is only applicable to Cohort 2 Group B. The collection at Week 32 is only applicable to Cohort 2 Group A.
q FSH test is required for female participants who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
r For female participants of childbearing potential, the serum pregnancy test will be performed at screening. Urine test will be performed at all other visits as indicated. Positive urine test will be confirmed with serum test. Pregnancy testing should include prevention counseling. FU Week 8 and Week 16 urine pregnancy test will be a virtual/telephonic visit for female participants of childbearing potential.
s SLGN tablets will be administered while fasting once a week on the same day.
CCI
u For Group A, intensive PK sample to be drawn at any one visit at Week 20, 24, 28 or 32 **relative to SLGN** dosing in clinic on the morning of the intensive PK visit. For Group B, sample will be collected Week 12 or later **relative to SLGN** dosing in clinic on the morning of the intensive PK visit.
v Group A and B: Collection will occur at Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12 and 24 hours postdose (8, 10 and 12 hour collections are optional).
w For Group A only, intensive PK sample to be drawn on Baseline/Day 1 and at Week 20 **relative to VIR-2218** dosing in clinic on the morning of the intensive PK visit.

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

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born participant 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.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) 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 female participant of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born participant 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

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Tenofovir alafenamide (TAF)

Data from clinical pharmacokinetic interaction studies of TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Nonclinical toxicity studies in animals (rats and rabbits) of TAF have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of TAF in pregnant women. Please refer to the latest version of the IB for additional information.

Nivolumab

There are no data on the use of nivolumab in pregnant women. Studies in animals have shown embryofetal toxicity. Nivolumab is not recommended during pregnancy. Women of childbearing potential should use effective contraception for at least 5 months following the last dose of nivolumab. It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. Please refer to the latest version of nivolumab product information for additional information.

Selgantolimod

There is no clinical data available on SLGN treatment in pregnant women. Nonclinical studies in rabbits showed no adverse effect on fertility but did show a possible risk of teratogenicity/fetotoxicity during embryo-fetal development. Therefore, the use of highly effective contraception will be required for participation in this study. Nonclinical studies showed no genotoxicity.

Nonclinical studies demonstrate low induction potential with once weekly dosing of SLGN. Based on this data, no reduction in the exposure of hormonal contraception is expected.

Please refer to the latest version of the IB for additional information.

VIR-2218

There are no available data on the use of VIR-2218 in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. No adverse effects on pregnancy or embryo-fetal development related to VIR-2218 were observed in rats and in rabbits. No studies have been conducted in animals on the effect of VIR-2218 on fertility and pre/postnatal development. Nonclinical studies showed no genotoxicity.

Women of childbearing potential are required to have a negative pregnancy test, cannot be breast feeding, must use highly effective contraception during the study, should continue using contraception for a least 1 month following the last dose of VIR-2218, and meet any other contraception requirements specified in the protocol. Male participants with female partners of childbearing potential must agree to meet the contraception requirements specified in the protocol.

Please refer to the latest version of the VIR-2218 IB for additional information.

There is no metabolic enzyme (or transporter) induction effect that is expected from either nivolumab or VIR-2218. Therefore, because SLGN is not an inducer, none of the drugs used in this trial either alone or in combination are expected to yield a reduction of exposure of hormonal contraception.

Because many medicinal products can be secreted in human milk, a risk to newborns/infants cannot be excluded.

b. Contraception Requirements for Female Participants of Childbearing Potential

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

Duration of required contraception for female participants in this clinical trial should start from screening visit until 30 days after the last dose of TAF, SLGN, or VIR-2218 or for 5 months after the last dose of nivolumab whichever contraception ending date is latest. If a participant requires a commercially approved nucleos(t)ide analog treatment, the investigator will provide contraception requirements according to the local label for the specific marketed product and again taking into consideration whichever contraception ending date is latest.

Female participants must agree to one 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:

- Hormonal or nonhormonal intrauterine device (IUD)
- Subdermal contraceptive implant
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female participants 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
  - 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.

Female participants must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Male Participants

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male participant's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male participants with female partners of childbearing potential must use condoms during treatment until 30 days after the last dose of TAF, SLGN, or VIR-2218 or for 5 months after last dose of nivolumab whichever contraception ending date is latest. If a participant requires a commercially approved nucleos(t)ide analog treatment, the investigator will provide contraception requirements according to the local label for the specific marketed product and again taking into consideration whichever contraception ending date is latest. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male participants 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

Female participants 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 the end of the study. Nivolumab, SLGN and VIR-2218 must be discontinued immediately. Interruption of other drugs should be considered upon discussion with the medical monitor.

Male participants whose partner has become pregnant or suspects she is pregnant from start of study to the end of the contraception requirement 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. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version 01 April 2015 will be used to grade all adverse events (AEs), with the exception of infusion-related reactions (IRRs).

For grading of IRRs, the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 found on the NCI website will be used:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months[#]**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 × ULN	>1.5 to 2.0 × ULN	>2.0 to 3.0 × ULN	> 3.0 × ULN
Activated Partial Thromboplastin Time	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 to <2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmol/L
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L > 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L > 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric** **≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmol/L	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/L to <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Adult**	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) **Pediatric >2 to <18 years**	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL.
** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for male participants > 70 years. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below				
Females	> ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	> 999 to 1999 mg/24 h	> 1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	> 499 to 799 mg/m^2/24 h	> 799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratory tests, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than ER visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (eg, tube feeding or total parenteral nutrition)
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hour	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24-hours.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24-hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48-hours	Persistent nausea resulting in minimal oral intake for > 48-hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (preexisting) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of preexisting seizures (nonrepetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24-hours post-ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5-20 minutes with < 24-hours post-ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (noninjection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding or total parenteral nutrition)

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

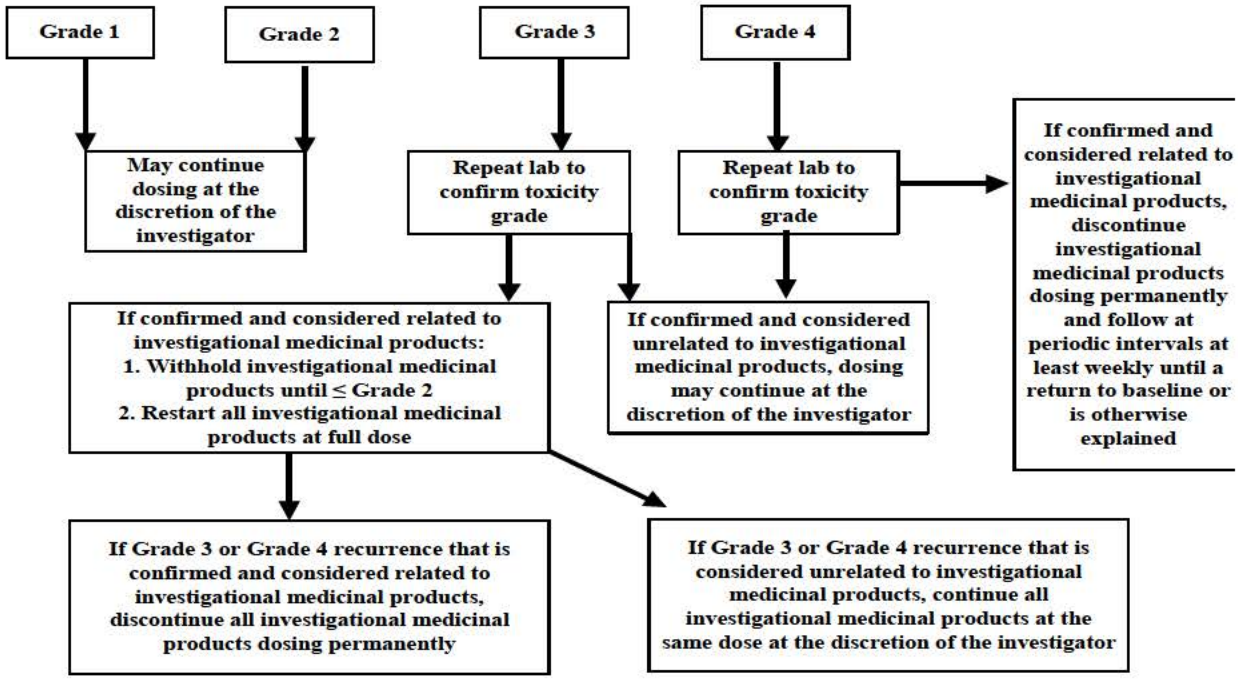
ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

11.6. Management of Clinical and Laboratory Adverse Events



If the adverse event is considered related to nivolumab, the investigator must follow the toxicity management guidance outlined in the local label for nivolumab.

11.7. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below, with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing the Protocol Amendment 1 to this amendment will be made available upon the publication of this protocol.

11.7.1. Amendment 2 (12 April 2023)

Rationale for Key Changes Included in Amendment 2	Affected Sections
References to nivolumab were modified throughout the protocol due to Gilead's decision to discontinue nivolumab dosing across study cohorts.	Throughout the protocol, as required
An ongoing study (GS-US-389-5458) assessing the safety, tolerability and efficacy of once-weekly administration of SLGN 3 mg in special populations with chronic hepatitis B virus (CHB) was added.	Section 1.2.1.1

Rationale for Key Changes Included in Amendment 2	Affected Sections
Figure 1 was updated in order to reflect the current changes to study design.	Section 3.2
A new section to describe the rationale for modifications to the study design was added following the decision to discontinue nivolumab dosing.	Sections 1.3.1
Benefit/Risk Assessment for nivolumab and Overall Benefit/Risk was updated following discontinuation of nivolumab in this study.	Section 1.5
Number of viremic chronic hepatitis B (CHB)-infected participants was reduced from 80 to 60 participants to reflect a prior sponsor decision that cohort 3 would not be enrolled.	Synopsis, Section 3.2, and throughout the protocol, as required
A new subsection for changes to the study design was added.	Section 3.2.1
All incidences of 'Participants who remain on nucleos(t)ide (NUC) treatment into follow-up (FU) period are not required to attend FU Weeks 2 and 8 visits' have been removed as all participants in Cohort 1 will remain on NUCs throughout the FU period.	Synopsis and Section 6.7
FU period was updated to outline the procedures following the change to study design.	Synopsis and Section 3.5
An individual treatment modification criterion (*Any on treatment uveitis, confirmed by ophthalmologic evaluation)* was moved to individual treatment discontinuation criteria after confirmation that no rechallenge is required following the resolution of the AE.	Synopsis and Section 6.9.1
A new section for toxicity management of irAEs observed with nivolumab was added.	Section 11.5
AE of special interest (eg, uveitis) was added to the safety analysis.	Section 8.6.2
FU Week 8 virtual/telephonic visit pregnancy test was changed across all cohorts.	Section 11.3 and throughout the protocol, as required.
The visit windows for FU Weeks 24 through FU Week 48 (for Cohorts 1 and 2) were extended to ± 14 days.	Sections 11.3 and 6.7
FU Week 2 was removed in order to simplify the FU period for participants.	Section 11.3 and throughout the protocol, as required
References to Cohort 3 were removed throughout the protocol due to the decision to discontinue this cohort.	Throughout the protocol, as required
Incidences of Global Patient Safety have been changed to Patient Safety (PS).	Section 7 and throughout the protocol, as required
Minor changes included to correct typographical errors.	Throughout the protocol, as required

Prot-GS-US-465-4439-amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
CCI	Clinical Development eSigned	13-Apr-2023 16:49:46