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
Clinical Trials.gov Identifier:	Not Available
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

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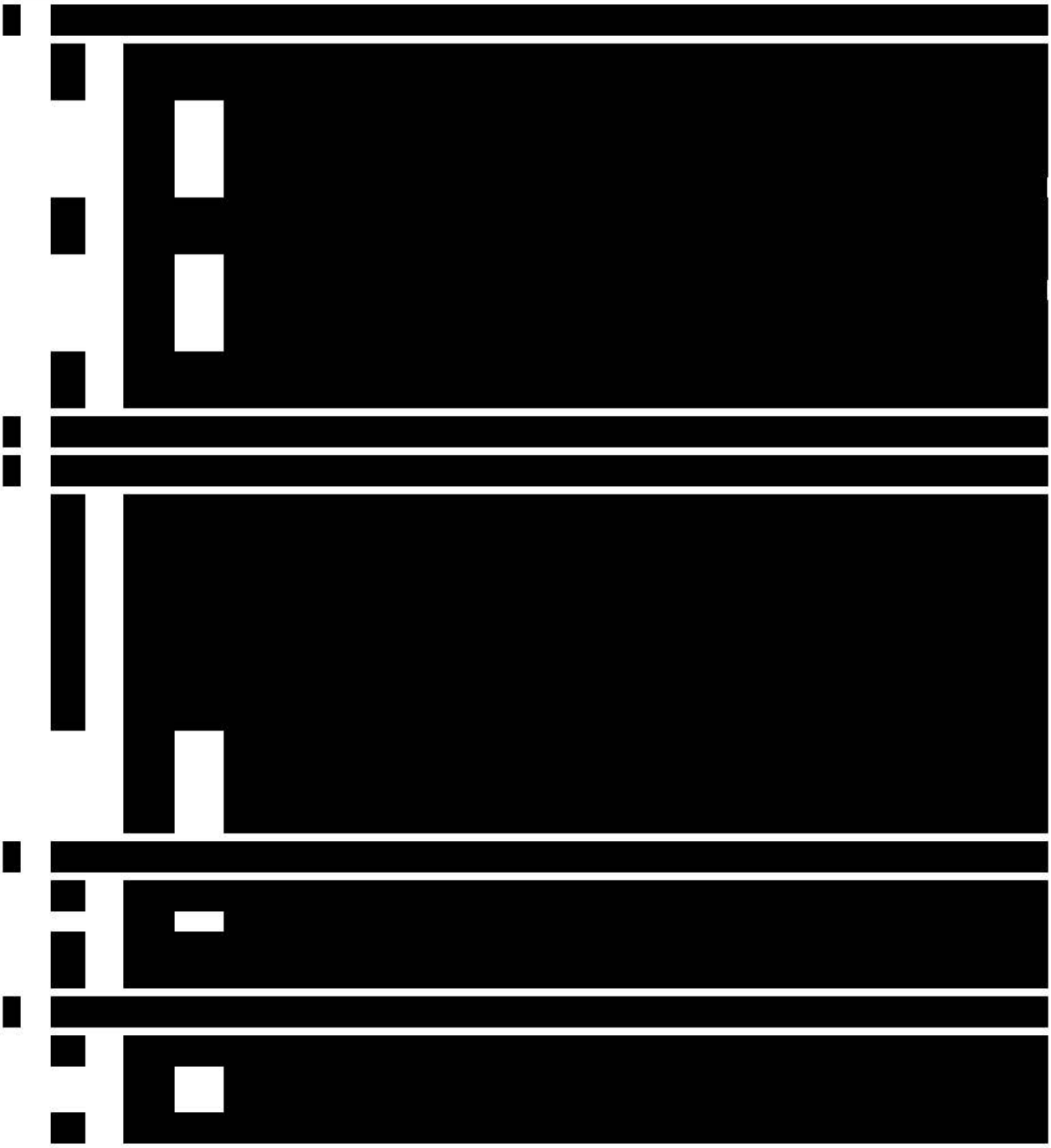

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LIST OF IN-TEXT TABLES

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

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 Not Available
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 subjects who achieve functional cure, defined as negative qualitative hepatitis B surface antigen (HBsAg loss) and hepatitis B virus (HBV) DNA < 20 IU/mL at Follow-Up (FU) Week 24 The secondary objectives of this study are as follows: • To evaluate the proportion of subjects with HBsAg loss with and without anti-HBsAg seroconversion during the study • To evaluate in subjects with CHB who are hepatitis B e antigen (HBeAg)-positive at baseline, the proportion of subjects who achieve HBeAg loss with and without anti-HBeAg seroconversion during the study • To evaluate the proportion of subjects who remain off nucleos(t)ide(s) (NUC) treatment during FU • To evaluate the proportion of subjects experiencing HBV virologic breakthrough during study treatment(s) CCI [redacted]

Study Design:

This is a Phase 2, open-label study to evaluate the safety and efficacy of SLGN-containing combination therapies in chronic hepatitis B (CHB) subjects.The study will consist of 3 cohorts (Cohorts 1, 2, and 3).

Approximately 40 NUC-suppressed and 80 viremic CHB-infected subjects, may be enrolled and assigned into a cohort below. Each cohort will enroll an approximate (± 10%) equal number of HBeAg positive and negative subjects; and up to 20% of subjects can have HBsAg ≤ 100 IU/mL

NUC-suppressed Cohort

Cohort 1 (n = 40):

- Tenofovir alafenamide (TAF) CCI
- VIR-2218 CCI

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- SLGN CCI

- Nivolumab CCI [redacted]

Viremic Cohorts (Cohorts 2 and 3)

Cohort 2

Subjects 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 CCI [redacted]

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- SLGN CCI [redacted]
- Nivolumab CCI [redacted]

Group B (n = 20):

- SLGN CCI [redacted]
- Nivolumab CCI [redacted]

Cohort 3 (n = 20):

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- VIR-2218 CCI [redacted]
- SLGN CCI [redacted]
- Nivolumab CCI [redacted]

Follow-Up Period:

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

- All subjects not on TAF treatment at end of treatment (EOT) will enter a treatment-free follow up (TFFU) period

- Subjects who are on TAF treatment and meet the criteria below at the EOT visit will stop all treatments, no later than FU Week 1 visit, and enter a TFFU period:
  - HBV DNA < 20 IU/mL
  - HBeAg negative
  - HBsAg ≤ 100 IU/mL
- All remaining subjects will continue on TAF or other NUC treatment and enter a FU period

Subjects who do not meet the above criteria but choose to discontinue NUC at EOT can do so with medical monitor approval.

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Pharmacogenomic Research:

All subjects who are willing to provide separate written consent will be eligible to participate in the PG research. This PG blood sample should be drawn at the Baseline/Day 1 visit. However, if the sample is not obtained at Baseline/Day 1 visit the sample may then be drawn at any time during the study. The sample will be stored, for future PG analysis.

Samples for Optional Future Research

Subjects will be requested to consent to allow for the use of the remainder of their already collected specimens for optional future research.

ALT Elevation or Flare Management

On-Treatment ALT Management

Subjects with on-treatment serum alanine aminotransferase (ALT) elevation > 2 × nadir or > 2 × baseline value and ≥ 5 × upper limit of normal (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 subject should be performed. The assessment should include a physical examination, evaluation of the subject'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 subjects 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, nivolumab and SLGN treatment. Subject should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting study treatment (VIR-2218, nivolumab, 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. **Cohorts 2-3**: Initiate TAF CCI CCI and hold VIR-2218, and/or nivolumab, and SLGN dose. Subject should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting study treatment (VIR-2218, nivolumab, 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 × baseline or nadir AND > 2.5 mg/dL in the absence of Gilbert's disease • Elevated INR > 0.5 above baseline AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	**Cohort 1:** Permanently discontinue study treatment(s) except TAF CCI CCI Subject should be monitored weekly until ALT < 5 × ULN, and total bilirubin, INR, and albumin values return to normal or baseline levels. **Cohorts 2-3:** Initiate commercially approved NUC treatment once daily and permanently discontinue study treatment(s). Subject should be monitored weekly until ALT < 5 × ULN, and total bilirubin, albumin, and/or INR values return to normal or baseline levels

Treatment-Free Follow-Up ALT Management

All eligible subjects will enter a TFFU period after completion of study treatment, in which they will undergo close safety monitoring. The proportion of subjects 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 subjects 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 subject should be performed. The assessment should include a physical examination, evaluation of the subject'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.

Subjects with HBV DNA < 20 IU/mL 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.

Subjects with HBV DNA > 20 IU/mL and ALT elevation/flare should be managed according to the table below:

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 subject 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.

Individual Treatment Modification and Discontinuation Criteria

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

- An on-treatment, uveitis, confirmed by ophthalmologic evaluation.
- A confirmed, clinically significant laboratory test abnormality (other than ALT) ≥ Grade 3 considered study drug(s) related by the investigator.

Study treatment(s) maybe 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 ≥ Grade 3 uveitis, or recurrence of uveitis after re-challenge with SLGN and/or nivolumab, confirmed by ophthalmologic evaluation
- Any study drug–related Grade 3 (excluding laboratory abnormalities) AE not able to be medical managed (eg, nausea with antiemetics) mandates permanent discontinuation of study drug(s)

- Any study drug-related Grade 4 (excluding laboratory abnormalities) AE
- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study specific procedures or is considered to not be in the subject's best interest

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
- Subject requests to discontinue for any reason
- Subject 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 Subjects Planned:	Approximately 120 subjects
Target Population:	Adult, noncirrhotic, subjects with CHB infection who are viremic or virally suppressed on a commercially approved HBV NUC treatment.
Duration of Treatment:	TA CCI [redacted] VIR-2218 CCI [redacted] Nivolumab CCI [redacted] SLGN CCI [redacted]
Diagnosis and Main Eligibility Criteria:	Male and nonpregnant female subjects, ages 18 to 65 years, inclusive, with chronic HBV infection without the presence of cirrhosis, and who are viremic or virally suppressed on NUC 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:

After consent is obtained, screening assessments will be completed within 30 days prior to the Baseline/Day 1 treatment, screening window can be extended to 45 days with sponsor approval. All subjects will complete the following study treatments below. Subjects who remain on NUC into FU period are not required to attend FU Weeks 2 and 8 visits.

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, 2, 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, 2, 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, 2, 4, 8, 12, 16 (for women of childbearing potential), 24 (Primary), 36, and 48

Cohort 3:

- Screening Visit
- Treatment Period Visits: Baseline/Day 1, Weeks 1, 2, 4, 8, 12, , 14, 16, 20, and 24
- FU Visits: Weeks 1, 2, 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) (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Chest x-ray
- Ophthalmologic examination
- 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 subjects 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), FSH (for female subjects 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 adverse events (AEs) related to protocol mandated procedures occurring after signing of the consent form.


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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 subjects who achieve functional cure, defined as HBsAg loss and HBV DNA < 20 IU/mL at FU Week 24 **Secondary efficacy endpoints:** • The proportion of subjects with HBsAg loss with and without anti-HBsAg seroconversion during the study • The proportion of subjects with HBeAg loss with and without anti-HBeAg seroconversion during the study in subjects with CHB who are HBeAg positive at baseline • The proportion of subjects who remain off NUC treatment during FU

- The proportion of subjects experiencing HBV virologic breakthrough during study treatment(s)

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

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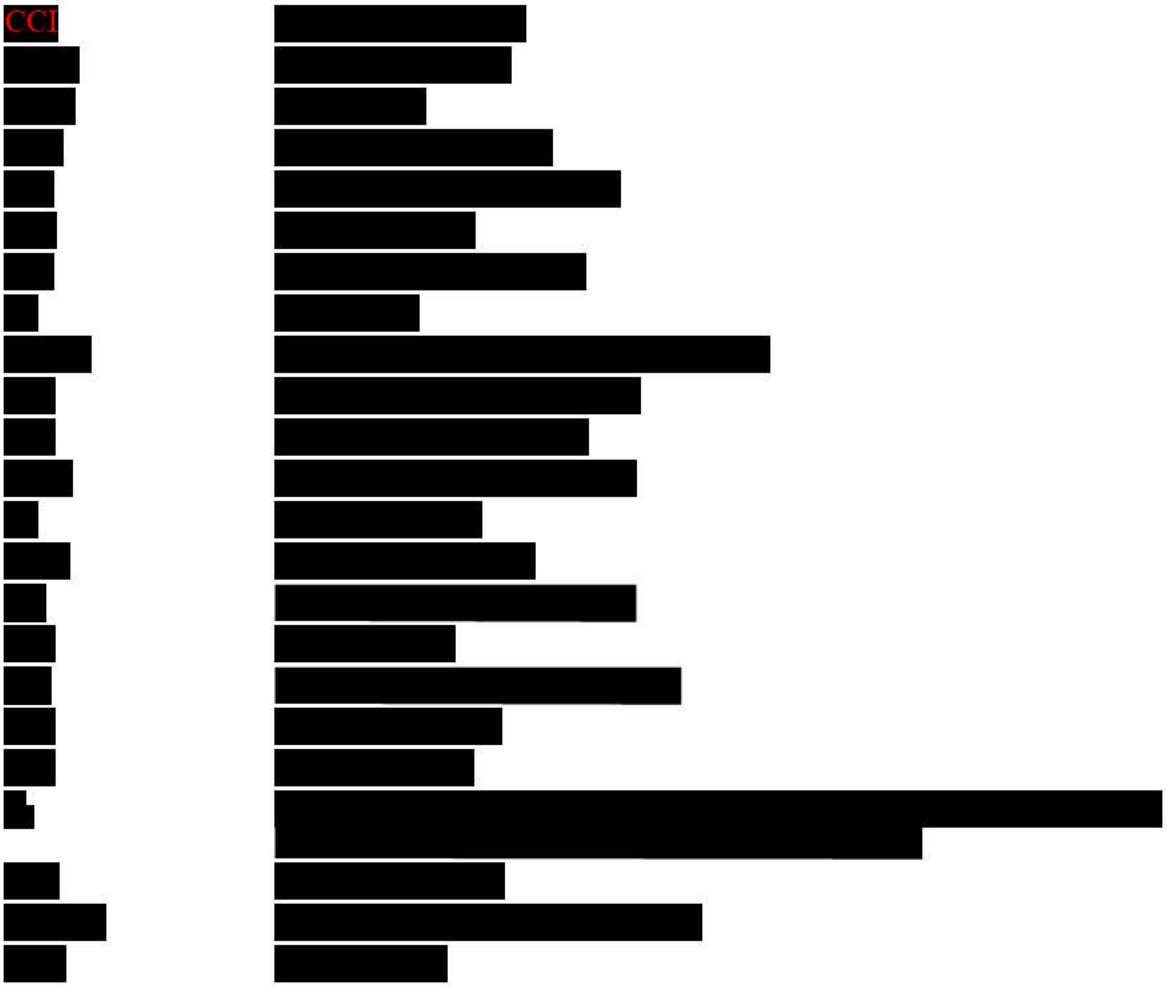
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1. INTRODUCTION

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 {World Health Organization (WHO) 2015a}, {Ratnam 2006}. 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) 2017}, {European Association for the Study of the Liver (EASL) 2012}, {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 NUC inhibitors 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 analogues 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 subjects. 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

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1.2.2. General Information About Nivolumab

Nivolumab (Opdivo®, BMS), an anti-PD-1 immunoglobulin (Ig)G4 monoclonal antibody, 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 subjects 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 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 were mild to moderate and resolved without intervention. Reductions in HCV RNA were modest and seen in 5/45 (11%) of treated subjects at doses as low as 0.1 mg/kg, although the highest dose of 10 mg/kg induced a > 4 $\log_{10}$ reduction in HCV RNA in 3 subjects (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 subjects with HCC were dosed with nivolumab at doses of 0.1 mg/kg to 3.0 mg/kg IV every 2 weeks. No subjects with HBV in either the dose escalation phase or in the expansion phase discontinued treatment due to study drug toxicity. Among the HBV-infected subjects with HCC who received 3.0 mg/kg IV every 2 weeks (n = 51), no subjects experienced Grade 3 or 4 ALT/aspartate aminotransferase (AST) increases and 6% (n = 3) experienced a Grade 3 or 4 treatment-related adverse event (AE) {El-Khoueiry 2017}.

For further information on nivolumab, refer to the current approved product label for nivolumab (Opdivo®).

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1.5. Risk/Benefit 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 nucleoside analogues 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 subjects with CHB. The longest duration of treatment were evaluated in 2 Phase 2 studies, GS-US-389-2024 (NUC-suppressed subjects with CHB) and GS-US-389-2025 (treatment-naive subjects with CHB), that administered placebo, SLGN 1.5 mg, or 3 mg once weekly with a NUC for 24 weeks to 93 subjects with CHB. Selgantolimod up to 3 mg once weekly was safe and well tolerated in 102 subjects with CHB (48 subjects in study GS-US-389-2024 and 54 subjects 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 subject 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.

Nivolomab

Nivolumab treatment alone have been well characterized and listed in the approved product label for nivolumab {OPDIVO 2021}. These risks generally result from off-target immune responses and occur in a dose-dependent manner with higher doses and longer durations of treatment leading to higher rates of AEs. In this study, nivolumab will be dosed at 1/10th of the clinically approved oncology dose used and only 1 infusion every 4 weeks over 24 weeks. Reducing the amount of drug and frequency given is expected to lead to a lower risk for AEs. This has been demonstrated in 2 Phase 1 studies in subjects with CHB, GS-US-330-1938 and GS-US-493-5342 (ongoing), for a single and multiple IV dose(s) of nivolumab 0.3 mg/kg every 4 weeks for 12 weeks, respectively. The IV dose(s) of nivolumab 0.3 mg/kg was safe and well tolerated in 22 subjects with single dose and 12 subjects with multiple doses. No Grade 3 or 4 AEs or laboratory abnormalities were observed or reported. The only nivolumab-related AEs as determined by the investigator were fatigue, headache, and cough in subjects administered a single dose and nausea and dysgeusia in subjects administered multiple doses; all were reported in 1 subject each.

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 subcutaneously in healthy subjects (Part A) and a regimen of 2 doses administered 4 weeks apart at doses up to 200 mg in subjects with CHB (Part B/C). In Part A, 59.5% of VIR-2218 subjects (22 of 37) and 50% of placebo subjects (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 subjects were headache (24.3%; 9 of 37 subjects), and upper respiratory tract infection, contact dermatitis, injection site bruising, and injection site pain (8.1% each; 3 of 37 subjects). Three VIR-2218 subjects (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 subjects (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 subjects (13 of 24) and 25% of placebo subjects (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 subject was receiving treatment. The most

common AEs in VIR-2218 subjects were headache (25.0%; 6 of 24 subjects), and dizziness, fatigue, and myalgia (8.3% each; 2 of 24 subjects). Five subjects (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 subjects (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 subject 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 sponsor determined that the constellation of concurrent symptoms (fever, headache, nausea, vomiting, and dehydration) were more consistent with a viral syndrome than a drug reaction and assessed the event as not related to study drug. Two subjects had a non-TE SAE considered not related to study drug by the investigator; 1 subject had depression and 1 subject PPD (outcome of death). The death PPD occurred approximately 9 months after last study drug administration.

Selgantolimod + Nivolumab

In an ongoing 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 have been evaluated in 12 subjects with CHB. The combination treatment for 12 weeks was generally safe and well tolerated. The most common (> 1 subject) AEs considered possibly 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) is allowed during the study. No Grade 3 or 4 AEs were reported, and no Grade 3 laboratory abnormalities were observed. A single Grade 4 laboratory abnormality of elevated lipase was reported in 1 asymptomatic subject 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 a monoclonal antibody 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 Risk Benefit

Based on available information, the benefit/risk balance for this study is considered positive.

All subjects enrolled in Cohort 1 will be switched from their prescribed antiviral to TAF (25 mg) in order to ensure consistency of treatment. Additionally, to further mitigate risk, subjects enrolled in this study will be required to have adequate hematologic function at study entry and sufficient hepatic reserve (F0-F2). The protocol will follow subjects closely with frequent virtual or in-clinic visits to monitor AEs, laboratory abnormalities, ophthalmologic examinations, and vital sign changes, routinely. 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. Based on historic enrollment rates (internal data), subjects 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. Enrollment in Cohort 3 will begin once Cohort 2 has completed enrollment. 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 2 for further details on the risks and risk mitigation strategy.

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 treatment(s) as measured by the proportion of subjects who achieve functional cure, defined as HBsAg loss and HBV DNA < 20 IU/mL at FU Week 24

The secondary objectives of this study are as follows:

- To evaluate the proportion of subjects with HBsAg loss with and without anti-HBsAg seroconversion during the study
- To evaluate in subjects with CHB who are hepatitis B e antigen (HBeAg)-positive at baseline, the proportion of subjects who achieve HBeAg loss with and without anti-HBeAg seroconversion during the study
- To evaluate the proportion of subjects who remain off NUC treatment during FU
- To evaluate the proportion of subjects experiencing HBV virologic breakthrough (defined as HBV DNA ≥ 69 IU/mL for 2 consecutive visits after having been < 20 IU/mL OR confirmed HBV DNA ≥ 1 $\log_{10}$ IU/mL increase from nadir on treatment) during study treatment(s)

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3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is as follows:

- The proportion of subjects who achieve functional cure, defined as HBsAg loss and HBV DNA < 20 IU/mL at FU Week 24

The secondary endpoints of this study are as follows:

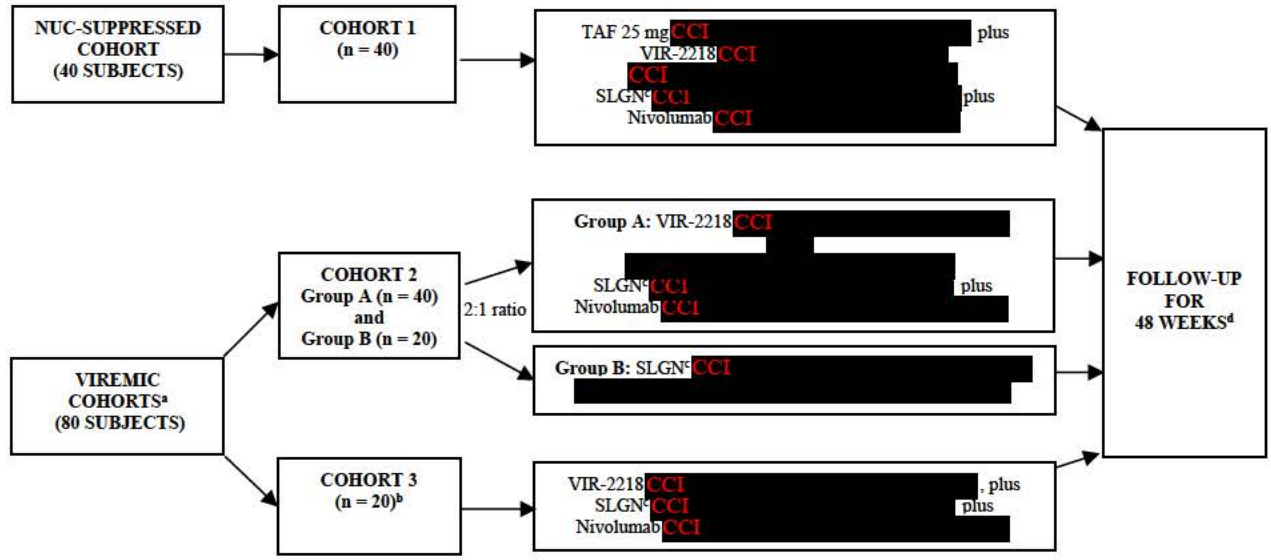
- The proportion of subjects with HBsAg loss with and without anti-HBsAg seroconversion during the study
- The proportion of subjects with HBeAg loss with and without anti-HBeAg seroconversion during the study in subjects with CHB who are HBeAg-positive at baseline
- The proportion of subjects who remain off NUC treatment during FU
- The proportion of subjects experiencing HBV virologic breakthrough (defined as HBV DNA ≥ 69 IU/mL for 2 consecutive visits after having been < 20 IU/mL or confirmed HBV DNA ≥ 1 $\log_{10}$ IU/mL increase from nadir) during study treatment(s)

3.2. Study Design

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

Approximately 40 NUC-suppressed and 80 viremic CHB-infected subjects, may be enrolled and assigned into a cohort below. Each cohort will enroll an approximate (±10%) equal number of HBeAg-positive and HBeAg-negative subjects; and up to 20% of subjects can have HBsAg ≤ 100 IU/mL.

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



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3.3. Study Treatments

NUC-suppressed Cohort

Cohort 1 (n = 40):

- TAF CCI
- VIR-2218 CCI

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- SLGN CCI
- Nivolumab CCI

Viremic Cohorts (Cohorts 2 and 3)

Cohort 2

Subjects 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 CCI [redacted]

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- SLGN CCI [redacted]
- Nivolumab CCI [redacted]

Group B (n=20):

- SLGN CCI [redacted]
- Nivolumab CCI [redacted]

Cohort 3 (n = 20):

Cohort 3 CCI [redacted]

- VIR-2218 CCI [redacted]
- SLGN CCI [redacted]
- Nivolumab CCI [redacted]

3.4. Duration of Treatment

The duration of study treatment are as follows:

- TAF CCI [redacted]
- VIR-2218 CCI [redacted]
- Nivolumab CCI [redacted]

- SLGN[redacted]

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

3.5. Follow-Up Phase

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

- All subjects not on TAF treatment at end-of-treatment (EOT) will enter a TFFU period
- Subjects who are on TAF treatment and meet the criteria below at the EOT visit will stop all treatments, no later than FU Week 1 visit, and enter a TFFU period:
  - HBV DNA < 20 IU/mL
  - HBeAg negative
  - HBsAg ≤ 100 IU/mL
- All remaining subjects will continue on TAF or other treatment and enter the FU period

Subjects who do not meet the above criteria but choose to discontinue NUC at EOT can do so with medical monitor approval.

3.6. Discontinuation Criteria

Refer to Section 6.9 for detail individual and study discontinuation criteria

3.7. End of Study

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

3.8. Poststudy Care

Once a subject has completed study participation, the long-term care of the subject 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).

[redacted]

biology of CHB. 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

In addition, serum, whole blood RNA, and PBMC, will be collected and stored from all subjects. These specimens, together with any residual specimens after performing the primary analysis, may be used for future biomarker analysis to address target-related biomarker issues, and for further understanding of the mechanism of action of study treatment(s) in patients with CHB.

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

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Cohorts 1-3 will enroll approximately 120 male and nonpregnant female subjects, ages 18 to 65 years, inclusive, with CHB infection without the presence of cirrhosis, and who are viremic or virally suppressed on NUC for at least 6 months.

4.1.1. Subject Replacement

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

4.2. Inclusion Criteria

Subjects 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 subjects, 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 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 subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4. Must be willing and able to comply with all study requirements.

Subjects 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 historic HBV DNA < 69 IU/mL, measured at least once at local laboratory, 6 or more months prior to screening.

9. HBV DNA < 20 IU/mL by central laboratory at screening

Subjects in Cohort 2 and 3 should meet the following additional criteria 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

Subjects 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 3 years 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) Historic FibroScan with a result > 9 kPa within ≤ 1 year of screening

      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. Subjects 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/mm3 if considered a physiological variant in a subject of African descent)

   d) ALT ≥ 2 × ULN (Cohort 1 only), ALT > 5 × ULN (Cohorts 2 and 3)

   e) International normalized ratio (INR) > ULN unless the subject is stable on ananticoagulant regimen affecting INR

   f) Albumin < 3.5 g/dL

g) Direct bilirubin > 1.5 × ULN

h) Platelet Count < 100,000/uL

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. Subjects in Cohort 2 and 3: Received OAV treatment for HBV within 6 months of screening

4. Co-infection with HIV, HCV, or hepatitis D virus (HDV). Subjects who are HCV 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). Subjects 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, monoclonal antibody, interferon, 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 subject 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 subjects unwilling to refrain from egg donation and in vitro fertilization during and until at least 5 months after last study drug dose.

19. Male subjects 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 5.3

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 coronavirus disease 19 (COVID-19) impact.

Cohort 1 and 2 will enroll in parallel.

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

Cohort 3 will be initiated at the discretion of the sponsor after Cohort 2 has completed enrollment.

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 subject results as needed for safety reasons.

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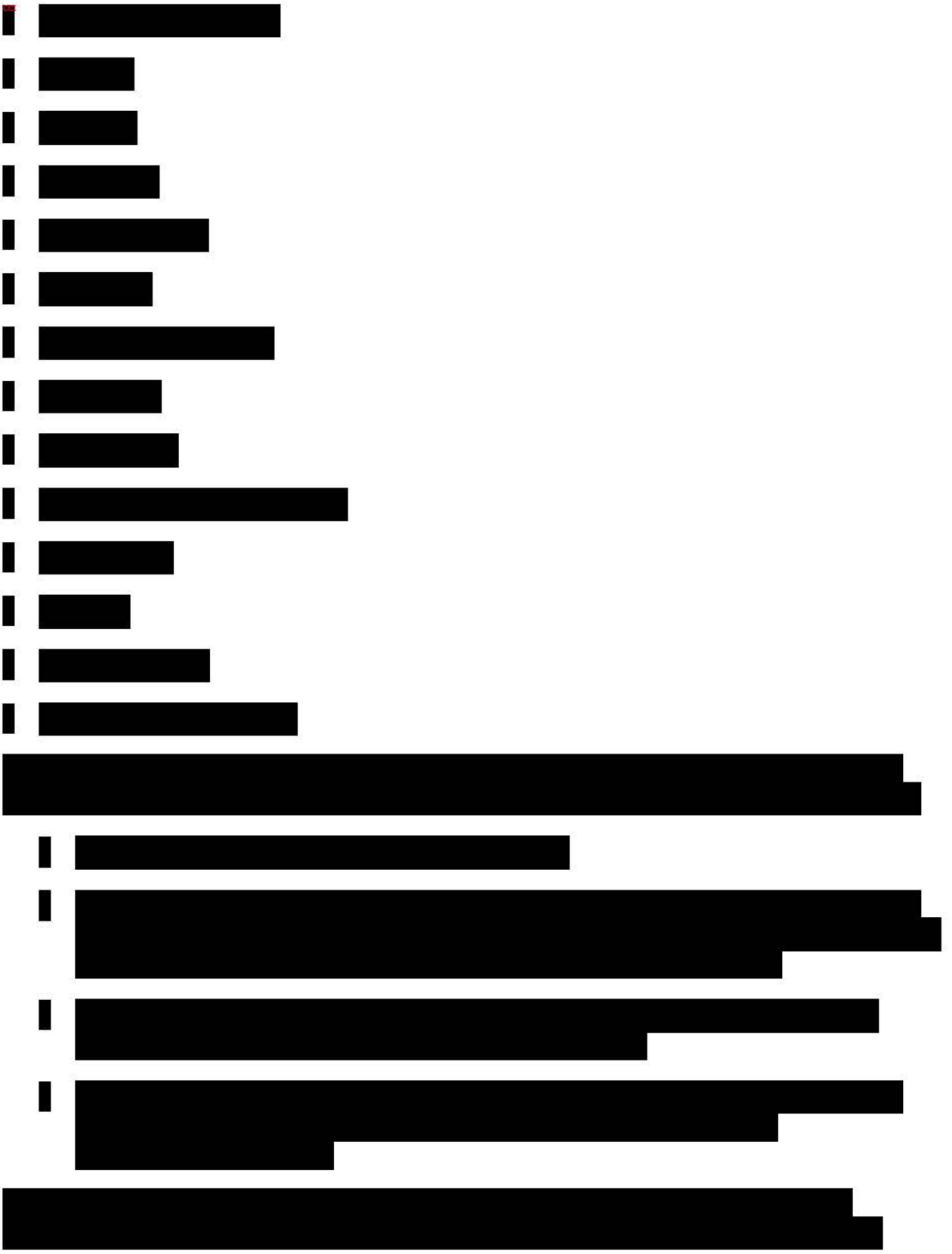

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5.5. Accountability for Investigational Medicinal Product: Selgantolimod, Tenofovir, VIR-2218 and Nivolumab

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 subjects 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, subject 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.

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 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:

- Subject 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 mmHg mark on the manometer or to the nearest whole number on an automatic device

6.1.4. 12-Lead ECGs

Subjects 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 subject's Day 1 as part of routine safety monitoring.

QTc interval will be reported using Fridericia's correction: $QTcF = QT/RR^{0333}$

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 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, gamma-glutamyl transferase (GGT, only at screening), 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 subjects with total lipase > 1.5 × ULN)

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

- Qualitative HBV serology (HBeAg and 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 subjects who are < 54 yers 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)

6.1.7. Ophthalmologic Examination

Ophthalmologic examinations will be performed for Cohorts 1 through 3 during screening, at Week 12, 24, 36 (as applicable), and 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 subjects in Cohorts 1-3.

See Section 6.6 and Schedule of Assessments Appendix 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 subject 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. ddPCR

If subject has HBV DNA ≤ 20 IU/mL, ddPCR will be conducted.

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6.1.13. Biomarker Optional Future Research

Subjects will be requested to consent to allow the use of the remainder of their already-collected specimens for optional future research.

Reference Section 3.9 for additional information on Biomarker Samples.

6.1.14. Optional Pharmacogenomic Sub Study

All subjects who are willing to consent will be eligible to participate in the PG research. This PG blood sample should be drawn at the baseline/Day 1 visit. However, if the sample is not obtained

at baseline/Day 1 visit the sample may then be drawn at any time during the study. The sample will be stored, upon specific consent, for future PG analysis.

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

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

6.2. Subject 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. Screening Visit

Subjects will be screened within 30 days prior to baseline Day 1 visit, screening window can be extended to 45 days with sponsor approval.

With sponsor 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. The sponsor 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 (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Chest x-ray
- Ophthalmologic examination

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

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 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.

6.3.2. Baseline/Day 1 Assessments

All baseline tests and procedures must be completed prior to the receipt of the first dose of study drug(s). Subjects screened within 30 days before baseline will be eligible to participate in the study or 45 days with prior sponsor approval.

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

Cohorts 1-3

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

[redacted]

6.4. Randomization

Viremic Cohort 2 (Group A and B) Only

Subjects 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

Cohort 3:

- Baseline/Day 1, and Weeks 4, 8, 12, 16, and 20 - SC VIR-2218, 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, 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 early discontinuation (ED), unless specifically noted:

All subjects 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)

Cohort 3: 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 Weeks 12, EOT, and as applicable for nivolumab administration)
- Review AEs and concomitant medications (at Weeks 1*, 2, 4, 8, 12, 13*, and 14 to EOT)
- 12-lead ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording) (at Weeks 12 and EOT)

- Optional blood sample for PG research (separate consent required prior to obtaining samples) to be obtained on or after the baseline visit

- Optional intensive PK sampling (separate consent required prior to obtaining samples): For VIR-2218 PK evaluation: on Day 1 and at Week 20 in-clinic treatment visits in Cohorts 1, 2 (Group A), and 3; For SLGN PK evaluation: at any one in-clinic treatment visit between Weeks 20 through 32 (in Cohorts 1 and 2 [Group A]) and at visit between Week 12 through 20 (in Cohorts 2 [Group B], and 3).

- Ophthalmologic Examination (−4 to +10 days of visit)

  — Cohort 1 and 2a: Week 24 and 36

  — Cohort 2b and 3: Week 12 and 24

- Symptoms-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, IV nivolumab 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: Week 1 (+ 3 days), Week 2 (+ 2 days), and Weeks 4 - 48 (± 5 days). FU assessments include the following (subjects who remain on NUC treatment into FU period are not required to attend FU Weeks 2 and 8):

- All subjects will complete following FU visits: Weeks 1, 2, 4, 8, 12, 16* (for women of childbearing potential), 24 (Primary), 36, and 48
- Vital signs (at Weeks 2 to 48)
- Symptom-directed physical examination (at Weeks 2 to 48)
- Symptom-directed ophthalmologic examination (at Weeks 2 to 48)
- Weight (At Week 48 only)
- 12-lead ECG (At Week 48 only)
- Review AEs and concomitant medications (At Week 1*, 16*, at Weeks 2 to 48)
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry; coagulation) (at Weeks 2 to 48)
  - APRI and fibro test (at Weeks 12 and 48)
  - Quantitative plasma HBV DNA (at Weeks 2 to 48)

  - — Quantitative HBV serum HBsAg, HBcrAg, HBeAg, and HBV RNA (at Weeks 2 to 48)
  - — Qualitative HBV serology HBeAg, HBeAb, HBsAg, and HBsAb (at Weeks 2 to 48)
- Urine pregnancy test (females of childbearing potential only, every 4 weeks through Week 48; Week 16 collection will be a virtual/telephonic visit)Serum sample for HBV viral sequencing and genotyping sample (baseline) (at Weeks 2 to 48)
- Estimated CL_{cr} (using Cockcroft-Gault method) (at Week 48 only)

*FU Visit Week 1 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

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

CCI [redacted]

[redacted]

[redacted]

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 subject until resolution of the event:

- An on-treatment, uveitis, confirmed by ophthalmologic evaluation.
- A confirmed, clinically significant laboratory test abnormality (other than ALT) ≥ Grade 3 considered study drug(s) related by the investigator.

Study treatment(s) maybe 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 ≥ Grade 3 uveitis, or recurrence of uveitis, confirmed by ophthalmologic evaluation, after re-challenge with SLGN and/or nivolumab

- 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 to not be in the subject's best interest

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

- Subject requests to discontinue for any reason

- Subject 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).

6.9.2. Criteria for Individual Dose Modification

Dose modification and discontinuation criteria for subjects 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 subjects if ≥ 3 subjects experience a Grade 3 AE or ≥ 2 subjects 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 subjects dosed to date.

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

6.10. End of Study

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

6.11. Poststudy Care

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

CCI [redacted]

[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 subject administered an 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 subject 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 subject 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 a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.3. 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 subject.

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 labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the subject 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 GSI Toxicity Grading Scale, Version 5. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 5).

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 subject 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 Global Patient Safety (GLPS) 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 GLPS.

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 GLPS (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 subject 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 GLPS 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 subject identification, maintaining the traceability of a document to the subject 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 subject'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 GLPS (or to the designated CRO) 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 GLPS
  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 GLPS.

- 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 subject identification, maintaining the traceability of a document to the subject 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 subject'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 GLPS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment FU period.

  Gilead GLPS
  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 GLPS utilizing the paper SSR form to:

  Gilead GLPS
  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 subjects and/or female partners of male subjects who are identified after initiation of study drug and throughout the study, including the posttreatment FU period, to Gilead GLPS 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 GLPS
  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 GLPS.

- The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS 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 GLPS. Gilead GLPS contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

- Refer to Appendix 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 Code of Federal Regulations, 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, 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 a safety letter 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. Reference table at link in Appendix 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 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 investigational medicinal product (IMP) 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 5)

- When restarting IMP following resolution of the AE, the IMP should be restarted at full dose or modified dose that is dependent upon discussion with the medical monitor

- Any recurrence of the IMP-related Grade 3 or 4 clinical or clinically significant laboratory AE following dose interruption mandates permanent discontinuation of IMP

- 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 subject

- 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 IMP at the discretion of the investigator

7.7.2. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 laboratory abnormality or clinical event, IMP may be continued if the event is considered to be unrelated to IMP

- 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 IMP, IMP should be withheld until the toxicity returns to ≤ Grade 2

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with IMP and is considered related to IMP, then IMP should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to IMP may not require permanent discontinuation

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 IMP should be permanently discontinued and the subject managed according to local practice. The subject 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

- Investigational study product 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. ALT Elevation or Flare Management on Treatment and Treatment-Free Follow Up

On-Treatment ALT Management

Subjects 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 subject should be performed. The assessment should include a physical examination, evaluation of the subject'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 subjects 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 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, nivolumab and SLGN treatment. Subject should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting VIR-2218, nivolumab 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. **Cohorts 2-3**: Initiate TAF [redacted] and hold VIR-2218, nivolumab, and SLGN dose. Subject should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN. Restarting VIR-2218, nivolumab 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 × baseline or nadir AND > 2.5 mg/dL in the absence of Gilbert's disease • Elevated INR > 0.5 above baseline AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	**Cohort 1:** Permanently discontinue study treatment(s) except TAF 25 mg once daily. Subject should be monitored weekly until ALT < 5 × ULN, and total bilirubin, INR, and albumin values return to normal or baseline levels. **Cohorts 2-3:** Initiate commercially approved NUC treatment once daily and permanently discontinue study treatment(s). Subject should be monitored weekly until ALT < 5 × ULN, and total bilirubin, albumin, and/or INR values return to normal or baseline levels

Treatment-Free Follow-Up ALT Management

All subjects will enter TFFU period after completion of study treatment, in which they will undergo close safety monitoring. The proportion of subjects 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 subjects 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 subject should be performed. The assessment should include a physical examination, evaluation of the subject'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.

Subjects with HBV DNA ≤ 20 IU/mL 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.

Subjects with HBV DNA > 20 IU/mL 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 subject 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.

[redacted]

CCI [redacted]

CCI [redacted]

8.5. Efficacy Analysis

8.5.1. Primary Analysis

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

The proportion of subjects 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, standard deviation [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 subjects 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 subjects 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 subject'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 Medical Dictionary for Regulatory Activities (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 subjects) 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

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 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 treatment emergent.

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 subject 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

The plasma concentrations of SLGN, VIR-2218, and nivolumab may be analyzed and listed.

The following plasma PK parameters of SLGN and VIR-2218 may be calculated, as appropriate, for the optional intensive PK substudy: AUC_{last}, AUC_{0-24}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, CL/F, and $t_{1/2}$.

For subjects in the Optional PK Substudy Analysis Set, PK parameters described above will be listed (as applicable) and summarized using descriptive statistics (eg, n, arithmetic mean, geometric mean, % coefficient of variation, SD, median, minimum, and maximum). Plasma concentrations of the study drug over time will be summarized using descriptive statistics. Plasma concentrations will be plotted in semi logarithmic and linear formats as mean ± SD.

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

8.8. Exploratory Analysis

Change from baseline in quantitative HBV RNA, HBV DNA (including ddPCR if available), HBcrAg, HBeAg, HBsAg, glycosylated fraction of HBsAg (if applicable) during and after study treatment(s) discontinuation will be analyzed by treatment group by visit.

Exploratory analyses may be performed to evaluate the effect of study treatment(s) on peripheral cytokine activation and immune response. Analyses to characterize the relationship between immunologic changes and circulating HBV viral markers as well as analyses to characterize HBV viral variants present at baseline and/or emerged during treatment that may be associated with response to the study treatment(s) may be provided. For subjects who provide their separate and specific consent, analyses related to genetic discovery research may be performed.

PBMC, whole blood, serum, and plasma specimens collected in this study may be used to evaluate the association of exploratory systemic biomarkers with study treatment(s) response, including efficacy and/or AEs and to increase knowledge and understanding of the biology of CHB. The specific analyses may include:

- Analysis of HBV-specific T-cell responses to hepatitis B peptides by ELIspot
- Flow cytometry to evaluate T-cell, NK-cell, and B-cell subsets
- Single-cell transcriptional profiling and T-cell and B-cell receptor sequencing
- Serum cytokine levels
- TLR8 SNP genotyping
- HLA genotyping

8.9. Sample Size

Due to the exploratory nature of this study, the sample size was not determined by any formal power calculation. The number of subjects in each treatment cohort was decided based on clinical experience.

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 subject 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 subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject 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 subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

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 subject or the subject'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 subjects about PG testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples for optional PG research. The results of the tests done on the samples will not be given to the subject or the investigator.

9.1.5. Confidentiality

The investigator must ensure that subjects' 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 subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions.

NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject 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) subject 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 subject:

- Subject identification
- Documentation that subject 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 subject 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 early discontinuation, if it occurs

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

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

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator

in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification (SDV) within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff 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. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her login credentials 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 by that site. 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 subjects, 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 Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. 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.

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

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator 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 subject 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. Study Discontinuation

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 subjects, 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 subjects' interests.

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11. APPENDICES

Appendix 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, Original, 04 March 2021

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

PPD

PPD (Printed)
Medical Monitor

PPD

04 March 2021

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

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

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

These risks can be summarized as follows:

1) Study drug supplies to subjects and sites:

    a) Subjects 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 subject visits. Without study drugs, the subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: Study drug supplies may be provided to the subject from the site without a clinic visit, once it is confirmed that the subject 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 subject 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 subjects 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 subject 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) Subject safety monitoring and FU:

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

        Mitigation plan: For subjects 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 subject within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

        i) Confirm if subject 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 subjects 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 subject to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Subjects 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 subject safety until the subject 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.

c) Subjects 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:

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

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

b) Monitors may be unable to carry out source data review (SDR) or source data verification (SDV), or study drug accountability or assess protocol and 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 subjects on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to subjects 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 subjects 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 [VIR-2218, nivolumab and TAF] in study subjects remains unchanged.


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Appendix 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 subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the subject 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 subject of any age.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

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 use highly effective contraception during the study and should continue using contraception for a least 1 month following the last dose of VIR-2218.

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 nor VIR-2218. Therefore, because Selgantolimod 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 Subjects of Childbearing Potential

The inclusion of female subjects 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 subjects 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 subject 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 subjects 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 subject'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 subjects 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 subjects must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male subject's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male subjects 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 subject 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 subjects 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 subjects 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 subjects 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.

Appendix 5. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

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**	5.6 to 6.0 mEq/L 5.6 to 6.0 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	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>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	> 6.5 to 7.0 mEq/L > 6.5 to 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 subjects > 70 yrs. 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 Males	 > ULN - 10 RBC/HPF 6-10 RBC/HPF	 > 10-75 RBC/HPF > 10-75 RBC/HPF	 > 75 RBC/HPF > 75 RBC/HPF	 NA NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years** **Pediatric > 3 Mo to < 10 Years**	 200 to 999 mg/24 h 201 to 499 mg/m^2/24 h	 > 999 to 1999 mg/24 h > 499 to 799 mg/m^2/24 h	 > 1999 to 3500 mg/24 h > 799 to 1000 mg/m^2/24 h	 > 3500 mg/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
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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	Dyspnea on exertion causing greater than minimal	Dyspnea at rest causing inability to perform usual	Respiratory failure with ventilatory support indicated

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pediatric < 14 Years	usual social & functional activities Wheezing OR minimal increase in respiratory rate for age	interference with usual social & functional activities Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	social & functional activities 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.

Appendix 6. Management of Clinical and Laboratory Adverse Events