CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Open-Label, Active-Controlled Study to Evaluate the Safety and Antiviral Activity of GS-9992 Plus Tenofovir Alafenamide (TAF) for 12 Weeks in Chronic Hepatitis B (CHB) Subjects	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	Non-IND Study	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	NCT03434353	
Indication:	Chronic Hepatitis B	
Protocol ID:	GS-US-464-4437	
Gilead Study Director:	Name: Telephone: Fax:	PPD PPD PPD
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Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3:	22 August 2017 05 December 2017 24 May 2018 11 March 2019 (Hong Kong)

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PROTOCOL SYNOPSIS

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Study Title:	A Phase 2, Randomized, Open-Label, Active-Controlled Study to Evaluate the Safety and Antiviral Activity of GS-9992 Plus Tenofovir Alafenamide (TAF) for 12 Weeks in Chronic Hepatitis B (CHB) Subjects
IND Number:	Non-IND Study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT03434353
Study Centers Planned:	Approximately 15 centers in South Korea and Hong Kong
Objectives:	The primary objectives of this study are: • To evaluate the safety and tolerability of the 12 week treatment regimens of GS-9992 (also known as SB 9200) plus TAF or commercially available nucleos(t)ide (NUC) • Groups 1-3 and 5 To evaluate the antiviral activity of 12 weeks of GS-9992 plus TAF versus TAF alone in viremic CHB subjects as measured by the proportion of subjects with ≥0.5 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating serum HBV surface antigen (HBsAg) • Group 4 To evaluate the antiviral activity of 12 weeks of GS-9992 with commercially available NUC(s) in virally suppressed CHB subjects as measured by the proportion of subjects with ≥0.5 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating serum HBV surface antigen (HBsAg) The secondary objectives of this study are: Groups 1-3 and 5 • To evaluate the safety and tolerability of the 48 week treatment regimens as assessed by review of the accumulated safety data • To evaluate the antiviral activity of 12 weeks of GS-9992 plus TAF versus TAF alone in CHB subjects as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating HBsAg

- To evaluate the proportion of HBeAg-positive CHB subjects who achieve HBeAg loss and seroconversion during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks
- To evaluate the proportion of CHB subjects who achieve HBsAg loss during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks
- To evaluate the incidence of drug resistance mutations during 48 weeks of treatment
- To characterize steady-state pharmacokinetics of study drugs
- To evaluate the change from Baseline in HBV DNA and quantitative HBsAg in CHB subjects during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

Group 4

- To evaluate the proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL) during 12 weeks of GS-9992 treatment
- To evaluate the antiviral activity of 12 weeks of GS-9992 in CHB subjects as measured by the proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating HBsAg
- To evaluate the proportion of HBeAg-positive CHB subjects who achieve HBeAg loss and seroconversion during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks
- To evaluate the proportion of CHB subjects who achieve HBsAg loss during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks
- To characterize steady-state pharmacokinetics of study drugs
- To evaluate the change from Baseline in quantitative HBsAg in CHB subjects during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks

CCI [redacted]

Study Design:

Approximately 120 chronic, immune-active, HBV-infected adults without cirrhosis may be enrolled; including 100 viremic subjects not currently on HBV nucleos(t)ide (NUC) treatment from Groups 1-3 and 5, and 20 virally suppressed subjects on an NUC from Group 4.

Approximately 40 viremic subjects not currently on HBV nucleos(t)ide treatment will be randomized (3:1) to Group 1 and Group 2, below:

- Group 1 (n = 30): GS-9992 50 mg once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks
- Group 2 (n = 10): TAF 25 mg once daily with food for 48 weeks

Approximately 40% of subjects enrolled will be HBeAg negative. Randomization will be stratified by HBeAg status (positive or negative) at Screening.

Group 3

Approximately 30 viremic subjects may be enrolled and assigned:

- GS-9992 200 mg (2 x 100 mg tablets) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks

Approximately 40% of subjects enrolled in Group 3 will be HBeAg negative.

Group 3 will not start enrolling subjects until the ACHIEVE (SB-9200-HBV-201) trial's independent Data Safety Monitoring Board has deemed it safe to proceed based on review of data for the 200 mg monotherapy cohort.

Group 4

Approximately 20 virally suppressed CHB subjects taking a commercially available NUC(s) may be enrolled. Subjects will remain on their current commercially available NUC(s) therapy for the duration of the study and receive:

- GS-9992 100 mg once daily one hour before or one hour after a meal for 12 weeks.

Approximately 50% of subjects enrolled in Group 4 will be HBeAg negative. All subjects will be followed through Week 48.

Group 5 (Hong Kong Only)

Approximately 30 viremic subjects may be enrolled and assigned:

- GS-9992 400 mg (2 x 200 mg tablets) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks

Approximately 40% of subjects enrolled in Group 5 will be HBeAg negative.

Safety of GS-9992 200mg plus TAF for 12 weeks (Group 3) will be confirmed prior to enrollment of Group 5.

24 Week Treatment-Free Follow-up

Subjects that meet any one of the following criteria will be followed for 24 weeks or until the initiation of alternative CHB therapy, whichever comes first:

- Subjects that discontinue all HBV therapy (e.g.GS-9992 and/or TAF or commercially available NUC), for any reason
- Subjects with HBsAg loss confirmed at least 12 weeks apart should discontinue all HBV therapy following confirmation
- **ALT Elevation or Flare 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 on-treatment 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, INR and serum albumin.

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, HAV IgM, HCV, and HEV.

For GS-9992 Management

Based on the results of the confirmatory tests, the following treatment modifications for GS-9992 are recommended:

GS-9992 Dose Modification and Monitoring

Liver Toxicity	Action
Confirmed ALT ≥ 10 × ULN without evidence of hepatic toxicity as defined below	Discuss with the Medical Monitor if GS-9992 should be dose reduced by 50% or discontinued if the safety of the subject is of immediate concern. Subject should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN
Confirmed ALT > 2 × nadir, with evidence of hepatic toxicity, defined as any one of the following: Total bilirubin > 2 × baseline or nadir AND > ULN in the absence of Gilbert's disease Elevated INR > 0.5 above baseline AND > ULN Abnormal serum albumin > 1 g/dL decrease from baseline	Permanently discontinue GS-9992. Subject should be monitored weekly until ALT < 5 × ULN, and total bilirubin and INR values return to normal or baseline levels
Confirmed ALT > 2 × Baseline and ≥ 5 × ULN without evidence of hepatic toxicity, as defined above	Continue GS-9992, ALT should be evaluated every 2 weeks or more frequently as clinically needed, until ALT < 5 × ULN

For TAF Management

Based on the results of the confirmatory tests, the following treatment modifications for TAF are recommended:

Liver Toxicity	Action
Confirmed ALT levels >10 × ULN, with evidence of hepatic toxicity, defined as any one of the following: • Total bilirubin > 2 × baseline or nadir AND > ULN in the absence of Gilbert's disease • Elevated INR > 0.5 above baseline AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	Discuss with the Medical Monitor if TAF should be discontinued, unless the safety of the subject is of immediate concern. Subject should be monitored weekly as long as ALT, total bilirubin and INR values remain elevated or above baseline values. If the ALT values remain persistently elevated, the investigator should discuss with the Medical Monitor if TAF should be discontinued.
Confirmed ALT levels ≥10 × ULN, without evidence of hepatic toxicity, as defined above	Continue TAF and monitor weekly until ALT values return to normal or baseline levels. If the ALT values remain persistently elevated, the investigator should discuss with the Medical Monitor if TAF should be discontinued.

Criteria for Discontinuation of Study Drug(s)

GS-9992 and/or TAF may also be discontinued if the following instances are met:

- A confirmed ≥ Grade 3 AE (excluding isolated ALT elevations) considered related to GS-9992 and/or TAF by the investigator, should discontinue one or both study drug(s)
- A confirmed, clinically significant lab abnormality ≥ Grade 3 (excluding isolated ALT elevations) considered related to GS-9992 and/or TAF by the investigator, should discontinue one or both study drug(s)
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- 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
- HBsAg loss confirmed at least 12 weeks apart
- Subject requests to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

For Group 5, study treatment(s) will be held in all subjects in the dosing group, if ≥3 subjects experience a Grade 3 adverse event or ≥2 subjects experience a Grade 4 or serious adverse event, in the same system organ class (excluding isolated ALT elevations) that is considered related by the investigator(s) to the Graded toxicity. Decisions to reinitiate continuation of dosing of study treatment(s) will be made by Gilead Medical Monitor upon review of all safety data generated by subjects dosed to date.

HBV will be managed according to local standard of care if subjects are discontinued from the study. Subjects that discontinue all study drug(s) will be followed for 24 weeks or until the initiation of alternative CHB therapy, whichever comes first.

Number of Subjects Planned:	Approximately 120 subjects
Target Population:	Chronic, immune-active, viremic and virally suppressed HBV-infected adults
Duration of Treatment:	Group 1: GS-9992 plus TAF for 12 weeks then TAF for 36 weeks Group 2: TAF for 48 weeks Group 3: GS-9992 plus TAF for 12 weeks then TAF for 36 weeks. Group 4: GS-9992 for 12 weeks Group 5: GS-9992 plus TAF for 12 weeks then TAF for 36 weeks
Diagnosis and Main Eligibility Criteria:	Male and non-pregnant female subjects, ages 18-70 years, inclusive, with chronic HBV infection 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 45 days prior to the Baseline/Day 1 visit. All subjects will complete the following study visits: Screening, Baseline/Day 1, Post-Day 1visits at the end of Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48. Subjects that discontinue all HBV therapy (GS-9992 and/or TAF or commercially available NUC) should complete Treatment-Free follow up visits at the end of Weeks 4, 8, 12, 16, 20, and 24, or until the initiation of alternative CHB therapy, whichever comes first. **Screening assessments include:** • 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 ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Sample Collection for:
  - Safety laboratory tests (hematology, chemistry, and coagulation)
  - Serology testing to exclude HCV, HDV, and HIV infection
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative])
  - HBV viral sequencing samples (resistance surveillance)
  - Estimated creatinine clearance (using the Cockcroft-Gault method)
  - Other screening laboratory tests: urinalysis, urine drug screen, and serum β-hCG (females of child bearing potential only)

Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

Day 1 (Baseline) assessments include:

- Review of inclusion/exclusion criteria and confirm medical history
- Complete Physical Examination including body weight
- Vital signs
- 12-lead ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Review adverse events prior to study drug administration, report AEs related to protocol mandated procedures and all SAEs. After drug administration, report all AEs and SAEs.

Review Concomitant Medications

- Sample Collection For:
  - Safety laboratory tests (hematology, chemistry, and coagulation)
  - HBV genotype for Groups 1-3 and 5 only; for Group 4 historic HBV genotype should be documented in EDC, if available
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative])
  - Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis (PBMC sample collection is only required at the sites that have access to PBMC processing laboratory)
  - Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR (Group 4)
  - Other laboratory tests: urinalysis, urine drug screen and pregnancy test for child bearing potential only)

  CCI [redacted]
- Estimated creatinine clearance (using Cockcroft-Gault method)
- Randomization
- Drug Administration of GS-9992 and/or TAF
  - Dispense study drug as directed by IWRS
  - Instruct the subject on the packaging, storage, and administration of study drugs
  - Observe the subject taking the first dose of study drug(s)

Post-Day 1 assessments include:

- Vital signs
- Weight at Weeks 12 and 48
- Review adverse events
- Review concomitant medications

- Complete Physical Examination (Week 12)
- Symptom-directed physical examination
- 12-lead ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording) (Week 12)
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry; coagulation on Week 12 only)
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) at Weeks 12, 24, 36, and 48
  - Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis at Weeks 1, 4, 12, 24, 48 (PBMC sample collection is only required at the sites that have access to PBMC processing laboratory).
  - Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR (Group 4)
  - Single plasma PK sample will be collected at each on-study treatment visit.
    - On Weeks 2 and 8, the sample will be collected between 15 minutes and 4 hours post-dose. In-clinic dose of GS-9992 required.
    - All PK samples will be collected anytime on all other on-treatment visit.
    - Single PK blood samples will only be collected through Week 12 for Group 4
  - Urine pregnancy test (females of child bearing potential only)
  - Urinalysis
  - Estimated creatinine clearance (using Cockcroft-Gault method) at Weeks 12 and 48
- [redacted]

[redacted]

- Perform study drug accountability (GS-9992 Weeks 1-12, TAF Weeks 1-48)
- Dispense study drug GS-9992 Weeks 1-8 (Groups 1, 3, 4, and 5), TAF Weeks 4-48 (Group 1, 2, 3, and 5) as outlined in Appendix 2.

Treatment-Free assessments include:

- Complete Physical examination at Week 4
- Symptom-directed physical examination
- Review adverse events at Week 4 and collect SAEs through the end of study
- Review concomitant medications
- Vital signs
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry)
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) to be collected at Weeks 12 and 24
  - Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis at Weeks 4, 8, 12, and 24

    (PBMC sample collection is only required at the sites that have access to PBMC processing laboratory).
  - Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR (Group 4)
  - Urine pregnancy test (females of child bearing potential only at Week 4)

Test Product, Dose, and Mode of Administration:	• Group 1: GS-9992 (also known as SB 9200) 50 mg (2 × 25 mg) capsules are administered orally once daily one hour before or one hour after a meal for first 12 weeks. • Group 3: GS-9992 200 mg (2 x 100mg) tablets are administered orally once daily one hour before or one hour after a meal for first 12 weeks. • Group 4: GS-9992 100 mg tablet is administered orally once daily one hour before or one hour after a meal for first 12 weeks. • Group 5: GS-9992 400 mg (2 x 200mg) tablets are administered orally once daily one hour before or one hour after a meal for first 12 weeks. • Groups 1, 3 and 5: TAF 25 mg tablet is administered orally once daily for 48 weeks with food
Reference Therapy, Dose, and Mode of Administration:	TAF 25 mg tablet for Group 2 is administered orally once daily for 48 weeks with food

Criteria for Evaluation:

Safety:	Safety will be evaluated by assessment of clinical laboratory tests and adverse events collected through end of treatment. Primary safety analysis will be evaluated through four weeks after last dose of GS-9992.
Antiviral Activity:	Antiviral Activity will be evaluated using scheduled assessments of quantified serum HBsAg levels. Primary antiviral activity analysis will be evaluated through Week 12.
Pharmacokinetics:	A single PK blood sample will be collected at each on-treatment visit through 48 weeks for Groups 1-3 and 5. Single PK blood samples will only be collected through Week 12 for Group 4. For all groups on Weeks 2 and 8, the sample will be collected between 15 minutes and 4 hours post-dose. PK sample can be collected at any time on all other on-treatment visits. CCI [redacted] The PK of GS-9992 (and its metabolites), TAF, and TFV (if applicable) will be assessed. CCI [redacted]

Statistical Methods:

The primary efficacy endpoint is the proportion of subjects with ≥ 0.5 $\log_{10}$ IU/mL decline in HBsAg from baseline at Week 12. It will be summarized in all randomized/enrolled and treated subjects for all groups. The 2-sided 95% confidence interval of the proportion difference (Group 1 – Group 2, Group 3 – Group 2, Group 5 – Group 2) will be constructed by using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factor HBeAg status (positive, negative).

The secondary endpoints may include the proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in HBsAg from baseline at Week 12, the proportion of HBeAg-positive CHB subjects who achieve HBeAg loss and seroconversion, and the proportion of CHB subjects who achieve HBsAg loss, the change from baseline in HBV DNA (Groups 1-3 and 5) and HBsAg, the proportion of subjects with drug resistant mutations (Groups 1-3 and 5) and the proportion of subjects experiencing HBV virologic breakthrough (Group 4).

All continuous efficacy endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, and maximum). All categorical efficacy endpoints will be summarized by number and percentage of subjects who meet the endpoint.

Safety will be evaluated by treatment group by the number and percentage of subjects with adverse events or laboratory abnormalities for categorical values or by the 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data.

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 group was decided based on clinical experience.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug
AUC	area under the plasma concentration-time curve
°C	degrees Celsius
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase (previously serum glutamic pyruvic transaminase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
bpm	beats per minute
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHB	Chronic hepatitis B
CI	confidence interval
CK	creatine kinase
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CPK	creatine phosphokinase
CRO	contract (or clinical) research organization
CSR	clinical study report
CTA	clinical trial application
C_{tau}	observed drug concentration at the end of the dosing interval
DDI	drug-drug interaction
ddPCR	digital droplet PCR
DNA	deoxyribonucleic acid
EASL	European Association for the Study of the Liver (EASL)
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment

EudraCT	European Clinical Trials Database
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
G	Genomics
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
HBV	hepatitis B virus
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV RT	HBV reverse transcriptase
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV, HIV-1	human immunodeficiency virus, type 1
HLGT	high-level group term
HLT	high-level term
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	Identification
IEC	independent ethics committee
IFN	interferon
IND	investigational new drug (application)
IRB	institutional review board
IUD	intrauterine device
LDL	low-density lipoprotein
LLT	lower-level term
LLOQ	lower limit of quantitation
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor

NDA	new drug application
NOAEL	no-observed-adverse-effect-level
NOD-2	nucleotide-binding oligomerization domain-containing protein 2
NUC	nucleos(t)ide
PD	pharmacodynamic(s)
PEG	pegylated interferon-α
PI	principal investigator
PHH	primary human hepatocytes
PK	pharmacokinetic(s)
PR interval	electrocardiographic interval occurring between the onset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively
PT	preferred term
PTM	placebo to match
PTT	partial thromboplastin time
PVE	Pharmacovigilance & Epidemiology
QA	quality assurance
QD	one a day
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected for heart rate using the Fridericia formulation
RBC	red blood cell
RIG-I	retinoic acid-inducible gene 1
RNA	ribonucleic acid
RT	reverse transcriptase
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TAF	Tenofovir Alafenamide
TEAE	treatment-emergent adverse event
TE	treatment-emergent
T_{last}	time (observed time point) of C_{last}
TFV	tenofovir
T_{max}	the time (observed time point) of C_{max}
TQT	thorough QT

$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
ULN	upper limit of normal
US, USA	United States, United States of America
V_z/F	apparent volume of distribution of the drug
WBC	white blood cell
WHO	World Health Organization

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) 2015}. 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 {Terrault 2016, Wright 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 (i.e., 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) 2015}. In 2013, an estimated 686,000 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 2015, Ott 2012}.

The loss of HBsAg is the accepted endpoint for anti-HBV therapy and has been associated with improvements in liver histology, including the reversal of cirrhosis, a decreased risk of HCC, and prolonged survival {Benias 2011, European Association for the Study of the Liver (EASL) 2017, Fattovich 1998, Kim 2013, Liaw 2012, Lok 2009}. Recent treatment guidelines, Terrault 2016, EASL 2017 {European Association for the Study of the Liver (EASL) 2017, Terrault 2016} and APASL 2016 {Sarin 2016}, acknowledge the importance of HBsAg clearance in CHB. HBsAg clearance is associated with definitive remission of the activity of CHB and an improved long term outcome {European Association For The Study Of The Liver 2009}; recent data show that the risk of HCC is lower if HBsAg clearance occurs before 50 years of age {Yuen 2008}. Loss of HBsAg is thus a primary goal of CHB therapy.

Nucleos(t)ide analogues are the standard of care for CHB, providing durable on-treatment suppression of viral replication and resulting in long-term clinical benefits with a reduced risk of liver complications {Dienstag 2003, Liaw 2011, Lok 2013}. With potent oral antivirals (NUCs), the yearly incidence of HBsAg loss is low but cumulative as duration of NUC treatment increases. As a result, continuous long-term use is advised for most patients. More, treatment with oral nucleos(t)ide inhibitors rarely results in clearance of HBsAg {Kwon 2011}. Therefore, new therapies that enhance rates of HBsAg loss after a finite treatment course are needed.

A finite course of subcutaneously injected pegylated interferon-α (PEG) given in CHB patients, can result in responses equivalent to a clinical cure of the virus in approximately 5% of treated patients {Ghany 2009, Perrillo 2009}. However, these rates vary dramatically depending on patient characteristics and virus subtype. Additionally, PEG has notable barriers to patient acceptance including the subcutaneous route of administration and a significant adverse effect

profile; fatigue, malaise, cytopenias, depression and induction of autoimmunity. These adverse effects have been associated with early drug discontinuation. In light of the relatively low response rates and barriers to use of PEG, orally administered immunomodulatory regimens with fewer side effects than exogenous interferons are needed. An ideal therapy would be oral and more tolerable than current therapies, more broadly applicable and associated with higher long-term viral eradication rates (as measured by HBsAg clearance).

The host immune response to HBV infection plays a pivotal role in whether acute infection is resolved or becomes chronic. Individuals who are able to clear HBV infection spontaneously following an acute infection display a vigorous, polyclonal HBV-specific CD8+ and CD4+ T cell response {Rehermann 2005}. In contrast, CHB is associated with a limited and dysfunctional CD8+ T cell response as well as impaired NK cell antiviral function {Peppa 2010, Rehermann 2005}. Various mechanisms have been identified which may play a role in immune dysfunction in CHB, including inefficient T cell priming, persistent antigen presentation leading to T cell "exhaustion", immunosuppressive cell types (e.g. T regulatory cells and myeloid derived suppressor cells) and cytokines (e.g. IL-10 and TGF-β), NK cell-mediated killing of antiviral T cells, as well as intrahepatic regulation of T cell metabolism by arginase 1 and indoleamine 2,3-dioxygenase 1 (IDO1) {Debes 2015, Maini 2010, Peppa 2013, Protzer 2012}.

GS-9992, also known as SB 9200, is a dinucleotide prodrug being developed as an oral antiviral agent for the treatment of chronic hepatitis infections. GS-9992 has a dual mechanism of action involving: (a) selective activation of the host cytosolic proteins – retinoic acid-inducible gene 1 (RIG-I) and nucleotide-binding oligomerization domain-containing protein 2 (NOD-2), which are involved in recognition of viral nucleic acids that result in the stimulation of interferon (IFN) production and induction of antiviral state in infected cells, and (b) direct inhibition of viral replication by blocking the access of the viral polymerase to the viral nucleic acid template. This is due to the interaction of GS-9992 with the nucleotide-binding domain of RIG-I and NOD-2 that sterically hinders the axis of viral polymerase to the viral ribonucleic acid (RNA) template. The stimulation of IFN production by GS-9992 also causes the induction of these innate immune responder genes, RIG-I and NOD-2, by a feed-back loop and further potentiates the antiviral activity.

1.2. GS-9992 (SB 9200)

GS-9992, also known as SB 9200, is being developed for use in combination with approved antiviral agents for HBV. Upon oral administration, the prodrug GS-9992 is converted to the active dinucleotide metabolite (SB 9000) by esterases. It is to be noted that GS-9992 is a mixture of 2 isomers, designated as Rp-SB 9000 and Sp-SB 9000. Both isomers have been shown to have similar activity. There is no evidence of any interconversion of the isomers in vitro or in vivo, but both prodrug isomers are converted to the active form at the same rate. In vitro studies using liver microsomes from different species and in vivo studies in both rodents and woodchucks have demonstrated that GS-9992 is not subject to Phase 1 metabolism or Phase 2 conjugation reactions and is eliminated predominately in the urine as the intact dinucleotide. Currently, there is no evidence that GS-9992 would have any drug-to-drug interactions with currently approved oral direct-acting antivirals (DAAs) for HBV.

1.2.1. General Information

Please refer to the SB 9200 Investigator's Brochure for further information on GS-9992 (SB 9200), including:

- In Vitro Anti-Hepatitis B Virus Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.2.2. Clinical Trials of GS-9992

Phase 1 Clinical Studies

The completed Phase 1 study (SB12-9200-101) evaluated the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of GS-9992 up to 900 mg in treatment-naive HCV-infected adults. The study was conducted in 2 parts: 1) a single ascending dose under fed or fasting conditions (Part A) and 2) a placebo-controlled multiple ascending dose under fasting conditions (Part B).

In Part A, single ascending doses of GS-9992 at doses of 100 to 800 mg were given as monotherapy. For subjects in whom GS-9992 was detectable (200, 400, and 800 mg GS-9992), no clear difference in the time to maximum analyte concentration (T_{max}) for the parent compound GS-9992 was observed following dosing in either the fed or fasted conditions. Due to the sparse data available, it was not possible to conclude whether food had any effect on either maximum analyte concentration (C_{max}) or area under the concentration versus time curve (AUC) for GS-9992 and its metabolites. The parent compound was rapidly cleared from the plasma with a mean half-life (t1/2) ranging from 1.16 to 1.42 hours. The metabolites Sp-SB 9000 and Rp-SB 9000 remained in the circulation much longer with a mean t1/2 ranging from 5.88 to 19.3 hours and 2.62 to 8.84 hours, respectively.

In Part B, multiple ascending doses of GS-9992 at doses of 200 to 900 mg were given QD as monotherapy for up to 7 days. There was a lack of measurable GS-9992 concentrations at the lowest dose level tested (200 mg). Based on dose-normalized area under the analyte concentration versus time curve from time zero to the last quantifiable time point (AUC0-t) and C_{max}, the exposure of GS-9992 appeared to increase in a dose proportional manner when GS-9992 was increased from 400 to 900 mg on Days 1 and 7.

Based on dose-normalized AUC0-t and C_{max}, taking into consideration the high intersubject variability in the exposure of the metabolites Sp-SB 9000 and Rp-SB 9000, increases in AUC0-t and C_{max} appeared to be dose proportional when GS-9992 oral doses were increased from 200 to 900 mg. GS-9992 was rapidly (t1/2 approximately 1 hour) cleaved into 2 metabolites via an esterase mediated process. The t1/2 of the metabolites were between 5 and 9 hours, an important distinction as it is the metabolites that contribute to the antiviral activity in the liver.

For the parent compound, the t1/2 was relatively short and ranged from 0.684 hours to 1.07 hours, while the t1/2 was slightly longer for the metabolites. Mean plasma Sp-SB 9000 t1/2 ranged from 4.65 to 8.90 hours on Days 1 and 7. Mean plasma Rp-SB 9000 t1/2 ranged from 4.31 to 5.94 hours on Days 1 and 7. Mean peak GS-9992 plasma concentrations and the area under the analyte concentration versus time curve from time zero extrapolated to 24 hours (AUC0-24) were consistently higher on Day 7 (mean C_{max} range: 0.885 to 6.66 ng/mL and mean AUC0-24 range: 0.770 to 13.7 ng•h/mL) compared with Day 1 (mean C_{max} range: 0.531 to 3.75 ng/mL and mean AUC0-24 range: 0.512 to 7.91 ng•h/mL). The time to peak plasma of GS-9992 concentration levels was similar after single or multiple oral doses of GS-9992 administration with median T_{max} ranging from 1.00 to 1.51 hours on Day 1 and 1.00 to 1.28 hours on Day 7.

Mean peak plasma Sp-SB 9000 concentrations across all dose levels were comparable between Day 7 (range: 7.13 to 16.5 ng/mL) and Day 1 (range: 7.76 to 22.0 ng/mL). The time to peak plasma Sp-SB 9000 concentration levels appeared slightly longer after single administration compared with multiple administrations with median T_{max} ranging from 4.32 to 7.51 hours on Day 1 and from 1.50 to 4.23 hours on Day 7. Mean peak plasma concentrations across all dose levels were comparable between Day 7 (range: 4.85 to 14.7 ng/mL) and Day 1 (range: 4.32 to 12.6 ng/mL). For the metabolites, based on the mean accumulation factor R (AUC) across dose levels for Sp-SB 9000 (i.e., from 1.39 to 1.61) and Rp-SB 9000 (i.e., 1.24 to 1.51), a low to moderate accumulation of Sp-SB 9000 and Rp-SB 9000 was observed following repeated QD oral dosing of GS-9992 for 7 days.

There were no relationships between GS-9992 or its metabolites and AUC0-t, the area under the plasma concentration-time curve from time zero to the end of the dosing interval (AUC0-τ), or the minimum drug concentration after dosing (C_{min}) and maximum suppression of HCV RNA. A significant relationship between GS-9992 C_{max} at steady state and maximum suppression of HCV RNA on Day 7 was observed ($p = 0.015$) after exclusion of 2 subjects with extreme C_{max} values for GS-9992. GS-9992 was generally well tolerated in both parts of the study. The most frequently reported treatment-emergent adverse event (TEAE) following multiple dosing with GS-9992 was headache (12 events reported by 10 subjects). Headache was mild and self-limited. Diarrhea, nausea, ALT increase, AST increase, and insomnia were reported for 2 subjects each. The ALT/AST elevations on treatment were less than 5 × the upper limit of normal (ULN), all occurred after treatment had been completed and no subject had hyperbilirubinemia.

Phase 2 Clinical Studies

GS-9992 (SB 9200) is currently being evaluated in the ACHIEVE trial (SBP-9200-HBV-201), a double-blind, placebo-controlled Phase 2 study in HBV treatment-naïve patients to identify the optimal dose of GS-9992 as both monotherapy and in combination with tenofovir DF 300mg daily. Enrollment was completed in South Korea, Taiwan, Hong Kong, and Canada. GS-9992 doses were administered one hour before or one hour after meals with approximately 240 ml of water.

Preliminary safety data from all cohorts in the ACHIEVE trial evaluating GS-9992 25mg, 50mg, 100mg, and 200mg for 12 weeks are provided below. Primary end points were safety and antiviral response defined by reduction in HBV DNA at Week 12.

Preliminary Safety

In the Ph 2 study (SBP-9200-HBV-201 [ACHIEVE]) in CHB patients at doses between 25 and 200 mg dosed daily for 12 weeks, all TEAEs were mild to moderate, and the majority were judged as unrelated to study drug administration by the investigator. There were no flu-like events, IFN-like side effects or non-specific immune side effects. At 200 mg there was a single SAE of hospitalization for knee pain which was considered unrelated by the investigator. Three placebo and 6 active patients had ALT flares as defined by elevation of ALT >5 X ULN or 2X nadir, which were considered AEs of special interest. ALT flare was the only Grade 3 laboratory abnormality noted with the exception of one subject who had a Grade 3 triglyceride elevation, which was not confirmed with repeat testing. No ALT flare was associated with a significant increase in bilirubin or INR or a decrease in albumen. No subjects with ALT flare met Hy's law defined as ALT >3xULN AND total bilirubin >2xULN. In the active arm, flares were associated with a reduction in HBV DNA and were considered immune flares. One patient who's ALT went above 10X ULN had inarigivir dosing discontinued at Week 4, with a switch to tenofovir disoproxil fumarate as per protocol. In 2 placebo patients, one ALT flare was secondary to a reversion from HBeAg negative to positive with an increase in HBV DNA by 1 log10 and the second flare was consistent with natural fluctuations of ALT in HBV patients. There were no other Grade 3 or 4 changes in hematology or biochemistry at the time of the flares. Additional data per Cohort are provided below

In Cohort 1 (25mg) there were Male 12: Female 8, mean age 40.5 years with 18 Asians and 2 Caucasians. 11 were HBeAg-positive and 9 HBeAg-negative, genotype A 2, B 9, C 7 and D 2. Baseline viral burden was higher in HBeAg+ (mean HBV DNA 7.1 $\log_{10}$; mean quantitative HBsAg 4.38 $\log_{10}$) compared to the HBeAg- patients (mean HBV DNA 5.5 $\log_{10}$; mean quantitative HBsAg 3.18 $\log_{10}$). There were no clinical, hematological or biochemical SAEs and no interferon-like side effects. 11 patients had treatment-emergent AEs and there was no notable difference in the number or type of AEs between GS-9992 or placebo patients with the most common (20%) being non-specific GI complaints of constipation, abdominal pain, nausea and diarrhea. All AEs were graded mild to moderate. Three patients had ALT flares > 200 IU. Two placebo patients had viral flares including an HBeAg-neg reversion to HBeAg-pos; the other flare was immune related at week 4 in a patient on GS-9992 who had an associated 2.32 $\log_{10}$ reduction in HBV DNA and a 1.01 $\log_{10}$ reduction in HBsAg. All 3 patients were dose-reduced to every other day.

In Cohort 2 (50mg), all subjects were Asian. Subjects administered GS-9992 50mg were primarily HBeAg positive (68.8%, n=11) and male (87.5%, n=14). The average age was 39.7 years old (SD = 11.80, range 19-61), and the average BMI at baseline was 23.88 (SD = 4.440, range 17.0-31.1). The median treatment duration was 12.10 weeks with range (0.3-12.3) weeks and the average daily dose was 46.21 mg (SD: 5.117; range [35-50]). Two subjects had dose modifications due to adverse event and 1 due to the subject decision. Eleven subjects (68.8%) had at least one TEAE. The most commonly reported (>1 subjects) TEAE were headache (n=2), fatigue (n=2), ALT (n=2) and AST elevations (n=2). Four subjects (25.0%) had at least one TEAE related to study treatment. Two subjects had at least 1 TEAE leading to discontinuation of the study treatment. One subject discontinued study treatment,

GS-9992, due to a TEAE of elevated ALT > 10 ULN and switched to tenofovir with resolution. The second patient withdrew from the study and discontinued study treatment at Week 2 due to a TEAE of a mild headache.

Two subjects (12.3%) had a Grade 3 ALT increase. Overall, 4 subjects (25.0%) had ALT > 3xULN, 2 subjects (12.5%) had ALT > 5ULN and 1 subject (6.3%) had ALT 10xULN. Two subjects (12.5%) had AST > 3xULN and no subjects had abnormal alkaline phosphatase or total bilirubin values. Subjects administered placebo were 50% HBeAg positive (n=2) and male (n=2) with an average age of 34.5 (SD = 11.62, range 18-45), and an average BMI at baseline of 22.50 (SD = 1.224, range 20.8-23.6). The median treatment duration on study was 12.08 weeks with range (12.0-12.1) weeks. No subjects had dose modification or dose reduction. Three subjects (75%) had at least one TEAE and 1 subject (25%) had at least one TEAE related to study treatment. No TEAE was reported in >1 subject, however, ALT and AST elevations was also reported in 1 PBO subject. No TEAE leading to discontinuation of study treatment were observed in the placebo arm. Two subjects (50.0%) had ALT > 3xULN and no subjects had abnormal AST, abnormal alkaline phosphatase or total bilirubin values.

In Cohort 3 (100mg), 19 subjects were Asian. Subjects administered GS-9992 100mg were primarily HBeAg positive (76.5%, n=13) and male (58.8%, n=10), with an average age of 36.7 years old (standard deviation = 7.48, range 23-51) and an average BMI at baseline of 26.28 (standard deviation (SD) = 5.043, range 18.2-33.9). The median treatment duration was 12.10 weeks with range (11.7-12.6) weeks and the average daily dose was 94.29 mg (SD: 8.809; range [74-100]). One subject (5.9%) had a dose reduction due to elevated ALT. Ten subjects (58.8%) had at least one TEAE and 3 subjects (17.6%) had at least one TEAE related to study treatment. The most commonly reported (>1 subject) TEAE was headache (n=2), influenza-like illness (n=2), and upper respiratory infection (n=2). No TEAE leading to discontinuation of study treatment were observed. One subject (5.9%) had Grade 3 ALT elevation and 1 subject (5.9%) had a transient Grade 3 hypertriglyceridaemia. Five subjects (29.4%) had ALT > 3xULN and 2 subjects (11.8%) had ALT > 5xULN. Three subjects (17.6%) had AST > 3xULN. No subjects had abnormal alkaline phosphatase or total bilirubin values. Of 3 subjects administered placebo two were HBeAg positive and one was male with an average age of 44.3 (standard deviation = 15.95, range 31-62) and average BMI at baseline of 23.14 (SD = 4.089, range 18.5-26.2). The median duration on study was 12.10 weeks (range 11.9-12.3 weeks). No subject had a dose modification or dose reduction. Two subjects (66.7%) had at least one TEAE and none were related to study treatment. No TEAE was reported in >1 subject, however, influenza-like illness was also reported in 1 PBO subject. No TEAE leading to discontinuation of study treatment were observed. No subjects had increase in ALT, AST, abnormal alkaline phosphatase or total bilirubin values.

In Cohort 4 (200mg), the preliminary demographics of first 15 subjects (12 active and 3 placebo) enrolled showed all were Asian and included equal proportion of HBeAg positive and negative CHB patients. Majority were female (60%, n=9), with an average age of 50.4 years old (range 24-64). These 15 subjects all completed 12 weeks of treatment with GS-9992 200 mg monotherapy. No subjects required dose modification or discontinuation. Eight of 15 subjects (73.3%) had at least one TEAE and none had a TEAE considered related to study treatment by the investigators. The most commonly reported (>1 subject) TEAE in the subjects was influenza

like illness (n=2) in 1 subject on active and 1 subject on placebo. 2 subjects had a clinically significant laboratory abnormality noted: 1 subject had an ALT elevation >5xULN at Week 2 that decreased to <5xULN by Week 5 while on treatment and 1 subject had a transient increase in AST >2x nadir at Week 4 that resolved by Week 6 on treatment. There was also, 1 SAE of a bilateral knee pain that required hospitalization for surveillance reported; the SAE was not considered related to study drug by the investigator. No other notable safety events have been observed.

Preliminary Efficacy

Cohort 1, at week 12, mean change in HBV DNA was -0.58 $\log_{10}$ IU/mL in GS-9992 compared to +0.37 $\log_{10}$ IU/mL in placebo patients (p = 0.014). HBV DNA reduction was greater in GS-9992 - treated HBeAg-negative patients (mean -0.86 $\log_{10}$ IU/mL) compared to HBeAg-positive patients (mean -0.37 $\log_{10}$ IU/mL). Overall 5 of 16 patients (31%) had a maximal >0.5 $\log_{10}$ IU/mL reduction in HBsAg (range 0.52 – 1.01 $\log_{10}$ IU/mL).

Cohort 2, at week 12, mean change in HBV DNA was -0.61 $\log_{10}$ IU/mL in HBeAg positive and -1.05 $\log_{10}$ IU/mL in HBeAg negative subjects administered GS-9992 compared to +0.33 $\log_{10}$ in placebo patients. Change in mean HBV RNA decline at week 12 was -0.46 $\log_{10}$ IU/mL in HBeAg positive and -3.15 $\log_{10}$ IU/mL in HBeAg negative subjects administered GS-9992 compared to +0.0.48 $\log_{10}$ IU/mL in placebo patients.

Cohort 3, at week 12, mean change in HBV DNA was -0.55 $\log_{10}$ IU/mL in HBeAg positive and -2.26 $\log_{10}$ IU/mL in HBeAg negative subjects administered GS-9992 compared to +0.25 $\log_{10}$ in placebo patients. Change in mean HBV RNA decline at week 12 was -0.49 $\log_{10}$ IU/mL in HBeAg positive and -3.2 $\log_{10}$ IU/mL in HBeAg negative subjects administered GS-9992 compared to +0.04 $\log_{10}$ IU/mL in placebo patients.

Additional details on GS-9992 are provided in the Investigator's Brochure (IB) for SB 9200.

1.2.3. Preclinical Pharmacology and Toxicology

The in vitro and in vivo studies conducted to date indicate that orally administered GS-9992 should be well tolerated. In a dose-range finding study in monkeys, GS-9992 was administered orally at 500 mg/kg/day for 4 consecutive days and the compound was clinically well tolerated with no overt toxicity except for up to a 2-fold elevation in alanine aminotransferase (ALT) and a 6 fold elevation in aspartate aminotransferase (AST) levels, which were reversible following cessation of dosing. In a 2-week repeat-dose toxicity and toxicokinetic study in monkeys, GS 9992 produced no adverse effects in the toxicological endpoints evaluated in this study at oral doses up to and including 360 mg/kg/day. Clinical chemistry changes on Day 10 and at termination consisted of increased ALT (up to 301%) and increased triglycerides (up to 118%) in males administered 360 mg/kg/day. These findings had generally resolved by the recovery interval. No changes were observed in females administered 360 mg/kg/day. In a single dose cardiovascular study in cynomolgus monkeys, oral administration of GS-9992 produced no effects on cardiovascular function at doses up to and including 500 mg/kg. Safety pharmacology studies in rats to evaluate pulmonary and central nervous system (CNS) function also

demonstrated no effects of GS-9992, at doses as high as 500 mg/kg, on any respiratory or neurophysiological endpoints.

Long-term toxicity was evaluated in a 13-week repeat-dose study with a 4-week recovery period. In this study, the potential subchronic toxicity of GS-9992 in cynomolgus monkeys was evaluated. In addition, the study included an evaluation of reversibility, progression, or delayed appearance of any observed changes following the 4-week postdose observation period. Animals were administered GS-9992 at 0, 90, 180, and 360 mg/kg once daily (QD). Dose-limiting toxicity (DLT) was observed at 360 mg/kg/day. Although several of the clinical chemistry and histopathological findings were reversible, the constellation of microscopic findings in the liver at the terminal and recovery necropsy, in conjunction with the increased liver enzyme values, were considered adverse in females at ≥ 90 mg/kg/day and males at ≥ 180 g/kg/day.

Accordingly, oral administration of GS-9992 produced adverse effects in females at all dose levels evaluated and males at doses ≥ 180 mg/kg/day. Although no observed adverse effect level (NOAEL) could be established for females in this study; the NOAEL for males was determined to be 90 mg/kg/day. A second study was conducted in cynomolgus monkeys that were administered GS-9992 daily at doses of 0, 15, 30, or 60 mg/kg/day for 13 weeks with a 4-week recovery period for the high dose group.

Assessment of toxicity was based on mortality, clinical observations, body weight, ophthalmoscopic, and electrocardiographic examinations; and clinical and anatomic pathology. The liver was the primary target organ with a constellation of microscopic findings. At doses of ≥ 30 mg/kg/day, there were dose-dependent findings of hepatocyte enlargement, hepatocyte vacuolar degeneration, mixed leukocyte infiltration/inflammation, and increased pigmentation and hypertrophy of Kupffer cells. Additional microscopic findings at 60 mg/kg/day included individual hepatocyte necrosis, increased mitotic figures, multinucleated hepatocytes, and bile duct hyperplasia. Following the recovery period, the findings at 60 mg/kg/day were reversing, although incomplete. These microscopic findings were supported by the alterations in the clinical chemistry parameters. The constellation of microscopic findings in the liver at the terminal and recovery necropsies, in conjunction with increased serum enzyme values and decreased serum albumin and fibrinogen values (changes generally associated with hepatocellular injury), were considered adverse in both sexes at ≥ 30 mg/kg/day. Accordingly, oral administration of GS 9992 produced adverse effects in both sexes at ≥ 30 mg/kg/day; therefore, the NOAEL was determined to be 15 mg/kg/day.

In a GLP 39-week oral gavage toxicity study, cynomolgus monkeys were administered inarigivir at doses of 0, 5, 10, 15, or 20 mg/kg/day for 39 weeks or at doses of 30 or 60 mg/kg three times weekly for 39 weeks. In animals that survived their scheduled termination, the oral administration of SB 9200 once daily at doses of 5, 10, 15, and 20 mg/kg/day or tri-weekly at 30 mg/kg/day was well tolerated and did not result in any signs of overt toxicity. Microscopic changes in animals administered tri-weekly at 30 mg/kg/day were noted in the liver, which included minimal hepatocellular single cell necrosis and minimal mixed cell infiltrate in 7/8 animals, and minimal intracellular hemosiderin pigment in 1/8 animals. However, there were no adverse events found in animals administered doses at or lower than 20mg/kg/day, therefore the

NOAEL in this study was judged to be 20 mg/kg/day. This study is still in the reporting phase and the toxicokinetic parameters have not yet been reported. However, the microscopic findings in the liver at 30 mg/kg dosed TIW was consistent with previous studies and lack of findings at 20 mg/kg/day was similar to the results in the 13 week study in cynomolgus monkeys where no findings were observed at the 15 mg/kg/day dose level.

Additional details of the nonclinical studies for GS-9992 are provided in the Investigator's Brochure (IB) for SB 9200.

1.3. TAF (GS-7340)

Vemlidy®, (GS-7340) (2:1) is a novel oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HIV-1 reverse transcriptase (RT) and HBV reverse transcriptase (HBV RT) that terminates the elongation of the viral DNA chain.

For further information on TAF (GS-7340), please refer to the current Investigator's Brochure for TAF.

1.3.1. General Information

Please refer to the TAF (GS-7340) Investigator's Brochure for further information on TAF, including:

- In Vitro Anti-Hepatitis B Virus Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.3.2. Clinical Trials of TAF

Overall, approximately 2403 subjects have been enrolled in the TAF clinical program, of which approximately 1856 subjects have received Vemlidy single agent (439 healthy volunteers, 1331 CHB infected subjects, and 86 HIV-1 infected subjects). The TAF clinical development program for CHB includes 2 ongoing Phase 3 studies in HBeAg-negative and HBeAg-positive subjects with CHB, a completed Phase 1b antiviral activity and safety/tolerability study in subjects with CHB, and a comprehensive Phase 1 program that also included evaluations of TAF and TFV PK in subjects with impaired renal or hepatic function (additional information is provided in the IB).

In some studies, TAF was administered as a single agent or as part of the F/TAF, FTC/RPV/TAF, or E/C/F/TAF FDC tablets.

TAF clinical studies which are currently ongoing are listed below:

- **GS-US-320-1092**, a Phase 2/3 Study to Evaluate the Pharmacokinetics, Safety, and Antiviral Efficacy of TAF in Adolescents with Chronic Hepatitis B Virus Infection (ongoing)
- **GS-US-320-3912**, a Phase 2 Study to Evaluate the Efficacy and Safety of TAF versus TDF 300 in Subjects with CHB and Stage 2 or Greater Chronic Kidney Disease who have received a Liver Transplant(ongoing)
- **GS-US-320-4018**, a Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Switching from Tenofovir Disoproxil Fumarate (TDF) 300 mg QD to Tenofovir Alafenamide (TAF) 25 mg QD in Subjects with Chronic Hepatitis B who are Virologically Suppressed (ongoing)
- **GS-US-320-4035**, A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of Switching to Tenofovir Alafenamide (TAF) from Tenofovir Disoproxil Fumarate (TDF) or Other Oral Antiviral Treatment (NUC) in Virologically Suppressed Chronic Hepatitis B (CHB) Subjects with Renal Impairment and/or Hepatic Impairment (ongoing)

Please refer to the latest version of the Investigator's Brochure for TAF for further information on the clinical program.

An overview of the ongoing 2 Phase 3 studies evaluating the efficacy and safety of TAF in Marketing Applications is provided in Table 1-1. The Phase 3 studies are described below as follows:

- **GS-US-320-0108:** This ongoing Phase 3, randomized, double-blind, non-inferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for 48 weeks for the treatment of CHB infection in treatment-naive and treatment-experienced HBeAg-negative subjects.
- **GS-US-320-0110:** This ongoing Phase 3, randomized, double-blind, non-inferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for 48 weeks for the treatment of CHB infection in treatment-naive and treatment-experienced HBeAg-positive subjects.

In both of these similarly designed non-inferiority studies, subjects were randomized in a 2:1 ratio to receive either TAF 25 mg or TDF 300 mg once daily for 96 weeks. Randomization was stratified by plasma HBV DNA level (< 7, ≥ 7 to < 8, and ≥ 8 $\log_{10}$ IU/mL for Study GS-US-320-0108; < 8 and ≥ 8 $\log_{10}$ IU/mL for Study GS-US-320-0110) and NUC treatment status (treatment naive vs treatment experienced) at screening. In both studies, all subjects completing at least 96 weeks of double-blind therapy are eligible to continue open-label treatment with TAF 25 mg for an additional 48 weeks. Both protocols were amended in February 2016 (Amendment 3 of GS-US-320-0108 and GS-US-320-0110) to extend the double-blind period to 144 weeks (3 years) and the open-label phase from Week 144 to Week 384 (8 year total study period).

Table 1-1. Clinical Studies to Support Efficacy for the TAF Marketing Applications

Study	Study Design	Treatment Regimen (Number of Subjects)	Primary Endpoint Analysis
GS-US-320-0108	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-negative subjects with CHB	TAF 25 mg once daily (N = 285) TDF 300 mg once daily (N = 140)	Week 48 efficacy, PK, and safety
GS-US-320-0110	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-positive subjects with CHB	TAF 25 mg once daily (N = 581) TDF 300 mg once daily (N = 292)	Week 48 efficacy, PK, and safety

Demographic and disease characteristics were generally similar between the TAF and TDF groups in both studies and are representative of patient population of HBeAg-negative subjects in Study GS-US-320-0108 and HBeAg-positive subjects in Study GS-US-320-0110. In both studies the majority of subjects were male (> 60%) and Asian (> 70%). As would be expected based on the 2 distinct study populations, subjects in Study GS-US-320-0108 were older (median age: 47 years; range: 19-80 years) than subjects in Study GS-US-320-0110 (median age: 36 years; range: 18-69 years). Differences in baseline characteristics between the 2 studies included HBV DNA levels (median levels were 5.7 and 7.9 $\log_{10}$ IU/mL for GS-US-320-0108 and GS-US-320-0110, respectively), serum ALT levels (median values were 67 and 85 U/L for GS-US-320-0108 and GS-US-320-0110, respectively), and number of years positive for HBV (6.0 and 4.0 years [median values] for GS-US-320-0108 and GS-US-320-0110, respectively). The distribution of HBV genotypes was similar between treatment groups in both studies with the most common genotypes being C (46.1%), D (24.3%), and B (20.4%).

Efficacy of TAF in Subjects with CHB

Primary Endpoint Analysis

For both studies, the primary efficacy endpoint was the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48. Table 1-2 presents HBV DNA outcomes for Studies GS-US-320-0108 {Buti 2016} and GS-US-320-0110 {Chan 2016} for subjects at Week 48. In both studies, similar rates of HBV DNA suppression were achieved in the 2 treatment groups when assessed using the M = F method at Week 48 for the Full Analysis Set (FAS). The percentages of subjects with HBV DNA levels < 29 IU/mL at Week 48 were as follows:

- **Study GS-US-320-0108:** TAF 94.0%, TDF 92.9%; difference in proportions (baseline stratum-adjusted): 1.8%, 95% CI: −3.6% to 7.2%
- **Study GS-US-320-0110:** TAF 63.9%, TDF 66.8%; difference in proportions (baseline stratum-adjusted): −3.6%, 95% CI: −9.8% to 2.6%

In both studies, because the lower bound of the 2-sided 95% CI of the difference (TAF − TDF) in the response rate was greater than the prespecified −10% margin, the TAF group met the primary endpoint of non-inferiority to the TDF group.

Table 1-2. GS-US-320-0108 and G -US-320-0110: HBV DNA Outcome at Week 48 Using HBV DNA of < 29 IU/mL, Missing = Failure (Full Analysis Set)

	GS-US-320-0108		GS-US-320-0110	
	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)
HBV DNA < 29 IU/mL	268 (94.0%)	130 (92.9%)	371 (63.9%)	195 (66.8%)
P-value[a]	0.47		0.25	
Difference in Proportions (95% CI)[b]	1.8% (−3.6% to 7.2%)		−3.6% (−9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	7 (2.5%)	4 (2.9%)	183 (31.5%)	88 (30.1%)
No Virologic Data at Week 48	10 (3.5%)	6 (4.3%)	27 (4.6%)	9 (3.1%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	1 (0.2%)	0
Discontinued Study Drug Due to AE/Death	3 (1.1%)	1 (0.7%)	6 (1.0%)	3 (1.0%)
Discontinued Study Drug Due to Other Reasons[c]	6 (2.1%)	4 (2.9%)	19 (3.3%)	6 (2.1%)
Missing Data During Window but on Study Drug	1 (0.4%)	1 (0.7%)	1 (0.2%)	0

a P-value for the superiority test comparing the percentages of HBV DNA < 29 IU/mL was from the CMH test stratified by baseline HBV DNA categories and oral antiviral treatment status strata.
b Difference in the proportion between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
c Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Source: GS-US-320-0108 Week 48 CSR, Section 15.1, Table 12; GS-US-320-0110 Week 48 CSR, Section 15.1, Table 12.

Serological Analyses

In Study GS-US-320-0108, no subject in either treatment group experienced HBsAg loss by Week 48. In Study GS-US-320-0110, 4 subjects (0.7%) in the TAF group and 1 subject (0.3%) in the TDF group experienced HBsAg loss at Week 48. Three of the 4 subjects in the TAF group and none in the TDF group also experienced HBsAg seroconversion at Week 48.

In Study GS-US-320-0110, the proportion of subjects with HBeAg loss or seroconversion to anti-HBe at Week 48 was also evaluated; these data are presented on Table 1-3. A total of 78 (13.8%) and 34 (11.9%) subjects in the TAF and TDF groups, respectively, had HBeAg loss at Week 48. A total of 58 (10.3%) and 23 (8.1%) subjects in the TAF and TDF groups, respectively, experienced HBeAg seroconversion at Week 48.

Table 1-3. GS-US-320-0110: Proportion of Subjects with HBeAg Loss or Seroconversion at Week 48, Missing = Failure (Serologically Evaluable Full Analysis Set)

	GS-US-320-0110			
			TAF 25 mg vs TDF 300 mg	
	TAF 25 mg (N = 565)	TDF 300 mg (N = 285)	p-value	Prop Diff (95% CI)
HBeAg Loss, n (%)	78/565 (13.8%)	34/285 (11.9%)	0.47	1.8% (−3.0% to 6.5%)
HBeAg Seroconversion, n (%)	58/565 (10.3%)	23/285 (8.1%)	0.32	2.1% (−2.0% to 6.3%)

P-values were from the Cochran-Mantel-Haenszel test stratified by baseline HBV DNA categories and oral antiviral treatment status. Differences in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion included subjects who were HBeAg positive and HBeAb negative/missing at baseline. HBeAg loss was defined as changes from HBeAg-positive at baseline to HBeAg-negative at a post-baseline visit with baseline anti-HBe negative/missing. HBeAg seroconversion was defined as HBeAg loss and anti-HBe change from negative/missing at baseline to positive at a post-baseline visit.
Source: GS-US-320-0110 Week 48 CSR, Section 15.1, Table 19.1

Virologic Resistance Analysis

In an integrated analysis of Studies GS-US-320-0108 and GS-US-320-0110, 24 subjects (2.8%) in the TAF group and 14 subjects (3.2%) in the TDF group qualified for population-based sequence analysis after up to 48 weeks of treatment. Among the 24 subjects in the TAF group who qualified for population-based sequence analysis, 15 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, and 5 had polymorphic site substitutions. Among the 14 subjects in the TDF treatment group who qualified for population-based sequence analysis, 6 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, 2 had polymorphic site substitutions, and 2 had a conserved site substitution. Overall, no HBV pol/RT amino acid substitutions associated with resistance to TFV were detected by sequencing and phenotypic analysis through 48 weeks of the study in either treatment group.

Safety of TAF in CHB Subjects

The principal sources of safety data for TAF are presented in Table 1-1 and consist of 2 Phase 3 studies in subjects with CHB, Study GS-US-320-0108 and GS-US-320-0110. Subjects included in the Safety Analysis Set received at least 1 dose of study drug.

Adverse Events for the TAF Phase 3 Safety Population

Summary of Adverse Events

Table 1-4 presents an overall summary of AEs by treatment group for the TAF Phase 3 Safety Population. Similar percentages of subjects in each treatment group had experienced at least 1 AE (TAF 70.2 %, 608 subjects; TDF 67.4%, 291 subjects) and had experienced at least 1 Grade 3 or 4 AE (TAF 4.5 %, 39 subjects; TDF 3.9 %, 17 subjects). In addition, 57 subjects (TAF 4.2%, 36 subjects; TDF 4.9 %, 21 subjects) had at least 1 SAE, with no subjects experiencing a treatment-related SAE. A similar percentage of subjects in each treatment group experienced an AE leading to discontinuation of study drugs (TAF 1.0%, 9 subjects; TDF 1.2%, 5 subjects). No deaths occurred in any subject on treatment. There were 2 deaths which occurred after treatment was discontinued and were considered non-treatment emergent (1 subject in each treatment group).

Table 1-4. GS-US-320-0108 and GS-US-320-0110: Overall Summary of Adverse Events in the TAF Phase 3 Safety Population (Safety Analysis Set)

Adverse Events	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Subjects Experiencing Any AE	608 (70.2%)	291 (67.4%)
Subjects Experiencing Any Grade 2, 3, or 4 AE	221 (25.5%)	120 (27.8%)
Subjects Experiencing Any Grade 3 or 4 AE	39 (4.5%)	17 (3.9%)
Subjects Experiencing Any Study Drug-Related AE	123 (14.2%)	68 (15.7%)
Subjects Experiencing Any Grade 2, 3, or 4 Study Drug-Related AE	33 (3.8%)	21 (4.9%)
Subjects Experiencing Any Grade 3 or 4 Study Drug-Related AE	6 (0.7%)	2 (0.5%)
Subjects Experiencing Any SAE	36 (4.2%)	21 (4.9%)
Subjects Experiencing Any Study Drug-Related SAE	0	0
Subjects Experiencing Any AE Leading to Premature Study Drug Discontinuation	9 (1.0%)	5 (1.2%)
Subjects Experiencing Any AE Leading to Dose Modification or Study Drug Interruption	17 (2.0%)	7 (1.6%)
Death[a]	0	0

a Treatment-emergent death refers to the death occurred between the first dose date and the last dose date (inclusive). Adverse events were mapped according to MedDRA Version 18.

Treatment-emergent AEs was defined as follows:
Any AEs with onset date of on or after the study drug start date and no later than the study drug stop date for those who discontinued study drug permanently, or
Any AE with an onset date on or after the study drugs start date for those who had not discontinued study drug permanently, or
Any AEs leading to study drug discontinuation
Source: TAF Week 48 ISS, Table 6

Common Adverse Events

Table 1-5 presents AEs reported for ≥ 5% of subjects for any treatment group by system organ class (SOC) and preferred term (PT) in the TAF Phase 3 Safety Population. The rate and types of AEs were similar in the 2 treatment groups. Overall, the 3 most frequently reported AEs by treatment group were as follows:

- **TAF group** — upper respiratory tract infection (9.9%, 86 subjects), nasopharyngitis (9.9%, 86 subjects), and headache (9.5%, 82 subjects)
- **TDF group** — headache (8.3%, 36 subjects), upper respiratory tract infection (7.4%, 32 subjects), and nasopharyngitis (7.2%, 31 subjects)

Table 1-5. GS-US-320-0108 and GS-US-320-0110: Adverse Events Reported for ≥ 5% of Subjects in Either Treatment Group in the TAF Phase 3 Safety Population (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c]	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Number of Subjects Experiencing Any Adverse Event	608 (70.2%)	291 (67.4%)
Gastrointestinal disorders	227 (26.2%)	108 (25.0%)
Nausea	43 (5.0%)	22 (5.1%)
General disorders and administration site conditions	125 (14.4%)	62 (14.4%)
Fatigue	49 (5.7%)	23 (5.3%)
Infections and infestations	259 (29.9%)	121 (28.0%)
Upper respiratory tract infection	86 (9.9%)	32 (7.4%)
Nasopharyngitis	86 (9.9%)	31 (7.2%)
Nervous system disorders	149 (17.2%)	60 (13.9%)
Headache	82 (9.5%)	36 (8.3%)
Respiratory, thoracic and mediastinal disorders	106 (12.2%)	44 (10.2%)
Cough	55 (6.4%)	27 (6.3%)

a Adverse events were mapped according to MedDRA Version 18.
b SOC were presented alphabetically, and PT was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: TAF Week 48 ISS, Table 7

Adverse Events by Severity

The majority of AEs reported in the TAF Phase 3 Safety Population were Grade 1 or 2. A similar percentage of subjects in each treatment group experienced at least 1 Grade 3 AE (TAF 4.5%, 39 subjects; TDF 3.9%, 17 subjects). No subjects in either group had a Grade 4 AE. The only Grade 3 AE that occurred in more than 2 subjects in either treatment group were increased ALT (TAF 0.6%, 5 subjects; TDF 0.7%, 3 subjects) and hepatocellular carcinoma (HCC) (TAF 0 subjects; TDF 0.7%, 3 subjects). Four Grade 3 ALT increases (TAF 3 subjects; TDF 1 subject) were assessed as related to study drug.

Serious Adverse Events

Table 1-6 presents SAEs reported for > 1 subjects for any treatment group in the TAF Phase 3 Safety Population. A similar percentage of subjects experienced SAEs in each treatment group (TAF 4.2%, 36 subjects; TDF 4.9%, 21 subjects). None of the SAEs were considered related to study drugs by the investigators. Hepatocellular carcinoma was reported for 6 subjects (TAF 0.1%, 1 of 866 subjects; TDF 1.2%, 5 of 432 subjects). Other SAEs reported in > 1 subject in either treatment group were cellulitis, hand fracture, dizziness, and calculus ureteric.

Table 1-6. GS-US-320-0108 and GS-US-320-0110: Serious Adverse Events by Treatment Regimen in > 1 Subject in the TAF Phase 3 Safety Population (Safety Analysis Set)

Preferred Term[a,b]	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Number of Subjects (%) Experiencing Any SAE	36 (4.2%)	21 (4.9%)
Hepatocellular carcinoma	1 (0.1%)	5 (1.2%)
Cellulitis	0	3 (0.7%)
Hand fracture	2 (0.2%)	0
Dizziness	2 (0.2%)	0
Calculus ureteric	2 (0.2%)	0

a Adverse events were mapped according to MedDRA Version 18.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: TAF Week 48 ISS, Table 14

Graded Laboratory Abnormalities

Most subjects participating in Studies GS-US-320-0108 and GS-US-320-0110 experienced at least 1 laboratory abnormality of Grade 1 or higher (TAF 94.8%, 814 of 859 subjects; TDF 91.1%, 390 of 428 subjects). The majority of subjects had abnormalities that were Grade 1 or 2 at worst severity (TAF 63.4%, 545 subjects; TDF 61.7%, 264 subjects). Grade 3 laboratory abnormalities occurred in 26.2% (225 subjects) in the TAF group and 22.4% (96 subjects) in the TDF group; Grade 4 laboratory abnormalities were less common, occurring in 5.1% (44 subjects) in the TAF group and 7.0% (30 subjects) in the TDF group. In total, a similar percentage of subjects in each group had at least 1 Grade 3 or 4 laboratory abnormality (TAF 31.3%, 269 subjects; TDF 29.4%, 126 subjects).

Table 1-7 presents a summary of the subject incidence of Grade 3 or 4 serum chemistry or urinalysis abnormalities reported for ≥ 1% in either treatment group for the overall TAF Phase 3 Safety Population. The only Grade 3 or 4 serum chemistry laboratory abnormality that occurred in > 5% of subjects overall in each of the treatment groups individually was ALT elevation (TAF 8.1%, 70 subjects; TDF 9.3%, 40 subjects). In the TDF group, Grade 3 or 4 elevations of AST also occurred in > 5% of subjects overall (TAF 3.3%, 28 subjects; TDF 5.4%, 23 subjects). Grade 3 urinalysis abnormalities included occult blood (TAF 7.7%, 66 subjects; TDF 7.0%, 30 subjects), urine erythrocytes (TAF 7.7%, 59 subjects; TDF 9.1%, 35 subjects), and urine glucose (TAF 4.8%, 41 subjects; TDF 1.2%, 5 subjects). The majority of subjects (88.6%; 124 of 140 subjects) who had Grade 3 urine occult blood or urine erythrocytes were women of child bearing potential (defined as age ≤ 54 years). The abnormalities were generally

asymptomatic and not associated with AEs; none of the events were considered related to study drugs. Among the 41 subjects in the TAF group with Grade 3 urine glucose on treatment, 18 subjects (43.9%) had Grade 3 urine glucose at either screening or baseline, while the majority of the remaining 23 subjects had a medical history relevant for diabetes mellitus and/or had a graded elevation in blood glucose, or experienced an isolated and transient occurrence of Grade 3 urine glucose.

Table 1-7. GS-US-320-0108 and GS-US-320-0110: Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group in the Overall TAF Phase 3 Safety Population (Safety Analysis Set)

	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Maximum Postbaseline Toxicity Grade (N)	859	428
Grade 3	225 (26.2%)	96 (22.4%)
Grade 4	44 (5.1%)	30 (7.0%)
Chemistry		
Alanine Aminotransferase (N)	859	428
Grade 3	52 (6.1%)	27 (6.3%)
Grade 4	18 (2.1%)	13 (3.0%)
Amylase (N)	859	427
Grade 3	22 (2.6%)	9 (2.1%)
Aspartate Aminotransferase (N)	859	428
Grade 3	25 (2.9%)	18 (4.2%)
Grade 4	3 (0.3%)	5 (1.2%)
Creatine Kinase (N)	859	428
Grade 3	16 (1.9%)	7 (1.6%)
Grade 4	9 (1.0%)	6 (1.4%)
Fasting Glucose (Hyperglycemia) (N)	857	425
Grade 3	9 (1.1%)	0
Fasting LDL Cholesterol (N)	837	417
Grade 3	37 (4.4%)	1 (0.2%)
Nonfasting Glucose (Hyperglycemia) (N)	856	426
Grade 3	25 (2.9%)	7 (1.6%)
Urinalysis		
Occult Blood (N)	859	426
Grade 3	66 (7.7%)	30 (7.0%)
Urine Erythrocytes (N)	768	386
Grade 3	59 (7.7%)	35 (9.1%)
Urine Glucose (N)	859	426
Grade 3	41 (4.8%)	5 (1.2%)

Denominator for percentage (N) is the number of subjects in the safety analysis set with at least 1 postbaseline laboratory value for the test.
Subjects were counted once for the maximum postbaseline severity for each laboratory test. For urinalysis (i.e., urine glucose, urine protein, and urine RBC), the highest grade is Grade 3.
For nonfasting glucose, the maximum postbaseline toxicity grades, instead of treatment-emergent abnormalities, were summarized, because nonfasting glucose test was not done at baseline.
'Hyper' means high and 'Hypo' mea ns low.
Source: TAF Week 48 ISS, Table 20

Hepatic Laboratory Abnormalities

In Studies GS-US-320-0108 and GS-US-320-0110 the incidence of graded hepatic laboratory abnormalities through the Week 48 data cutoff date was generally lower for subjects in the TAF group compared with subjects in the TDF group, and included ALT increased (TAF 22.8%,196 subjects; TDF 30.4%, 130 subjects), AST increased (TAF 22.2%, 191 subjects; TDF 25.2%, 108 subjects), total bilirubin increased (TAF 12.7%, 109 subjects; TDF 10.0%, 43 subjects), gamma-glutamyltransferase (GGT) increased (TAF 7.5%, 64 subjects; TDF 10.0%, 43 subjects), alkaline phosphatase increased (TAF 2.2%, 19 subjects; TDF 5.4%, 23 subjects), and albumin decreased (TAF 0.9%, 8 subjects; TDF 1.9%, 8 subjects).

Hepatic laboratory abnormalities in both treatment groups were generally Grade 1 or 2 at maximum severity; Grade 3 or 4 ALT abnormalities and Grade 3 or 4 AST abnormalities were observed in lower percentages of subjects in the TAF group compared with the TDF group (ALT: TAF 8.1%, 70 subjects; TDF 9.3%, 40 subjects; AST: TAF 3.3%, 28 subjects; TDF 5.4%, 23 subjects), while Grade 3 or 4 bilirubin elevations were observed in comparable percentages of subjects in the TAF group (0.3%, 3 subjects) compared with the TDF group (0.2%, 1 subject). Hepatic laboratory abnormalities were generally not associated with hepatic AEs.

Hepatic Flares

An ALT elevation was defined as treatment-emergent serum ALT > 2 × baseline value and > 10 × ULN, with or without associated symptoms. Through Week 48, ALT elevations were observed for 16 subjects (1.8%) in the TAF group and 9 subjects (2.1%) of subjects in the TDF group. Most of the events were at isolated time points within the first 8 weeks of dosing and resolved without recurrence while the subject remained on study drug. An ALT elevation that was confirmed at 2 consecutive post baseline visits was considered an ALT flare. The incidence of these events was balanced between the treatment groups. Five subjects (0.6%) in the TAF group and 4 subjects (0.9%) in the TDF group had a treatment-emergent ALT flare. With the exception of 2 events, ALT flares occurred early in the dosing period; for 7 of the 9 subjects, the ALT flares resolved without recurrence while the subject remained on study drug.

Metabolic Laboratory Parameters

Administration of TDF has been associated with lower fasting low-density lipoprotein (LDL) and high-density lipoprotein (HDL) as compared with other antiviral agents. As plasma TFV exposures are approximately 90% lower with TAF administration than with TDF, fasting lipid concentrations remained relatively stable through Week 48 in the TAF treatment group, while TDF administration resulted in the expected lipid-lowering TFV effect, with decreases from baseline in fasting lipid parameters observed in the TDF group. Median decreases from baseline in total cholesterol, LDL, HDL, and triglycerides were greater in the TDF group than the TAF group, with TDF subjects demonstrating reductions in all parameters at Week 48. The difference between groups in median change from baseline was statistically significant a Week 48 for total cholesterol, direct LDL, HDL, and triglycerides ($p < 0.001$). Median (Q1, Q3) changes from baseline at Week 48 for fasting lipid parameters were as follows:

- **Total cholesterol:** TAF −2 (−17, 17) mg/dL; TDF −24 (−42, −6) mg/dL
- **LDL:** TAF 4 (−9, 20) mg/dL; TDF −9 (−25, 5) mg/dL
- **HDL:** TAF −3 (−10, 2) mg/dL; TDF −9 (−17, −3) mg/dL
- **Triglycerides:** TAF 6 (−13, 26) mg/dL; TDF −7 (−27, 10) mg/dL

The median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.2 (−0.1, 0.5) in the TAF group and 0.2 (−0.2, 0.5) in the TDF group (p = 0.16 for the difference between treatment groups).

Eight subjects (0.9%) in the TAF group had Grade 3 elevated fasting cholesterol; 7 of the 8 subjects had a history of hyperlipidemia and/or elevated fasting cholesterol at baseline. There were no subjects with Grade 4 elevated fasting cholesterol in the TAF group, and none with Grade 3 or 4 elevated fasting cholesterol in the TDF group. Thirty-seven subjects (4.4%) in the TAF group and 1 subject (0.2%) in the TDF group had Grade 3 elevated fasting LDL. Overall, changes in median values of total cholesterol, LDL, HDL, and triglycerides in the TAF group were not clinically relevant, and none of the subjects with Grade 3 elevations in fasting lipids had clinical AEs associated with lipid abnormalities.

Please refer to the latest version of the Investigator's Brochure for TAF for further information on the clinical program.

1.4. Rationale for This Study

Given the low rate of HBsAg loss with currently available therapies and the treatment burden associated with life-long treatment to maintain viral suppression, there is a need to identify new therapies that may provide durable HBsAg loss with a finite treatment duration. The primary objective is to evaluate the safety, tolerability and efficacy of GS-9992 in association with an oral nucleotide (NUC) HBV polymerase inhibitor (TAF or other commercially available NUC) for the treatment of CHB subjects, while also evaluating the changes in HBV specific immune responses following treatment with GS-9992.

This Phase 2 study will be conducted in subjects with CHB, who are currently not receiving treatment for CHB (can be either treatment naïve or previously treated) or are virally-suppressed on a commercially available oral NUC. Viremic subjects with CHB generally have a rapid decline in viremia in response to beginning antiviral treatment. The decrease in viral burden may allow for an increased responsiveness to immune stimulation and forms the basis for the design of Groups 1-3 and 5 in this study. To further evaluate GS-9992 ability to improve immune response, an additional group, Group 4, will enroll virally-suppressed CHB subjects on a commercially available NUC. The immune responsiveness of CHB patients has been shown to improve in patients who are on chronic suppressive antiviral therapy with less antigen burden. Virally-suppressed patients will have lower levels of HBV virions and proteins, including HBsAg, within the serum as well as lower expression of HBV antigens within infected hepatocytes. Therefore Group 4 will evaluate the potential maximal efficacy benefits of GS-9992 in virally-suppressed CHB subjects.

Further, the safety data with GS-9992 in treatment naive subjects and in virally-suppressed subjects was evaluated in a Phase 1b study SBP-9200-101 and in the ongoing Phase 2 study SBP-9200-HBV-201. Both studies support the evaluation of GS-9992 in these populations. Subjects will be stratified by HBeAg status. HBeAg status has been shown in prior studies of TDF (GS-US-174-0102 and GS-US-174-0103) to be a predictor of eventual HBsAg loss with TDF treatment irrespective of HBV genotype.

1.4.1. Rationale for Dose Selection

GS-9992 for Groups 1-4

In a 3-month, repeat-dose toxicology study conducted in rat (50, 150, and 250 mg/kg/day) and monkey (15, 30, and 60 mg/kg/day), the NOAEL was determined to be 250 mg/kg for the rat and 15 mg/kg for the monkey. Thus, monkey was considered to be the most sensitive species and was used to designate the minimum recommended starting dose (MRSD) for clinical studies. The NOAEL in humans corrected for body surface area (equation 1) using the NOAEL from monkey (15 mg/kg) and the mean body weight of the monkeys in that dose group (2.9 kg) resulting in a human equivalent dose (HED) for the human equivalent NOAEL of 3.43 mg/kg. To allow for a 10-fold safety margin, a dose of 0.34 mg/kg was selected as the MRSD. This is equivalent to a dose of 24 mg to a 70 kg human. Thus, the starting dose for the clinical study in HBV patients is proposed to be 25 mg (or 0.36 mg/kg).

Equation 1: $HED = (\text{animal dose in mg/kg} * \text{body weight in kg})^{0.33}$

The MRSD chosen for the proposed clinical study is 25 mg to be incrementally increased up to 400 mg. These doses are expected to be effective against HBV in patients, based upon nonclinical studies. A dose of 9 mg/kg administered to a woodchuck model of hepatitis for 4 weeks was efficacious against hepatitis B infection as assessed by a decline in HBV DNA. In a subsequent study, a dose of 15 mg/kg/day for 12 weeks resulted in dose and time-related decline in HBV viral DNA that was at or near baseline values at the end of the study. In a transgenic HBV mouse model, a dose of 10 mg/kg produced statistically significant decline in HBV DNA. By correcting for body surface area, the human equivalent efficacious dose calculated from woodchuck efficacy studies ranged from 2.5 to 5 mg/kg (mean body weight 2.8 kg). The human equivalent efficacious dose calculated from the murine efficacy studies was 0.62 mg/kg (mean body weight of 0.034 kg). Since the proposed doses in the clinical study range from 25 mg up to 400 mg or 0.36 to 5.76 mg/kg in a 70 kg patient, it is reasonable to expect that this dose range will be therapeutically effective in HBV patients.

In the ongoing Phase 2 ACHIEVE trial, all subjects in Cohorts 1,2, 3, and 4 (n = 20/ cohort) have completed treatment with GS-9992 (SB 9200) 25 mg, 50mg, 100mg, and 200mg once daily monotherapy for 12 weeks. There were no clinical, hematological or biochemical SAEs and all AEs were graded mild to moderate in severity.

There were no interferon-like side effects, except for 3 subjects with mild AE of flu-like symptoms in Cohort 3, 1 of the 3 subjects was administered placebo. There were no dose proportional increases in the number or severity of treatment-emergent adverse events reported.

Overall, 6 subjects experienced an ALT flare >200 IU/mL, 2 subjects were on placebo; no subjects have met Hy's law.

GS-9992 50 mg and 100 mg monotherapy for 12 weeks demonstrated a mean change in HBV DNA of -0.61 log_{10} IU/mL and -0.55 log_{10} IU/mL in HBeAg positive subjects, respectively, and -1.05 log_{10} IU/mL and -2.26 log_{10} IU/mL in HBeAg negative subjects, respectively. The mean change in HBV RNA decline at week 12 was -0.46 log_{10} IU/mL and -0.49 log_{10} IU/mL in HBeAg positive and -3.15 log_{10} IU/mL and -3.2 log_{10} IU/mL in HBeAg negative subjects administered GS-9992 50 mg and 100 mg, respectively.

The safety and efficacy results from the Phase 2 ACHIEVE trial support further evaluation of the 50 mg and 100 mg dose of GS-9992 in combination with a NUC in this study. The 200mg GS-9992 monotherapy for 12 weeks is currently being evaluated in Cohort 4 in the ACHIEVE trial. Safety of the 200mg GS-9992 monotherapy has been confirmed by ACHIEVE trial's independent Data Safety Monitoring Board. To date, no safety concerns have been observed.

GS-9992 for Group 5 (400 mg)

GS-9992 (aka inarigivir and SB 9200), developed by Spring Bank Pharmaceuticals, is a prodrug of SB 9000, which consists of two diastereomers Rp-9000 and Sp-9000 for the treatment of hepatitis B virus (HBV) infection. *In vitro* and *in vivo* studies have established that both forms of SB 9200 have antiviral activity against HBV and HCV ribonucleic acid (RNA) viruses. Upon oral administration, both prodrug SB 9200 isomers are equivalently converted to their active dinucleotide metabolites SB 9000 by esterases. Phase 1 clinical testing is complete, and a 12-week Phase 2 study (SBP-9200-HBV-201) is currently ongoing in HBV-infected patients. The safety and pharmacokinetic profile of SB 9200 and its active diastereomer metabolites have been extensively characterized in healthy subjects and patients. Both the pharmacokinetic properties and accumulated pre-clinical and clinical safety of all active moieties of SB 9200 support extended administration of 400 mg in the target patient population (reference SB 9200 IB).

In vitro binding studies showed dose-dependent binding of SB 9200 and SB 9000 to RIG-1 and equipotent activity of Rp and Sp isomers of SB 9000. Additionally, in vitro, SB 9000 demonstrated a dose dependent reduction in viral replication in either primary human hepatocytes or HepG2.2.1.5 cells infected with HBV with EC50 ranging from 0.2 uM to 2 uM depending on treatment duration. To connect the inarigivir concentrations that were seen to be active in vitro to the clinical setting it is necessary to consider that inarigivir and SB 9000 are found to concentrate in the liver at levels greater than 20-fold as compared to the plasma as was shown in rat distribution studies and when inarigivir levels were measured in the rat following repeated administration. The plasma Cmax values of SB 9000 observed in the DDI study (SBP-9200-HBV-202) at 400 mg were 11.19 ng/ml and assuming similar concentrative activity of SB 9000 in the liver of humans as was observed in the rat there would be liver concentrations of SB 9000 of approximately 405 nM at the time of maximal concentration. Anti-viral activity of SB 9000 was observed in vitro in various test systems at concentrations below and above this value.

In vivo pharmacology studies following IP injection of 100 mg/kg/day showed significant reduction of viral DNA load in the liver of transgenic mice, with antiviral activity similar to that of adefovir.

The minimally effective dose in this model was 1 mg/kg. Similar studies conducted with oral SB 9200 showed the minimal effective dose to be between 1 and 10 mg/kg. Other, in vivo studies in naturally infected (WHV) woodchucks showed induction of RIG-1 in liver biopsies after 12 weeks treatment, with dose-dependent activity following 12 weeks of 15 and 30 mg/kg/day resulting in reduced surface antigen and serum WHV DNA; delayed viral relapse at higher dose; elevated IFN, RIG-1, NOD2; and significant reductions in hepatic viral DNA, RNA, cccDNA. Although the pharmacokinetics of SB 9000 were not measured in the pharmacology studies, the lowest doses of SB 9200 shown to have efficacy in these pharmacology models were 10 mg/kg/day in the mouse and 15mg/kg in the woodchuck, on the basis of body surface area, the human equivalent doses of either the mouse or the woodchuck would be adequately covered by a 400 mg/day dose in humans.

The pre-clinical and clinical profile of inarigivir supports its exploration as a potential treatment option for patients with HBV at 400 mg. The pre-clinical toxicology studies have consistently indicated that the monkey is the more sensitive species and that the liver is the sole target organ of inarigivir mediated toxicity. The exposure parameters Cmax and AUC(0-t) at the identified NOAEL in the longest term completed GLP toxicology study are 3.5 and 1.7-fold higher respectively than those observed when 400 mg was administered in the clinic. In all of the clinical studies conducted so far where doses between 25 and 900 mg have been administered daily for durations between 7 days and 12 weeks, the safety profile has been acceptable and there have been no changes in liver safety parameters that were independently associated with inarigivir, instead the changes in liver enzyme levels to date have been correlated with immune flares consistent with an ongoing HBV infection.

The clinical safety of a 400 mg daily dose of inarigivir in HCV patients has been tested in two different studies for durations of either 7 or 12 days and demonstrated a benign safety profile in each case. Additionally, inarigivir has been shown to be well tolerated at doses more than 2-fold greater than the target dose of 400 mg QD for 7 consecutive days. In the ongoing ACHEIVE Ph 2 study (SBP-9200-HBV-201), HBV patients have been administered up to 200 mg daily for 12 weeks with a similar benign safety profile as was observed in the shorter-term studies. The clinical pharmacokinetics of inarigivir and its primary active metabolites Sp-9000 and Rp-9000 have demonstrated predictable and linear PK over a dose range of 25-900 mg. Accumulation of its active metabolites is minimal following multiple dose administration and the change in exposure with dose is consistent with dose proportionality. In the Ph1 study (SB12-9200-101), a statistically significant relationship between SB 9200 Cmax at steady-state and maximum suppression of HCV RNA on Day 7 was observed ($p=0.015$). In the HCV trial (SB12-9200-101), the peak individual viral load drop was observed to improve from 1.5 to 1.9 log10 when the dose of SB 9200 increased from 200 to 400 mg. Further dose increases did not result in response increases. In the ongoing Ph 2 study (SBP-9200-HBV-201) in CHB patients, at doses between 25 and 100 mg there was an observed dose response in anti-viral clinical activity without an as yet observed plateau, indicating that higher doses could have increased levels of efficacy. This observation parallels with the observed dose proportionality of the plasma pharmacokinetics of inarigivir. Based on these observations it is proposed that a 400 mg daily dose administered to patients with HBV would lead to plasma and liver levels of inarigivir consistent with increased activity on the hepatitis B virus infection as well as a benign safety profile. To further ensure safety of the administration of GS-9992 400 mg plus TAF for 12 weeks in Group 5, safety data of 200mg GS-9992 plus TAF through Week 12 in all subjects enrolled in Group 3 will be confirmed by the Medical Monitor prior to enrollment of Group 5.

TAF

TAF 25 mg (Vemlidy®) is the marketed dose approved for the treatment of chronic hepatitis B infection in adults.

1.5. Risk/Benefit Assessment for the Study

GS-9992

GS-9992 is a new class of pharmaceuticals known as small molecule nucleic acid hybrids. GS-9992 is being developed to provide patients with CHB with a finite duration, curative treatment option and for beneficial antiviral response. GS-9992 has a dual mechanism of action involving: (a) selective activation of the host cytosolic proteins – retinoic acid-inducible gene 1 (RIG-I) and nucleotide-binding oligomerization domain-containing protein 2 (NOD-2), which are involved in recognition of viral nucleic acids that result in the stimulation of interferon (IFN) production and induction of antiviral state in infected cells, and (b) direct inhibition of viral replication by blocking the access of the viral polymerase to the viral nucleic acid template. This is due to the interaction of GS-9992 with the nucleotide-binding domain of RIG-I and NOD-2 that sterically hinders the axis of viral polymerase to the viral ribonucleic acid (RNA) template. The stimulation of IFN production by GS-9992 also causes the induction of these innate immune responder genes, RIG-I and NOD-2, by a feed-back loop and further potentiates the antiviral activity.

This stimulation results in the induction the innate immune response critical to achieve hepatitis B surface antigen (HBsAg) loss. The loss of HBsAg is the gold standard endpoint for anti-HBV therapy and allows for cessation of treatment {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 hepatocellular carcinoma 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 10% of patients achieve clearance of HBsAg with the therapeutic options currently available. Thus, new treatment options that enhance rates of HBsAg loss are needed. Through these effects on the innate and adaptive response and immune effectors and HBV-specific T cell and B cell responses, activation of retinoic acid inducible gene (RIG-I) and nucleotide-binding and oligomerization domain 2 (NOD2), may provide a novel component of treatment for patients with chronic HBV infection. The warnings and precautions for GS-9992 that may be relevant to a human population include observations of elevated AST and ALT in monkey studies and in the Phase 1 study (SB12-9200-101) in treatment-naïve HCV-infected adults. GS-9992 up to 900 mg was generally well tolerated in the study. The most frequently reported treatment-emergent adverse event (TEAE) following multiple dosing with GS-9992 was headache (12 events reported by 10 subjects). Headache was mild and self-limited. Diarrhea, nausea, ALT increase, AST increase, and insomnia were reported for 2 subjects each. The ALT/AST elevations on treatment were less than 5 × the upper limit of normal (ULN), all occurred after treatment had been completed and no subject had hyperbilirubinemia (see full details in the SB 9200 IB).

To minimize potential risks in the proposed study, patients will be required to have adequate hematologic function at study entry and sufficient hepatic reserve (F0-F2). The protocol will follow patient laboratory and vital sign changes routinely and allows for more frequent monitoring based on clinically significant changes. Also, specific parameters that would lead to dose interruption or discontinuation are included in Section 6.11.

In summary, the goal of the GS-9992 program is to address a major unmet need for CHB patients, namely to enhance rates of serum HBsAg loss with a finite duration treatment regimen. Study GS-US-464-4437 will investigate the efficacy of 50 mg, 200 mg, and 400 mg of GS-9992 administered orally once daily to patients with CHB currently not on treatment and 100 mg of GS-9992 in virally suppressed patients on a commercially available NUC. Patient safety will be carefully monitored by periodic safety assessments, and by implementation of stringent pre-defined stopping rules.

In view of the potential for developing GS-9992 as a finite-duration, curative treatment for CHB, the existing safety data and the GS-US-464-4437 study design defined to carefully monitor patient safety, the benefit/risk balance for this study is considered positive.

TAF

TAF 25 mg (Vemlidy®) has been approved globally for the treatment of CHB in adults. In adult subjects with CHB, a global Phase 3 program for TAF consisting of 2 prospective, randomized, active-controlled studies with 1 each in HBeAg-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) subjects is currently ongoing. Primary endpoint data shows that TAF is as effective as TDF for viral suppression at Week 48. In addition, renal and bone safety parameters were improved with TAF treatment relative to TDF. In a pooled analysis of both studies, patients receiving TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at week 48 ($p < 0.001$), and the median change in estimated glomerular filtration rate ($eGFR_{CG}$) from baseline to week 48 was less with TAF compared with TDF (-1.2 mL/min vs. −5.4 mL/min; $p < 0.001$). In addition, significantly smaller changes in biomarkers of bone turnover (bone formation markers: osteocalcin, bone-specific alkaline phosphatase, and procollagen type 1 N-terminal propeptide, and the bone resorption marker, C-type collagen sequence) and quantitative markers of proximal tubular function (beta-2 microglobulin to creatinine and retinol binding protein to creatinine ratios) were seen in TAF subjects compared with TDF subjects at Week 48.

For subjects receiving TAF, adult data from the Phase 3 studies indicates that TAF is safe and effective.

The benefit/risk for this study is therefore considered positive.

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:

- To evaluate the safety and tolerability of the 12 week treatment regimens of GS-9992 plus TAF or commercially available NUC

- **Groups 1-3 and 5**

  To evaluate the antiviral activity of 12 weeks of GS-9992 plus TAF versus TAF alone in viremic CHB subjects as measured by the proportion of subjects with ≥0.5 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating serum HBV surface antigen (HBsAg)

- **Group 4**

  To evaluate the antiviral activity of 12 weeks of GS-9992 with commercially available NUC(s) in virally suppressed CHB subjects as measured by the proportion of subjects with ≥0.5 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating serum HBV surface antigen (HBsAg)

The secondary objectives of this study are:

- **Groups 1-3 and 5**

- To evaluate the safety and tolerability of the 48 week treatment regimens as assessed by review of the accumulated safety data

- To evaluate the antiviral activity of 12 weeks of GS-9992 plus TAF versus TAF alone in CHB subjects as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating HBsAg

- To evaluate the proportion of HBeAg-positive CHB subjects who achieve HBeAg loss and seroconversion during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

- To evaluate the proportion of CHB subjects who achieve HBsAg loss during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

- To evaluate the incidence of drug resistance mutations during 48 weeks of treatment

- To characterize steady-state pharmacokinetics of study drugs

- To evaluate the change from Baseline in HBV DNA and quantitative HBsAg in CHB subjects during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

- **Group 4**

- To evaluate the proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL) during 12 weeks of GS-9992 treatment

- To evaluate the antiviral activity of 12 weeks of GS-9992 in CHB subjects as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating HBsAg

- To evaluate the proportion of HBeAg-positive CHB subjects who achieve HBeAg loss and seroconversion during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks

- To evaluate the proportion of CHB subjects who achieve HBsAg loss during 12 weeks of GS-9992 and after GS-9992 discontinuation though 48 weeks

- To characterize steady-state pharmacokinetics of study drugs

- To evaluate the change from Baseline in quantitative HBsAg in CHB subjects during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks

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3. STUDY DESIGN

3.1. Endpoints

Groups 1-3 and 5

The primary efficacy endpoint of this study is the proportion of subjects with ≥ 0.5 $\log_{10}$ IU/mL decline in HBsAg from Baseline at Week 12.

Group 4

The primary efficacy endpoint of this study is the proportion of subjects with ≥ 0.5 $\log_{10}$ IU/mL decline in HBsAg from Baseline at Week 12 in virally suppressed CHB subjects.

The secondary endpoints of this study are:

Groups 1-3 and 5

- Proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in HBsAg from Baseline at Week 12
- Proportion of HBeAg-positive subjects who achieve HBeAg loss and seroconversion through 48 weeks of treatment
- Proportion of subjects who achieve HBsAg loss through 48 weeks of treatment
- Proportion of subjects with drug resistance mutations during 48 weeks of treatment
- Change from Baseline in HBV DNA and quantitative HBsAg through 48 weeks of treatment

Group 4

- Proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL) during 12 weeks of GS-9992 treatment
- Proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in HBsAg from Baseline at Week 12 in circulating HBsAg
- Proportion of HBeAg-positive subjects who achieve HBeAg loss and seroconversion during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks
- Proportion of subjects who achieve HBsAg loss during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks
- Change from Baseline in quantitative HBsAg during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks

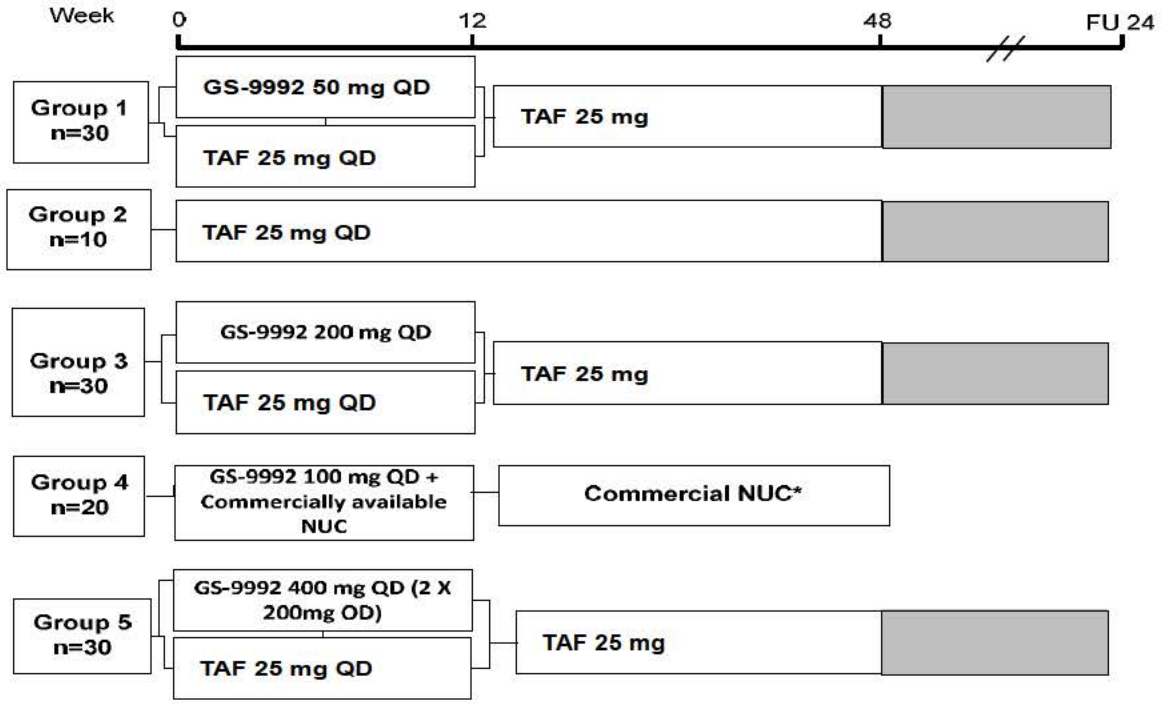
3.2. Study Design

This is a randomized, open label study to evaluate the antiviral activity of GS-9992 plus TAF or commercially available NUC. Subjects will be randomized in a 3:1 ratio to Group 1 and Group 2. Randomization will be stratified by HBeAg positive or negative status with approximately 40% of subjects enrolled with HBeAg negative status.

Groups 3, 4, and 5 treatment will be assigned. Group 3 will not start enrolling subjects until the ACHIEVE (SB-9200-HBV-201) trial's independent Data Safety Monitoring Board has deemed it safe to proceed based on review of data for the 200 mg monotherapy cohort.

Group 5 will not start enrolling subjects until safety of the first 12 weeks of the combination treatment in Group 3 has been confirmed by the Medical Monitor.

Figure 3-1. Study Schema



**Group 4: Subjects who discontinue NUCs should be followed in Treatment-Free Follow-up*

24 Week Treatment-Free Follow-up

Subjects that meet any one of the following criteria will be followed for 24 weeks or until the initiation of alternative CHB therapy, whichever comes first:

- Subjects that discontinue all HBV therapy (e.g. GS-9992 and/or TAF or commercially available NUC), for any reason

- Subjects with HBsAg loss confirmed at least 12 weeks apart should discontinue all HBV therapy following confirmation

3.3. Study Treatments

Approximately 120 chronic, immune-active, HBV-infected adults without cirrhosis will be enrolled; including 100 viremic subjects not currently on HBV nucleos(t)ide (NUC) and 20 virally suppressed subjects on a commercially available NUC.

Approximately 40 viremic subjects will be randomized (3:1) to Group 1 and Group 2, below:

Groups 1 and 2: Subjects will be randomized (3:1) to the following:

- Group 1: Approximately 30 subjects will be administered GS-9992 50 mg (2 × 25 mg capsules) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks.

- Group 2: Approximately 10 subjects will be administered TAF 25 mg once daily with food for 48 weeks

Randomization will be stratified by HBeAg status (positive or negative) at screening with approximately 40% of HBeAg negative subjects enrolled.

Group 3: Approximately 30 viremic subjects will be administered GS-9992 200 mg (2 x 100 mg) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks.

Approximately 40% of subjects enrolled in Group 3 will be HBeAg negative.

Group 4: Approximately 20 virally suppressed subjects currently being treated with a commercially available NUC(s) for CHB will be administered GS-9992 100 mg tablet once daily one hour before or one hour after a meal for 12 weeks.

Approximately 50% of subjects enrolled in Group 4 will be HBeAg negative. Subjects will remain on their current commercially available NUC(s) therapy for the duration of the study. All subjects will be followed through Week 48.

Group 5 (Hong Kong): Approximately 30 viremic subjects may be enrolled and assigned:

GS-9992 400 mg (2 x 200 mg tablets) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks.

3.4. Duration of Treatment

The duration of study treatment is 48 Weeks. Groups 1, 3, and 5 consist of 12 weeks treatment of GS-9992 and TAF followed by TAF only treatment for 36 weeks, and Group 2 is 48 Weeks of

TAF only treatment. Group 4 consist of 12 weeks of treatment of GS-9992 and subjects will remain on their current commercially available NUC therapy for the duration of the study. All subjects will be followed through Week 48.

All groups include a screening period of up to 45 days.

3.5. Biomarker Testing

3.5.1. Biomarker Samples to Address the Study Objectives

Biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or adverse events and to increase knowledge and understanding of the biology of chronic hepatitis B or related diseases and/or the validation of a companion diagnostic for GS-9992. Plasma samples will be collected to measure cytokines and whole blood will be collected to measure potential changes in transcript levels and immune cell subsets

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3.6. End of Study

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

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A total of approximately 120 subjects will enrolled in the study, aged 18-70 years inclusive, with chronic hepatitis B including viremic subjects not currently on HBV oral antiviral (Groups 1-3 and 5) and virally suppressed subjects on an NUC (Group 4).

4.2. Groups 1-3 and 5 Inclusion Criteria

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

1) Ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.

2) Aged 18 to 70 years of age, inclusive, based on the date of screening visit.

3) Females of childbearing potential (as defined in Appendix 4) must have a negative serum pregnancy test at screening and a negative urine test at Baseline before dosing.

4) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception until 90 days after the last dose of GS-9992 and as described in Appendix 4.

5) Chronic hepatitis B infection defined as, HBsAg or HBV DNA positivity for at least 6 months prior to the Baseline visit, or medical records indicating a chronic HBV infection, and meeting the following criteria.

   a) Screening HBV DNA $\geq 2 \times 10^4$ IU/mL for HBeAg-positive subjects

   b) Screening HBV DNA $\geq 2 \times 10^3$ IU/mL for HBeAg-negative subjects

   c) Screening serum ALT level > 35 U/L (males) or > 25 U/L (females) and $\leq 5 \times$ ULN (by central laboratory range).

6) Subjects not taking any prescribed HBV NUC treatment for at least 3 months prior to the Baseline visit.

7) Screening ECG without clinically significant abnormalities, including QTcF interval (QT corrected using Fridericia's formula) < 450 msec for males and < 470 msec for females.

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

4.3. Groups 1-3 and 5 Exclusion Criteria

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

1) Pregnant women, women who are breastfeeding or who believe they may wish to become pregnant during the course of the study.

2) Co-infection with HCV, HIV, or HDV.

3) Extensive bridging fibrosis or cirrhosis as defined clinically, by imaging or by the following:

   a) Metavir ≥ 3 or Ishak fibrosis score ≥ 4 by a liver biopsy within 5 years of screening, or, in the absence of an appropriate liver biopsy, either:

   b) Screening FibroTest score of > 0.48 and APRI > 1, or

   c) Historic FibroScan with a result > 9 kPa within ≤ 6 months of screening (if available)

   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.

4) Evidence of hepatocellular carcinoma on imaging (e.g., ultrasound, CT scan, or MRI) performed within 3 months prior to the Baseline visit.

5) Any history of, or current evidence of, clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage).

6) Abnormal hematological and biochemical parameters at Screening, including:

   - Hemoglobin < 12 g/dL for males and < 11 g/dL for females
   - Absolute neutrophil count < 1000 cells/mm^3
   - White blood cell count < 2500 cell/uL
   - Platelets < 100,000/mm^3
   - AST or ALT > 5 × ULN
   - Total Bilirubin > 2.5 × ULN
   - Albumin < 3.5 g/dL
   - INR > 1.5 × ULN (unless stable on anticoagulant regimen)
   - Creatinine clearance < 50 mL/min

7) Received solid organ or bone marrow transplant.

8) Significant immunodeficiency disorder, autoimmune, cardiovascular, pulmonary, or neurological disease in the opinion of the investigator.

9) Chronic liver disease of a non-HBV etiology (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis, steatohepatitis).

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

11) Currently on or have received therapy with an approved or investigational immunomodulators (e.g. systemic corticosteroids) or biologics (e.g., monoclonal antibody, IFN) within 3 months or any other investigational agents within 30 days of Screening.

12) Subjects on prohibited concomitant medications (reference Table in Section 5.4).

13) Known hypersensitivity to study drugs, metabolites, or formulation excipients.

14) Current alcohol or substance abuse judged by the investigator that will potentially interfere with subject compliance.

15) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements.

4.4. Group 4 Inclusion Criteria

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

1) Ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.

2) Aged 18 to 70 years of age, inclusive, based on the date of screening visit.

3) Females of childbearing potential (as defined in Appendix 4) must have a negative serum pregnancy test at screening and a negative urine test at Baseline before dosing.

4) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception until 90 days after the last dose of GS-9992 and as described in Appendix 4.

5) Documented evidence of chronic HBV infection (e.g. HBsAg positivity) for more than 6 months with detectable HBsAg at Screening.

6) Have at least one prior documented result of HBV DNA ≤ lower limit of quantitation (LLOQ) from the local lab 6 or more months prior to Screening.

7) HBV DNA ≤ 20 IU/mL at Screening by Central Lab.

8) Have been on a commercially available HBV NUC treatment(s) (tenofovir alafenamide, tenofovir disoproxil fumurate, entecavir, adefovir, lamivudine, telbivudine, either as single agents or in combination) for less than 2 years, with no change in regimen for 3 months prior to screening.

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

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

4.5. Group 4 Exclusion Criteria

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

1) Pregnant women, women who are breastfeeding or who believe they may wish to become pregnant during the course of the study.

2) Co-infection with HCV, HIV, or HDV.

3) Extensive bridging fibrosis or cirrhosis as defined clinically, by imaging or by the following:

   a) Metavir ≥ 3 or Ishak fibrosis score ≥ 4 by a liver biopsy within 5 years of screening, or, in the absence of an appropriate liver biopsy, either:

   b) Screening FibroTest score of > 0.48 and APRI > 1, or

   c) Historic FibroScan with a result > 9 kPa within ≤ 6 months of screening (if available)

   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.

4) Evidence of hepatocellular carcinoma on imaging (e.g., ultrasound, CT scan, or MRI) performed within 3 months prior to the Baseline visit.

5) Any history of, or current evidence of, clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage).

6) Abnormal hematological and biochemical parameters at Screening, including:

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

   b) White Blood cell count < 2500 cells/mm^3

   c) Neutrophil count < 1000 cell/mm^3

   d) ALT > 3x ULN

   e) INR > 1.5 X ULN (unless stable on an anticoagulant regimen)

   f) Albumin < 3.5 g/dL

   g) Total bilirubin >1.5x ULN

   h) Platelet Count < 100,000/uL

   i) Estimated creatinine clearance (CrCl) < 50 mL/min

7) Received solid organ or bone marrow transplant

8) Significant immunodeficiency disorder, autoimmune, cardiovascular, pulmonary, or neurological disease in the opinion of the investigator.

9) Chronic liver disease of a non-HBV etiology (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis, steatohepatitis).

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

11) Received prolonged therapy with immunomodulators (e.g. corticosteroids) or biologics (e.g. monoclonal antibody, interferon) within 3 months of screening

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

13) Known hypersensitivity to study drug or formulation excipients

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) 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 Codes

The randomization will be performed via an Interactive Web Response System (IWRS), whereby study treatment will be assigned to subjects according to the randomization schedule. A unique subject number will be provided during randomization. Groups 1 and 2 will be randomized in a 3:1 ratio to receive either GS-9992 and TAF or TAF alone. Groups 3 and 5 will be enrolled based on HBeAg status and receive GS-9992 and TAF. Group 4 will be enrolled based on HBeAg status and receive GS-9992.

5.2. Description and Handling of GS-9992 and TAF

5.2.1. Formulation

5.2.1.1. GS-9992

GS-9992 is provided in capsule formulation containing 25 mg strengths. The current composition of the capsules includes Active Pharmaceutical Ingredient (API) GS-9992 and the following excipients: lactose and sodium stearyl fumarate.

GS-9992 tablets, 100 mg, are blue, round, film-coated tablets. In addition to the active ingredient, each film-coated tablet contains the following ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, sodium stearyl fumarate, colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, Fd&C Blue #1/Brilliant Blue FcF aluminum lake, and Fd&C Blue #2 Indigo Carmine aluminum lake.

GS-9992 tablets, 200 mg, are blue, oval, modified capsule shape, film-coated tablets. In addition to the active ingredient, each film-coated tablet contains the following ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, sodium stearyl fumarate, colloidal silicon dioxide, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, Fd&C Blue #1/Brilliant Blue FcF aluminum lake, and Fd&C Blue #2 Indigo Carmine aluminum lake.

5.2.1.2. Tenofovir Alafenamide [TAF] Tablets

TAF 25 mg tablets contain 28 mg of tenofovir alafenamide fumarate, which is equivalent to 25 mg of tenofovir alafenamide. The tablets are yellow, round-shaped, and film-coated. The tablets are debossed with “GSI” on one side and “25” on the other side. In addition to the active ingredient, each film-coated tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

5.2.2. Packaging and Labeling

5.2.2.1. GS-9992

GS-9992 capsules, 25 mg are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 17 capsules, silica gel desiccant and packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

GS-9992 tablets, 100 mg are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 17 tablets, silica gel desiccant and packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

GS-9992 tablets, 200 mg are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 35 tablets, silica gel desiccant and packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.2.2. TAF

TAF tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.3. Storage and Handling

GS-9992

GS-9992 capsules, 25 mg, GS-9992 tablets, 100 mg and GS-9992 tablets, 200mg, should be stored at 2°C to 8°C (36°F to 46°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

TAF

TAF tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of GS-9992 and TAF

Study drug(s) are to be taken at the same time each day (i.e., 24 hour window between TAF doses and 24 hour window between GS-9992 doses, if applicable).

Groups 1 and 2: Subjects will be randomly assigned (3:1) the following treatments:

- Group 1 (n = 30): GS-9992 50 mg (2 × 25 mg capsules) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks.

- Group 2 (n = 10): TAF 25 mg once daily with food for 48 weeks

Groups 3,4, and 5 will be assigned:

- Group 3 (n = 30): GS-9992 200 mg (2 x 100 mg tablets) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks.

- Group 4 (n = 20): GS-9992 100 mg tablet once daily one hour before or one hour after a meal for 12 weeks. Subjects will remain on their current commercially available NUC(s) therapy for the duration of the study. All subjects will be followed through Week 48.

- Group 5 (n=30): GS-9992 400 mg (2 x 200 mg tablets) once daily one hour before or one hour after a meal plus TAF 25 mg once daily with food for 12 weeks then TAF 25 mg once daily with food for 36 weeks.

5.4. Prior and Concomitant Medications

Concomitant/previous medications **taken within 30 days of screening**, up to and including the date of the last study visit, need to be recorded in the source documents and eCRFs.

The following medications are excluded while subjects are participating in the study. These medications are **prohibited during the screening period and for a minimum of 30 days prior to the Screening** visit through the end of treatment:

- Investigational agents or devices for any indication
- Nephrotoxic agents (e.g., aminoglycosides, amphoterecin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Probenecid
- Agents that reduce renal function or compete for active tubular secretion with tenofovir (e.g., cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir)
- Antiretroviral regimens that contain pharmacokinetic boosters (i.e. ritonavir or cobicistat) for the treatment of HIV.
- Concomitant use of certain medications or herbal/natural supplements (inducers of drug transporters i.e., P-gp and/or inhibitors of OATP 1B1/1B3) with study drug(s) may result in PK interactions.
- Systemic chemotherapeutic agents, systemic corticosteroids (except short-term use of prednisone as a steroid burst [≤ 1 week of use], immunosuppressant, or immunomodulating agents are prohibited for a minimum of 3 months prior to screening period and during the study.

Examples of representative medications which are prohibited from 21 days prior to Day 1 through the end of treatment are listed below:

Table 5-1. Disallowed Concomitant Medications

Medication Class	Prohibited Medications
Anticonvulsants	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Antimycobacterials	Rifapentine, Rifabutin, Rifampin
Hematopoietic Growth Factor*	Eltrombopag
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Lipid Regulating Agents*	Gemfibrozil

* For subjects receiving GS-9992 in combination with TAF (Groups 1, 3 and 5 only)

Should subjects have a need to initiate treatment with any excluded concomitant medication, including herbal/natural products/therapies, and over the counter medications, the

Gilead Sciences Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the investigator must notify Gilead Sciences as soon as he/she is aware of the use of the excluded medication.

5.5. Accountability for GS-9992 and TAF

The investigator is responsible for ensuring adequate accountability of all used and unused IMP capsules. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition of capsules and/or tablets). All used and unused IMP capsules and/or tablets dispensed to subjects must be returned to the site.

GS-9992 and TAF accountability records will be provided to each study site to:

- Record the date received and quantity of IMP kits.
- Record the date, subject number and the IMP kit number dispensed.
- Record the date, quantity of used and unused IMP capsules and/or tablets, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

At the beginning of the study, the study monitor will evaluate the study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drug supplies performed in accordance with the site's (hospital/pharmacy) SOP. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies. A copy of the site's SOP will be obtained for central files. Where possible, study drug will be destroyed at the site.

Upon study completion, a copy of the Investigational Drug Accountability records must be filed at the site. Another copy will be returned to Gilead Sciences. If drug is destroyed on site, the investigator must maintain accurate records for all study drug kits and/or bottles destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug. All study drug records must be maintained at the site and copies must be submitted to Gilead Sciences at the end of the study.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

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

6.1. Subject Enrollment and Treatment Assignment

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

6.2. Pretreatment Assessments

Prior to the conduct of any screening procedures, each candidate must sign an Informed Consent Form. Consent is to be obtained in accordance with regulatory and local Ethics Committee requirements.

6.2.1. Screening Visit

Subjects will be screened within 45 days before randomization/enrollment to determine eligibility for participation in the study.

- 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 ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Sample Collection for:
  - Safety laboratory tests (hematology, chemistry, and coagulation)
  - Serology testing to exclude HCV, HDV, and HIV infection

— Quantitative plasma HBV DNA

— Quantitative serum HBsAg, CCI [redacted]

— Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative])

— HBV viral sequencing samples (resistance surveillance)

— Estimated creatinine clearance (using the Cockcroft-Gault method)

— Other screening laboratory tests: urinalysis, urine drug screen, and serum β-hCG (females of child bearing potential only)

Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

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

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Baseline Assessments (Day 1)

All baseline tests and procedures must be completed prior to the receipt of the first dose of study drug. Subjects screened within 45 days before Baseline will be eligible to participate in the study. Initiation of treatment with study drug should take place on the day of the Baseline Visit.

- Review of inclusion/exclusion criteria and confirm medical history
- Complete Physical Examination including body weight
- Vital signs
- 12-lead ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Review adverse events prior to study drug administration, report AEs related to protocol mandated procedures and all SAEs. After drug administration, report all AEs and SAEs.
- Review Concomitant Medications

- Sample Collection For:
  - Safety laboratory tests (hematology, chemistry, and coagulation)
  - HBV genotype for Groups 1-3 and 5 only, for Group 4 historic genotype should be documented in EDC if available
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative])
  - Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis (PBMC sample collection is only required at the sites that have access to PBMC processing laboratory).
  - Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR (Group 4)
  - Other laboratory tests: urinalysis, urine drug screen and pregnancy test for child bearing potential only)
  - CCI [redacted]
- Estimated creatinine clearance (using Cockcroft-Gault method)
- Randomization
- Drug Administration of GS-9992 and TAF
  - Dispense study drug as directed by IWRS
  - Instruct the subject on the packaging, storage, and administration of study drugs
  - Observe the subject taking the first dose of study drug(s)

6.3. Post-Day 1 Assessments (Weeks, 1, 2, 4, 8, 12, 16, 24, 36, and 48, All Visits Have Window of ± 3 Days)

- Vital signs
- Weight at Weeks 12 and 48
- Review adverse events

- Review concomitant medications
- Complete Physical Examination (Week 12)
- Symptom-directed physical examination
- 12-lead ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording) (Week 12)
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry; coagulation on Week 12 only)
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) at Weeks 12, 24, 36, and 48
  - Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis at Weeks 1, 4, 12, 24, 48 (PBMC sample collection is only required at the sites that have access to PBMC processing laboratory).
  - Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR (Group 4)
  - Single plasma PK sample will be collected at each on- study treatment visit.
    - On Weeks 2 and 8, the sample will be collected between 15 minutes and 4 hours post-dose. In-clinic dose of GS-9992 required.
    - All PK samples will be collected anytime on all other on-treatment visit.
    - Single PK blood samples will only be collected through Week 12 for Group 4
  - Urine pregnancy test (females of child bearing potential only)
  - Urinalysis
  - Estimated creatinine clearance (using Cockcroft-Gault method) at Weeks 12 and 48

[redacted]

[redacted]

- Perform study drug accountability (Groups 1, 3, and 5: GS-9992 Weeks 1-12, TAF Weeks 1-48; Group 2 TAF Weeks 1-48; and Group 4: GS-9992 Weeks 1-12)
- Dispense study drug GS-9992 Weeks 4-8 (Groups 1, 3, 4, and 5), TAF Weeks 4-36 (Group 1, 2, 3 and 5) as outlined in Appendix 2.

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[redacted]

[redacted]

6.5. 24-Week Treatment Free Assessments (Weeks 4, 8, 12, 16, 20, and 24, All Visits Have Window of ± 5 Days)

Subjects that meet the criteria for the treatment free follow-up (Section 3.2) will be followed for 24 weeks or until the initiation of alternative CHB therapy, whichever comes first.

The following assessments will be completed:

- Complete Physical examination at Week 4
- Symptom-directed physical examination
- Review adverse events at Week 4 and collect SAEs through the end of study
- Review concomitant medications
- Vital signs
- Sample collection for:
  - Safety laboratory tests (hematology and chemistry)
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) to be collected at Weeks 12 and 24

- Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis at Weeks 4, 8, 12, and 24 (PBMC sample collection is only required at the sites that have access to PBMC processing laboratory).
- Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR (Group 4)
- Urine pregnancy test (females of child bearing potential only at Week 4)

6.6. Assessments for Early Discontinuation from the Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.5 Post-Treatment Assessments).

If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

Criteria for study treatment discontinuation and Toxicity Management can be found in Section 6.11 and Section 7.6.

The Early Discontinuation (ED) Visit should be performed within 14 days from notification of study discontinuation. The following assessments will be performed at the ED visit:

- Vital signs
- Review AEs and concomitant medications
- Complete Physical Examination
- Body Weight
- 12-lead ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Sample collection for:
  - Safety Laboratory Tests (hematology, chemistry, and urinalysis)
  - Quantitative plasma HBV DNA
  - Quantitative serum HBsAg, CCI [redacted]
  - Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative])
  - Estimated creatinine clearance (using the Cockcroft-Gault method)

- Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR (Group 4)
- Single Plasma PK sample
- Urine pregnancy test (females of child bearing potential only)
- Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis (PBMC sample collection is only required at the sites that have access to PBMC processing laboratory).

- GS-9992 and TAF accountability, as applicable

[redacted]

6.7. Unscheduled Visits

The assessments at the unscheduled visits are at the investigator's discretion.

6.8. Study Procedure Details

6.8.1. Medical History

Medical history will include 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.

6.8.2. 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. At the screening visit, the Complete Physical Examination will include documentation of subject height.

6.8.3. Electrocardiogram Assessment

Subjects should rest quietly in the supine position for a minimum of 5 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete. There should be no environmental distractions (including TV, radio, video games, and conversation) while the subjects are resting prior to and during the recordings. Electrocardiograms will be recorded using the site's standard ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven with a check to confirm that the aVR lead is not inverted.

The investigator or other qualified individuals at the study center will review ECGs to assess for changes in ECG intervals and morphology as compared with pretreatment ECGs. ECG interval measurements output by the machine will be used for bedside safety monitoring.

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

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

6.8.4. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and oral temperature. Subject body weight will be obtained at: Screening, Baseline, Weeks 12 and 48, and ED.

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.

6.8.5. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Appendix 2.

6.8.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology:
  - Hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume (MCV), and
- Coagulation panel
  - Prothrombin time, partial thromboplastin time [PTT] and international normalized ratio [INR])

- Chemistry:

  — Alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total protein, albumin, lactic acid dehydrogenase (LDH), creatine kinase (CK), bicarbonate, blood urea nitrogen (BUN), 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 × upper limit of normal [ULN])

- Serum pregnancy test (females of childbearing potential only)

- Follicle-stimulating hormone (FSH) testing (For female subjects post-menopausal for less than two years, if FSH < 40 mIU/ mL a serum pregnancy test will be required)

6.8.5.2. Urine Samples

Urine samples will be collected for urinalysis and drug screen assessments and urine pregnancy as applicable.

6.8.5.3. Creatinine Clearance

Creatinine Clearance

Weight will be collected at screening and upon admission calculate creatinine clearance (CL_{cr}) for inclusion criteria.

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft 1976} using actual bodyweight (BW).

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

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

S_{cr} = serum creatinine (mg/dL)

6.8.5.4. HIV, HDV, and HCV Reflex Testing

In the event of a positive result for serology and/or antigen testing for HIV, HDV or HCV serology, reflex tests will automatically be performed.

Co-infection with HIV, HDV, or HCV is exclusionary.

6.8.6. Adverse Events/Concomitant Medications/Protocol Restrictions

Evaluation for AEs, review of concomitant medications, and review of protocol restrictions will occur at the times shown in Appendix 2. See Section 7 for more information regarding AEs and Section 5.4 for more information about concomitant medications.

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6.10. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.11, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.11. Criteria for Discontinuation of Study Treatment

GS-9992 and/or TAF may be discontinued if the following instances are met:

- A confirmed ≥ Grade 3 AE (excluding isolated ALT elevations) considered related to GS-9992 and/or TAF by the investigator, should discontinue one or both study drug(s)
- A confirmed, clinically significant lab abnormality ≥ Grade 3 (excluding isolated ALT elevations) considered related to GS-9992 and/or TAF by the investigator, should discontinue one or both study drug(s)
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- 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
- HBsAg loss confirmed at least 12 weeks apart
- Subject requests to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

For Group 5, study treatment(s) will be held in all subjects in the dosing group, if ≥3 subjects experience a Grade 3 adverse event or ≥2 subjects experience a Grade 4 or serious adverse event, in the same system organ class (excluding isolated ALT elevations) that is considered related by the investigator(s) to the Graded toxicity. Decisions to reinitiate continuation of dosing of study treatment(s) will be made by Gilead Medical Monitor upon review of all safety data generated by subjects dosed to date.

Refer to Section 7.6 for additional discontinuation criteria for Toxicity Management.

HBV will be managed according to local standard of care if subjects are discontinued from the study. Subjects that discontinue all HBV therapy should be followed for 24 weeks or until the initiation of alternative CHB therapy, whichever comes first.

6.12. Resistance Surveillance and ddPCR

Sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT) to assess the incidence of resistance mutations will be attempted for any subject with viremia (HBV DNA ≥ 69 IU/mL) at Week 48 or at early discontinuation at or after Week 24. 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 resistance surveillance will be collected at each study visit.

For Group 4, if subject has HBV DNA ≥ 69 IU/mL, a sequence analysis may be conducted if applicable. If HBV DNA < 20 IU/mL, ddPCR will be conducted.

6.13. End of Study

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

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

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, 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 medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

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 adverse event and must be reported.
- Pre-existing 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (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. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

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 each IMP therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

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

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

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

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

- **Yes:** The adverse event occurred as a result of protocol procedures, (e.g., venipuncture)

7.2.2. Assessment of Severity

Severity of adverse events is to be determined based on GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 3). A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event: both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above in Section 7.1.2.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel must record all SAE data in the eCRF database and transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If it is not possible to record and submit the SAE information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the SAE on the paper serious adverse event report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to:

  Gilead PVE: Fax: PPD
  E-mail: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions 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.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail 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 event description section of the SAE form.

7.4. 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 Investigator's Brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. 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.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events and Toxicity Management

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, X-rays, and 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 (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 3). 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.

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines below.

ALT Elevation or Flare 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 on-treatment 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, INR and serum albumin.
- 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, HAV IgM, HCV, and HEV.

For GS-9992 Management

Based on the results of the confirmatory tests, the following treatment modifications for GS-9992 are recommended:

Table 7-1. GS-9992 Dose Modification and Monitoring

Liver Toxicity	Action
Confirmed ALT ≥ 10 × ULN without evidence of hepatic toxicity as defined below	Discuss with the Medical Monitor if GS-9992 should be dose reduced by 50% or discontinued if the safety of the subject is of immediate concern. Subject should be monitored weekly or more frequently if clinically indicated until ALT < 5 × ULN
Confirmed ALT > 2 × nadir, with evidence of hepatic toxicity, defined as any one of the following: • Total bilirubin > 2 × baseline or nadir AND > ULN in the absence of Gilbert's disease • Elevated INR > 0.5 above baseline AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	Permanently discontinue GS-9992. Subject should be monitored weekly until ALT < 5 × ULN, and total bilirubin and INR values return to normal or baseline levels
Confirmed ALT > 2 × Baseline and ≥ 5 × ULN without evidence of hepatic toxicity, as defined above	Continue GS-9992, ALT should be evaluated every 2 weeks or more frequently as clinically needed, until ALT < 5 × ULN

For TAF Management

Based on the results of the confirmatory tests, the following treatment modifications for TAF are recommended:

Table 7-2. TAF Dose Modification and Monitoring

Liver Toxicity	Action
Confirmed ALT levels ≥ 10 × ULN, with evidence of hepatic toxicity, defined as any one of the following: • Total bilirubin > 2 × baseline or nadir AND > ULN in the absence of Gilbert's disease • Elevated INR > 0.5 above baseline AND > ULN • Abnormal serum albumin > 1 g/dL decrease from baseline	Discuss with the Medical Monitor if TAF should be discontinued, unless the safety of the subject is of immediate concern. Subject should be monitored weekly as long as ALT, total bilirubin and INR values remain elevated or above baseline values. If the ALT values remain persistently elevated, the investigator should discuss with the Medical Monitor if TAF should be discontinued.
Confirmed ALT levels ≥ 10 × ULN, without evidence of hepatic toxicity, as defined above	Continue TAF and monitor weekly until ALT values return to normal or baseline levels. If the ALT values remain persistently elevated, the investigator should discuss with the Medical Monitor if TAF should be discontinued.

Specific toxicity discontinuation criteria in Section 6.11 supersede below general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply. The Gilead Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue investigational medicinal product at the discretion of the investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality (except ALT evaluations) confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product 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 baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 CK after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, pregnancy reports regardless of an associated AE, and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

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

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product 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).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. 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 Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD .

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD.

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All special situations reports (SSRs) will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Special Situations Report (eSSR) Reporting Process:

Site personnel record all SSR data in the eCRF database and from there transmit the SSR information to Gilead DSPH within 24 hours of the investigator's knowledge of the event throughout the duration of the study, including the protocol–required post treatment follow-up period. Detailed instructions can be found in the eCRF completion guidelines.

If for any reason it is not possible to record the SSR information electronically, i.e., the eCRF database is not functioning, record the SSR on the paper serious adverse event reporting form and submit within 24 hours to: **Gilead PVE:** Email: PPD
Fax: PPD

As soon as it is possible to do so, any SSR reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report 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.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports 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.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the safety and tolerability of the 12 week treatment regimens of GS-9992 plus TAF or commercially available NUC

- **Groups 1-3 and 5**

  To evaluate the antiviral activity of 12 weeks of GS-9992 plus TAF versus TAF alone in viremic CHB subjects as measured by the proportion of subjects with ≥0.5 log10 IU/mL decline from Baseline at Week 12 in circulating serum HBV surface antigen (HBsAg)

- **Group 4**

  To evaluate the antiviral activity of 12 weeks of GS-9992 with commercially available NUC(s) in virally suppressed CHB subjects as measured by the proportion of subjects with ≥0.5 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating serum HBV surface antigen (HBsAg)

The secondary objectives of this study are:

Groups 1-3 and 5

- To evaluate the safety and tolerability of the 48 week treatment regimens as assessed by review of the accumulated safety data

- To evaluate the antiviral activity of 12 weeks of GS-9992 plus TAF versus TAF alone in CHB subjects as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating HBsAg

- To evaluate the proportion of HBeAg-positive CHB subjects who achieve HBeAg loss and seroconversion during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

- To evaluate the proportion of CHB subjects who achieve HBsAg loss during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

- To evaluate the incidence of drug resistance mutations during 48 weeks of treatment

- To characterize steady-state pharmacokinetics of study drugs

- To evaluate the change from Baseline in HBV DNA and quantitative HBsAg in CHB subjects during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

Group 4

- To evaluate the proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL) during 12 weeks of GS-9992 treatment
- To evaluate the antiviral activity of 12 weeks of GS-9992 in CHB subjects as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from Baseline at Week 12 in circulating HBsAg
- To evaluate the proportion of HBeAg-positive CHB subjects who achieve HBeAg loss and seroconversion during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks
- To evaluate the proportion of CHB subjects who achieve HBsAg loss during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks
- To characterize steady-state pharmacokinetics of study drugs
- To evaluate the change from Baseline in quantitative HBsAg in CHB subjects during 12 weeks of GS-9992 and after GS-9992 discontinuation through 48 weeks

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8.1.2. Primary Endpoint

Groups 1-3 and 5

The primary efficacy endpoint of this study is the proportion of subjects with ≥ 0.5 $\log_{10}$ IU/mL decline in HBsAg from Baseline at Week 12.

Group 4

The primary efficacy endpoint of this study is the proportion of subjects with ≥ 0.5 log_{10} IU/mL decline in HBsAg from Baseline at Week 12 in virally suppressed CHB subjects.

8.1.3. Secondary Endpoint

The secondary endpoints of this study are:

Groups 1-3 and 5

- Proportion of subjects with ≥ 1 log_{10} IU/mL decline in HBsAg from Baseline at Week 12
- Proportion of HBeAg-positive subjects who achieve HBeAg loss and seroconversion through 48 weeks of treatment
- Proportion of subjects who achieve HBsAg loss through 48 weeks of treatment
- Proportion of subjects with drug resistance mutations during 48 weeks of treatment
- Change from Baseline in HBV DNA and quantitative HBsAg through 48 weeks of treatment

Group 4

- Proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL) during 12 weeks of GS-9992 treatment
- Proportion of subjects with ≥ 1 log_{10} IU/mL decline in HBsAg from Baseline at Week 12
- Proportion of HBeAg-positive subjects who achieve HBeAg loss and seroconversion through 48 weeks
- Proportion of subjects who achieve HBsAg loss through 48 weeks
- Change from Baseline in quantitative HBsAg through 48 weeks

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is the full analysis set (FAS), defined as all subjects who were randomized to Group 1 or 2, or enrolled in Group 3 or 4 or 5 and who took at least 1 dose of any study drug. Subjects will be analyzed according to the randomized or enrolled treatment assignment.

8.2.1.2. Safety

The primary analysis set for safety analysis is the safety analysis set (SAS), defined as all subjects who took at least 1 dose of any study drug. Subjects will be analyzed according to the treatment actually received.

8.2.1.3. Pharmacokinetics

The pharmacokinetics (PK) analysis set will include all subjects who were randomized to Group 1 or 2, or enrolled in Group 3 or 4 or 5 and took at least 1 dose of any study drug and have at least 1 nonmissing concentration value reported by the PK laboratory.

8.2.1.4. Biomarkers

The primary analysis set for biomarker analysis is the biomarker analysis set, defined as all subjects who were randomized to Group 1 or 2 or enrolled in Group 3 or 4 or 5 and who took at least 1 dose of any study drug and have at least 1 nonmissing biomarker value for each respective biomarker.

8.3. Data Handling Conventions

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

For the drug resistant mutations endpoint, a missing = excluded approach will be employed.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized by treatment group and overall using standard descriptive methods.

Demographic summaries will include age, sex, race and ethnicity.

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

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint, i.e. the proportion of subjects with ≥ 0.5 $\log_{10}$ IU/mL decline in HBsAg from baseline at Week 12, will be evaluated for all groups in the FAS. The 2-sided 95% confidence interval (CI) of the proportion difference (Group 1 – Group 2, Group 3 − Group 2, Group 5 − Group 2) will be constructed by using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factor HBeAg status (positive, negative).

8.5.2. Secondary Analyses

Continuous secondary endpoints will be summarized using conventional descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) by treatment group.

Categorical secondary endpoints will be summarized by number and percentage of subjects that meet the endpoint by treatment group.

8.5.3. Analysis of Other Endpoints of Interest

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

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

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests and adverse events. Primary safety analysis will be evaluated through four weeks after last dose of GS-9992.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug(s) will be generated from the study drug(s) administration data. Exposure data will be summarized by treatment group

8.6.2. Adverse Events

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Summaries (number and percentage of subjects) of treatment-emergent (TE) AEs (by SOC and PT) will be provided by treatment group:

- All TEAEs
- TEAEs of Grade 3 or higher
- TEAEs of Grade 2 or higher
- All TE treatment-related AEs
- TE treatment-related AEs of Grade 3 or higher
- TE treatment-related AEs of Grade 2 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 conventional 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 3.

Incidence of treatment-emergent laboratory abnormalities will be summarized. All laboratory abnormalities will be included in the listings of laboratory data.

8.7. Pharmacokinetic Analysis

CCI [redacted] 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 ± standard deviation. Details of pharmacokinetic analyses will be provided in the statistical analysis plan.

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[redacted]

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 group 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 the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, 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 IEC. The investigator will not begin any study subject activities until approval from the IEC has been documented and provided as a letter to the investigator.

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

9.1.3. 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 and before undertaking any study-related procedures. The investigator must use the most current IEC -approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only Year of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IEC, or 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 in lab manual. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. 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 Investigator's Brochure, this protocol, eCRF, the IMP, 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.

9.1.5. 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 two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IEC and governmental approval with correspondence, informed consent, 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 (name, Year of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., 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 IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including 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 until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., United States, 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, until 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.

9.1.6. 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 EDC. 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. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator 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 (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in 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 trial, Gilead will provide the site 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 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. 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 IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IEC, 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 the IEC accordance with local requirements and receive documented IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). 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 9.1.4).

- 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, e.g., attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the 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 on the 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 of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead 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 the sponsor 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 appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Open-Label, Active-Controlled Study to Evaluate the Safety and Antiviral Activity of GS-9992 Plus Tenofovir Alafenamide for 12 Weeks in Chronic Hepatitis B Subjects

GS-US-464-4437, Amendment 3, 11 March 2019

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

PPD

PPD
Author

11 March 2019
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. Study Procedures Table

Procedures	Screening (45 days)	Baseline Day 1	Weeks (± 3 Days)									Early Discontinuation[a]	24 Week Treatment-Free Follow-up (± 5 Days) (End of Weeks 4, 8, 12, 16, 20, and 24)
			1	2	4	8	12	16	24	36	48		
Informed Consent (at, or prior to, screening visit)[n]	X												
Review of Inclusion/ Exclusion Criteria	X	X											
Medical History	X	X											
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Complete Physical Examination	X	X					X					X	X[c]
Symptom-directed physical examination[b]			X	X	X	X		X	X	X	X		X
Height	X												
Body Weight	X	X					X				X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X					X					X	
Pregnancy Test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Drug Screen	X	X											
Safety laboratory tests (hematology and chemistry,	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X					X						

Procedures	Screening (45 days)	Baseline Day 1	Weeks (± 3 Days) 1	2	4	8	12	16	24	36	48	Early Discontinuation[a]	24 Week Treatment-Free Follow-up (± 5 Days) (End of Weeks 4, 8, 12, 16, 20, and 24)
Quantitative plasma HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X
FibroScan	X												
HCC imaging	X												
Quantitative serum HBsAg, CCI	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative HBV serology[g]	X	X					X		X	X	X	X	X
Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis		X	X		X		X		X		X	X	X[h]
HBV Genotyping [o]		X											
Serum sample for HBV viral sequencing (resistance surveillance) or ddPCR [p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Single Plasma PK[j]			X	X[i]	X	X[i]	X	X	X	X	X	X	
CCI													
Other Viral Serology (HCV, HIV, HDV) [l]	X												
Creatinine Clearance	X	X					X				X	X	
Randomization		X											
Dispense TAF		X			X	X	X	X	X	X			
Dispense GS-9992		X			X	X							

Procedures	Screening (45 days)	Baseline Day 1	Weeks (± 3 Days) 1	2	4	8	12	16	24	36	48	Early Discontinuation[a]	24 Week Treatment-Free Follow-up (± 5 Days) (End of Weeks 4, 8, 12, 16, 20, and 24)
In-Clinic Dose with GS-9992		X		X[m]	X[m]	X[m]							
In-Clinic dose with TAF		X											
GS-9992 Accountability			X	X	X	X	X					X	
TAF Accountability			X	X	X	X	X	X	X	X	X	X	
CCI [redacted]													

a The Early Discontinuation (ED) visit should be performed within 14 days from notification of study discontinuation.
b Symptom-directed physical exam will only be performed when subject is experiencing symptoms.
c To completed at Treatment-Free Follow up Week 4 only: AE review, complete physical examination, and urine pregnancy test.
d Vital signs include blood pressure, pulse, respiration rate and temperature.
e QTc interval will be reported using Fridericia's correction: $QTcF=QT/RR^{0333}$. Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording.
f For female subjects of childbearing potential, the serum pregnancy test will be performed at Screening. Urine test will be performed at all other visits as indicated. Positive urine test will be confirmed with serum test. Pregnancy testing should include prevention counseling.
g Qualitative HBV serology: (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]). Collected every 12 weeks during the study. Post-Treatment visit Weeks 12 and 24.
h PBMCs to be collected at Weeks 4, 8, 12, and 24 only. PBMC sample collection is only required at the sites that have access to PBMC processing laboratory.
i Weeks 2 and 8 PK samples will be collected between 15 minutes and 4 hours post-dose. CCI [redacted]
j Single PK sample will be collected at any time on all other Post-Day 1 visits, CCI [redacted]. For Group 4, single PK will be collected through Week 12 only.
k [redacted]
l In the event of a positive result and/or antigen testing for HIV, HDV, or HCV serology, reflex tests will automatically be performed.
m In-clinic dose required for Weeks 2 and 8 single PK samples CCI [redacted]
n [redacted]
o HBV genotyping for Groups 1-3 and 5 only, for Group 4 historic genotype should be documented in EDC if available.
p Serum sample collected will be used for HBV viral sequencing and possible phenotypic analyses for all groups or ddPCR for Group 4.

Appendix 3. 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 (PT)	> 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 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 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%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 to <2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmol/L
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L > 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L > 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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
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/Lto <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

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

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, 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 (e.g., 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) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization (other than ER visit) indicated Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room 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 (e.g., tamponade) OR Urgent intervention indicated

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

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

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

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., 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 (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year** **Pediatric < 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr Liquid stools (more unformed than usual) but usual number of stools	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs. Liquid stools with increased number of stools OR Mild dehydration	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated Liquid stools with moderate dehydration	Life-threatening consequences (e.g., hypotensive shock) 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 (e.g., 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 (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 weak-ness 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 (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (pre-existing) 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 pre-existing seizures (non-repetitive) 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 (e.g., severity or focality)	Seizures of any kind that are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., 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 (non-injection 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 [e.g., 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 (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., myxedema coma)
Lipoatrophy (e.g., 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 (e.g., 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 antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial 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 (e.g., 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 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 post-menopausal, unless permanently sterile or with 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. 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 of fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-9992

The risk of treatment with GS-9992 has not been evaluated in pregnant women. Relevant non-clinical reproductive toxicity studies for human pregnancy do not indicate a strong suspicion of human teratogenicity/fetotoxicity. Non-clinical early embryonic development and fertility studies with GS-9992 have not been conducted to date. GS-9992 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Pregnancy tests will be performed regularly throughout this study. Please refer to the latest version of the investigator's brochure for additional information.

TAF

Data from clinical pharmacokinetic interaction studies of TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical 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 Investigator's Brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective or an acceptable contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. At minimum, a pregnancy test will be performed at 4 weeks post-treatment. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to one of the following from Screening until 7 days after the last dose of TAF and until 90 days after the last dose of GS-9992.

Highly effective contraceptive measures:

- 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.
  - Intrauterine device (IUD) with a failure rate of < 1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Or, Acceptable contraceptive measures:

- Barrier methods (one female barrier and one male barrier must be used in combination)
  - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
  - Male barriers: Male condom (with or without spermicide)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until 7 days after the last dose of TAF and until 90 days after the last dose of GS-9992.

3) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential during treatment with TAF and for 90 days after the last dose of GS-9992.

Male subjects must also refrain from sperm donation during treatment with GS-9992 and until 90 days after the end of last dose of GS-9992.

Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.