CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-center Study to Evaluate the Safety, Tolerability and Antiviral Activity of GS-9688 in Viremic Adult Subjects with Chronic Hepatitis B who are not currently on Treatment
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	Non-IND Study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT03615066
Indication:	Chronic Hepatitis B
Protocol ID:	GS-US-389-2025
Gilead Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Protocol Version/Date:	Original: 23 March 2018 Amendment 1: 27 August 2019

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-center Study to Evaluate the Safety, Tolerability and Antiviral Activity of GS-9688 in Viremic Adult Subjects with Chronic Hepatitis B who are not currently on Treatment
IND Number:	Non-IND Study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT03615066
Study Centers Planned:	Approximately 12 centers in Canada, South Korea, and Taiwan
Objectives:	**The primary objectives of this study are as follows:** • To evaluate the safety and tolerability of multiple oral doses of GS-9688 at Week 24 in chronic hepatitis B (CHB) adult subjects who are viremic and not currently not being treated • To evaluate the antiviral activity of GS-9688 as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from baseline in serum quantitative hepatitis B surface antigen (qHBsAg) at Week 24 **The secondary objectives of this study are as follows:** • To evaluate the antiviral activity of GS-9688 at Weeks 4, 8, 12 and 48 as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from baseline in serum qHBsAg • To evaluate the change in serum qHBsAg ($\log_{10}$ IU/mL) from baseline to Weeks 4, 8, 12, 24 and 48 • To evaluate the proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48 • To evaluate the proportion of subjects with HBsAg loss at Weeks 12, 24 and 48 • To evaluate the proportion of subjects with Hepatitis B e-Antigen (HBeAg) loss and seroconversion at Weeks 12, 24 and 48

- To characterize the pharmacokinetics (PK) of GS-9688
- To evaluate the proportion of subjects experiencing Hepatitis B virus (HBV) virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL)
- To evaluate the incidence of drug resistance mutations

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Study Design:

This is a multicenter, randomized, double-blind, placebo-controlled Phase 2 study of GS-9688 in viremic CHB subjects who are not currently being treated.

Approximately 65 viremic subjects who are not currently being treated for CHB will be enrolled into two cohorts within this study that will run in parallel.

- Cohort 1 (n = 40): HBeAg-positive CHB subjects
- Cohort 2 (n = 25): HBeAg-negative CHB subjects

Within each cohort, subjects will be randomized in a 1:2:2 in ratio to one of the three treatment arms (A: B: C) for weekly dosing of GS-9688/Placebo to Match (PTM) for 24 doses. All subjects will also be treated with tenofovir alafenamide (TAF) 25 mg oral daily for 48 weeks, in addition to the following treatments:

Treatment Arm A: Approximately 8 subjects in Cohort 1 and approximately 5 subjects in Cohort 2 will be administered placebo-to-match (PTM) orally on the same day once a week (every 7 days) for 24 doses

Treatment Arm B: Approximately 16 subjects in Cohort 1 and approximately 10 subjects in Cohort 2 will be administered GS-9688/PTM 1.5 mg orally on the same day once a week (every 7 days) for 24 doses

Treatment Arm C: Approximately 16 subjects in Cohort 1 and approximately 10 subjects in Cohort 2 will be administered GS-9688/PTM 3 mg orally on the same day once a week (every 7 days) for 24 doses

All GS-9688/PTM study drug doses will be administered in fasted state.

After the 24th dose (Week 23 visit), GS-9688/PTM will be discontinued. Subjects will continue being treated with TAF and will be followed until Week 48/ED. The total study duration for each subject will be 48 weeks with up to an additional 48 weeks if continued into the Treatment Free Follow-up (TFFU) phase. Subjects should take TAF and other commercially available medications no earlier than 2 hours after GS-9688/PTM dosing. Ondansetron dosing is allowed around GS-9688/PTM dosing; dosing of other antiemetics should be discussed with the Gilead medical monitor (MM) for approval.

Following completion of the 48-week study period the Investigators will be responsible for assessing the need to continue study subjects on treatment for CHB. At Week 48, at Principal Investigator (PI) discretion, subjects will be managed in one of two ways:

1) Continue in the study for 48 weeks following the discontinuation of TAF (Treatment Free Follow-Up, TFFU, window of ± 7 days) or until an alternative commercially approved CHB treatment is started, whichever occurs first
2) Initiate other standard of care CHB therapy immediately at end of study.

At the PI's discretion, subject(s) in the TFFU phase may initiate other standard of care CHB therapy at any time per local treatment guidelines. If a subject initiates other standard of care CHB therapy for their CHB, TFFU visits will continue for 2 more TFFU visits or until the end of the TFFU phase (Week 96), whichever comes first.

The primary analysis will occur after all subjects have completed Week 24 assessment post last dose of GS-9688/PTM or prematurely discontinued with the primary endpoints being the safety and tolerability of GS-9688/PTM, as well as assessment of the antiviral activity of GS-9688/PTM at Week 24 as measured by the proportion of subjects with $\geq$1 $\log_{10}$ (IU/mL) decline from baseline in serum qHBsAg.

The study will be unblinded to appropriate Gilead Sciences Inc. (GSI) study team personnel at the time of primary analysis (Week 24 assessment). An Internal Data Review, external to the study team, may be unblinded at Week 12 assessment visit to review the unblinded safety and efficacy data in order to guide strategic decisions regarding the future of the program. Investigators and subjects will remain blinded through the end of the study.

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Pharmacokinetic (PK) Assessments

Sparse (*pre-identified*) PK plasma sampling will occur on Day 1 and Week 23 at pre-dose, 1, 4, and 24 hours post-dose and at Week 11 at pre-dose, 1, and 4 hours post-dose.

Sparse (*timed*) plasma PK samples will be obtained on any two of the following visits: Weeks 2, 4, 8, 12, 16, and/or 20 at pre-dose and any time between 30 minutes to 4 hours post-dose.

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Number of Subjects Planned:	Approximately 65 subjects Cohort 1 will enroll approximately 40 subjects and Cohort 2 will enroll approximately 25 subjects (within each cohort, enrollment will be PTM: GS-9688 1.5 mg: GS-9688 3 mg at a ratio of 1:2:2)
Target Population:	Adult subjects with CHB who are viremic and not currently on treatment for CHB for at least 3 months.
Duration of Treatment:	GS-9688 or PTM will be administered once a week (every 7 days) for 24 treatment doses. All subjects will take TAF 25 mg oral daily through Week 48. At Week 48, per PI's discretion, subjects can continue in the TFFU phase for up to an additional 48 weeks.
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria** Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures. 2) Adult male and non-pregnant, non-lactating female subjects, 18-65 years of age inclusive based on the date of the Screening visit. 3) Documented evidence of chronic HBV infection (e.g., HBsAg positive for more than 6 months) with detectable HBsAg levels at Screening. 4) Females of childbearing potential (as defined in Appendix 3) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline prior to enrollment. 5) Male and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3 6) Screening HBV Deoxyribonucleic acid (DNA) ≥ 2000 IU/mL. 7) Screening Electrocardiogram (ECG) without clinically significant abnormalities and with QTcF interval (QT corrected using Fridericia's formula) ≤ 450 msec for males and ≤ 470 msec for females. 8) Must be willing and able to comply with all study requirements.

Exclusion Criteria

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

1) 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 3 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
2) Received a commercially available HBV OAV treatment(s) (tenofovir alafenamide, tenofovir disoproxil fumarate, entecavir, adefovir dipivoxil, lamivudine, telbivudine, either as single agents or in combination) within the 3 months prior to screening.
3) Received prolonged therapy with immunomodulators (e.g., corticosteroids) or biologics (e.g., monoclonal antibody, interferon) within 3 months of screening
4) Subjects meeting any of the following laboratory parameters at screening:
   a) Hemoglobin < 12 g/dL (for males) or <11 g/dL (for females)
   b) White Blood cell count < 2500 cells/mm^3
   c) Neutrophil count < 1500 cells/mm^3 (or < 1000 cells/mm^3 if considered a physiological variant in a subject of African descent)
   d) Alanine aminotransferase (ALT) >5x ULN
   e) International normalized ratio (INR) > ULN unless the subject is stable on an anticoagulant regimen affecting INR
   f) Albumin < 3.5 g/dL
   g) Direct bilirubin >1.5x ULN

h) Platelet Count < 100,000/μL

i) Estimated creatinine clearance (CrCl) < 60 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the screening evaluation, i.e.,

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

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

5) Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV)

- Subjects who are HCV Ab positive, but have a documented negative HCV RNA, are eligible

6) Prior history of hepatocellular carcinoma (HCC) (e.g., as evidenced by prior imaging) or screening alpha-fetoprotein (AFP) ≥ 50 ng/mL without imaging to rule out HCC.

7) 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.

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

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

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

11) Received solid organ or bone marrow transplant.

12) Use of another investigational agent within 90 days of screening, unless allowed by the Sponsor.

13) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance.

14) Known hypersensitivity to study drugs or formulation excipients.

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

16) Female subjects unwilling to refrain from egg donation and in vitro fertilization during and until at least 30 days after the last study drug dose.

17) Male subjects unwilling to refrain from sperm donation during and until at least 90 days after the last study drug dose.

18) Use of any prohibited concomitant medications as described in Section 5.5 and Table 5-1.

Believed by the Study Investigator to be inappropriate for study participation for any reason not otherwise listed.

Study Procedures/ Frequency:

All subjects will be required to participate in the following visits:

- Screening Visit (up to -30 days of Baseline visit)
- On-Treatment Period Visits: Day 1 (includes post-dose 1 and 4 hour assessments), Day 1 + 24 hours (Day 2), Weeks 2, 4, 8, 11 (includes post-dose 1 and 4 hour assessments), 12, 16, 20, 23 (includes post-dose 1 and 4 hour assessments), and 23 + 24 hours
- Post GS-9688/PTM Study Treatment Period: Weeks 24, 28, 36, and 48

Screening assessments include:

- Obtain Informed Consent[redacted]
- Review of inclusion/exclusion criteria
- Obtain medical history (including HBV disease and treatment history)
- Review concomitant medications
- Complete Physical examination (including weight, height, BMI, vital signs)
- Safety laboratory tests (serum chemistry, hematology, and coagulation)
- 12-lead ECG

- Ophthalmologic exam (Days -10 to -1)
- Qualitative HBV serology (HBeAg [reflex Hepatitis B e-Antigen (HBeAb) if HBeAg is negative] and HBsAg [reflex Hepatitis B surface Antigen (HBsAb) if HBsAg is negative])
- HBV DNA levels and resistance surveillance sample
- HBV Genotyping by history (if known) and laboratory testing
- Quantitative HBsAg
- HCV, HDV and HIV Ab testing (with reflex testing performed if positive)
- FibroTest
- AFP (Imaging test required to rule out HCC for subjects with AFP ≥ 50 ng/mL)
- Urinalysis and urine drug screen
- For all female subjects of child-bearing potential, serum beta human chorionic gonadotropin (β-hCG)
- For female subjects post-menopausal for less than two years, serum follicle-stimulating hormone (FSH) testing (if FSH < 40 mIU/mL a serum pregnancy test will be required)
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form

On-treatment assessments

All Day 1 (Baseline) tests and procedures must be completed prior to the receipt of the first dose of study drug.

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All On-Treatment Assessments (Day 1 through Week 23 +24 hours) should be obtained pre-dose unless otherwise indicated:

- Review of inclusion/exclusion criteria and confirm medical history on Day 1
- Complete pre-dose physical examination (includes weight, height, BMI, vital signs, concomitant medications and adverse events [AEs]) on Day 1 and Weeks 2, 4, 8, and 12.
- Symptom directed physical exam (includes weight, vital signs, concomitant medications and AEs) on Day 2, Weeks 11, 16, 20, 23 and 23 + 24 hours.

- Ophthalmologic exam on Week 12 (Days -4 to +10)
- In clinic GS-9688/PTM study drug dosing on Day 1 and Weeks 2, 4, 8, 11, 12, 16, 20, and 23. Self/Home GS-9688/PTM study drug dosing on Weeks 1, 3, 5, 6, 7, 9, 10, 13, 14, 15, 17, 18, 19, 21, and 22. Study drug will be taken orally at approximately the same time on the same day once a week (every 7 days) for 24 doses.
- TAF is to be dosed at approximately the same time daily with food or, in jurisdictions in which TAF has been approved, consult the local prescribing information for TAF dose recommendations with concomitant medications. Day 2 through Week 23, TAF dosing will be no earlier than 2 hours post GS-9688/PTM weekly dose.
- Safety laboratory tests (serum chemistry, hematology, and coagulation) on Day 1 and Weeks 2, 4, 8, 11, 12, 16, 20, and 23
- Urinalysis on Day 1 and Weeks 2, 4, 8, 11, 12, 16, 20, and 23
- FibroTest on Day 1
- Serum β-hCG, for all female subjects of child-bearing potential on Day 1 and Weeks 4, 8, 12, 16, and 20
- Urine Pregnancy Test, for all female subjects of child-bearing potential on Day 1 and Weeks 2 and 11
- HBV DNA and resistance surveillance on Day 1 and Weeks 2, 4, 8, 11, 12, 16, 20, and 23
- Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) on Day 1 and Week 12
- Quantitative HBsAg on Day 1 and Weeks 2, 4, 8, 11, 12, 16, 20, and 23
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- Whole blood gene expression (Paxgene RNA) samples on Days 1 Pre-dose, 1+4 hour, 1 + 24 hours (Day 2) and Weeks 11 Pre-dose, 11+4 hours, 12, 23, 23 +4 hours, and 23 + 24 hours
- PBMC samples will be collected on Days 1, 1 + 4 hours, 1 + 24 hours (Day 2) and Weeks 11 Pre-dose, 11 + 4 hours, 12, 23, 23 + 4 hours, and 23 + 24 hours
- [redacted]
- Sparse (*pre-identified*) PK plasma sampling will occur on Day 1 and Week 23 at pre-dose, 1, 4, and 24 hours post-dose and Week 11 at pre-dose, 1, and 4 hours post-dose.
- Sparse (*timed*) plasma PK samples will be obtained on any two of the following visits: Weeks 2, 4, 8, 12, 16, and/or 20 at pre-dose and any time between 30 minutes to 4 hours post-dose.
- Holter Monitoring:

  Day 1: Pre-dose (≤ 5 minutes of dose) through 4 hours, and 24 hours

  Week 11: Pre-dose (≤ 5 minutes of dose) through 4 hours

  Week 23: Pre-dose (≤ 5 minutes of dose) through 4 hours, and 24 hours
- [redacted]
- [redacted]
- Randomization on Day 1

If a subject chooses to terminate the study anytime during the treatment period, all subjects should complete <u>all</u> of the above assessments at the ED visit except for the sparse (*pre-identified*) plasma PK sample.

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Post GS-9688/PTM treatment assessments include the following, performed at all visits from Week 24 through Week 48, or in event of ED, unless specifically noted:

- Complete physical examination (includes weight, height, BMI, vital signs, concomitant medications and AEs)
- Ophthalmologic exam on Week 24 (Days -4 to +10)
- Safety laboratory tests (serum chemistry, hematology, and coagulation)
- Urinalysis
- FibroTest on Weeks 24 and 48/ED
- Serum β-hCG, for all female subjects of child-bearing potential
- HBV DNA levels and resistance surveillance samples
- Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) on Weeks 24, 36, and 48/ED
- Quantitative HBsAg
- [redacted]
- [redacted]
- [redacted]
- Whole blood gene expression (PAXgene RNA) samples on Weeks 24 and 48/ED
- PBMC samples will be collected on Weeks 24 and 48/ED
- [redacted]
- If a subject chooses to terminate the study anytime during the post GS-9688/PTM treatment period, all subjects should complete all of the above assessments at the ED visit.

Test Product, Dose, and Mode of Administration:	GS-9688 will be supplied as tablets in strengths of 1.5 mg. Treatment Arm A (PTM): No GS-9688 tablets Treatment Arm B (GS-9688 1.5 mg): 1 x GS-9688 1.5 mg tablet Treatment Arm C (GS-9688 3 mg): 2 x GS-9688 1.5 mg tablets Study drug(s) will be orally administered at approximately the same time, on the same day, once weekly, following an overnight fast (no food or drinks, except water, for at least 8 hours with no food or drinks, including water, for the 1 hour before dosing). After dosing, subjects will continue to fast (no food or drinks, including water) for 2 hours. After 2 hours postdose, water is allowed and after 4 hours postdose, patients are allowed to eat any food or drinks. Subjects should take their other prescribed medications no earlier than 2 hours after GS-9688/PTM dosing or, if medications require dosing with food, no earlier than 4 hours after GS-9688/PTM dosing. Ondansetron dosing is allowed around GS-9688/PTM dosing; dosing of other antiemetics should be discussed with the Gilead MM for approval. TAF will be supplied as a tablet (25 mg) to be given orally at approximately the same time once daily with food or, in jurisdictions in which TAF has been approved, consult the local prescribing information for TAF dose recommendations with concomitant medications for 48 weeks.
Reference Therapy, Dose, and Mode of Administration:	PTM GS-9688 tablets will also be supplied and will be identical in size, shape, color and appearance to the active GS-9688 tablets. Treatment Arm A (PTM): 2 x PTM tablets Treatment Arm B (GS-9688 1.5 mg): 1 x PTM tablet Treatment Arm C (GS-9688 3 mg): No PTM tablets All study treatments will be administered in the same manner, as described above.

Criteria for Evaluation:

Safety:	Safety will be evaluated by assessment of clinical laboratory tests, ECGs/Holter monitoring, periodic physical examinations including vital signs at various time points during the study, including the TFFU Phase, and by documentation of AEs and concomitant medications. An independent, external Data Monitoring Committee (DMC) will review the progress of the study and perform safety data review after

20 subjects have completed randomization. Subsequent meetings may be held approximately every 3 months until the last subject enrolled has completed the GS-9688/PTM study drug dosing period. The DMC will provide recommendations as needed regarding study conduct and the need for additional meetings or an alternative meeting schedule. The DMC will be immediately notified in the event of any dose limiting toxicities (DLT).

Grade 3 and 4 clinically significant laboratory abnormalities, ALT elevations meeting definition of ALT flare or dose-limiting flare, and Grade 2 neutropenia should be confirmed by repeat testing within 7 calendar days of receipt of results.

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Management of Dose Limiting Toxicities

In the event of any DLT, the investigator should discuss with the Gilead Medical Monitor the subject's status until the DLT has resolved.

GS-9688/PTM dosing for a subject will be held if the subject experiences at least one of the following DLTs:

- A confirmed, clinically significant lab abnormality (other than ALT) ≥ Grade 3 considered drug-related by the investigator or Sponsor
- Dose-limiting ALT flare defined as confirmed ALT ≥ 10x ULN

If a subject experiences any of the above DLTs, then GS-9688/PTM will be held until repeat labs demonstrate that the lab abnormality returns to ≤ Grade 2 levels. Once the lab abnormality returns to ≤ Grade 2, GS-9688/PTM can be restarted with Gilead Medical Monitor consultation. Subjects who experience a dose interruption DLT will continue to be monitored at least once a week, or more frequently as clinically needed, until resolution.

GS-9688/PTM dosing for a subject will be permanently discontinued if the subject experiences at least one of the following DLTs:

- A confirmed ALT increase (i.e., grade shift or 2x previous value) with evidence of worsened hepatic function (e.g., Total Bilirubin > 2mg/dL above BL, elevated INR ≥ 1.7 or > 0.5 over BL, abnormal serum albumin > 1g/dL decrease from BL)
- Prolonged (2 sequential), confirmed, clinically significant lab abnormality (other than ALT) ≥ Grade 3 considered drug-related by the investigator
- Any confirmed recurrence of study drug-related Grade 3 or 4 clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of study drug.
- A confirmed ≥ Grade 3 AE (excluding ALT) considered drug-related by the investigator

Subjects who experience a permanent discontinuation DLT will be monitored at least once a week, or more frequently as clinically needed, until resolution.

Refer to Section 7.6.3 for TAF dose modification and monitoring guidelines.

Other Criteria for Discontinuation of Study Drug

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management Section 7.6 of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Subject requests to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3

- Investigator discretion
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC).
- Continuation of dosing will be suspended if three or more Grade 3 or two or more Grade 4 treatment-emergent, drug related AEs or laboratory abnormalities occur. Decisions to reinitiate continuation of dosing will be made by the Sponsor upon review of all safety data generated by subjects dosed to date.

Efficacy:

The **primary efficacy endpoint** is:

- Proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in serum qHBsAg from baseline at Week 24

The **secondary efficacy endpoints** are:

- Proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in serum qHBsAg from baseline at Weeks 4, 8, 12 and 48
- Change in serum qHBsAg ($\log_{10}$ IU/mL) from baseline at Weeks 4, 8, 12, 24 and 48
- To evaluate the proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48
- Proportion of subjects with HBsAg loss at Weeks 12, 24 and 48
- Proportion of subjects with HBeAg loss and seroconversion at Weeks 12, 24 and 48
- Proportion of subjects with virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL)
- Proportion of subjects with drug resistance mutations

Statistical Methods:

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

The primary efficacy endpoint is the proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in qHBsAg from Baseline at Week 24. The primary analysis will be performed in all randomized and treated subjects after the last subject has completed Week 24 assessments or discontinued prematurely. To compare the GS-9688 1.5 mg group and the GS-9688 3 mg group to the PTM group for HBeAg positive

and negative subjects separately, the 95% confidence intervals (CI) on the proportion difference (1.5 mg – PTM, 3 mg - PTM) will be constructed, by baseline HBeAg status (positive, negative), based on the standardized statistic and inverting 2 1-sided tests.

The secondary endpoints include the proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in HBsAg from baseline at Weeks 4, 8, 12 and 48; the proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48; the proportion of subjects with HBsAg loss; the proportion of subjects with HBeAg loss and seroconversion; the change in $\log_{10}$ qHBsAg from baseline; the proportion of subjects with virologic breakthrough; the proportion of subjects with drug resistance mutations; and the PK parameters. Analysis of secondary efficacy endpoints will be performed by treatment group by baseline HBeAg status (positive, negative).

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

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 arm 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
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
°C	degrees Celsius
°F	degrees Fahrenheit
Ab	Antibody
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase (previously serum glutamic pyruvic transaminase)
ANOVA	analysis of variance
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
BCRP	breast cancer resistance protein
BID	twice daily, two a day
BL	baseline
BLQ	below limit of quantitation
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
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable concentration of the drug
C_rC_l	creatinine clearance
C_{max}	maximum observed concentration of drug
COPD	chronic obstructive pulmonary disease
CPN	chronic progressive nephropathy
CRF	case report form
CRO	clinical research organization
CSR	clinical study report

C_{tau}	observed drug concentration at the end of the dosing interval
CYP	cytochrome
cccDNA	covalently closed circular DNA
DDI	drug-drug interaction
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSPH	Drug Safety and Public Health
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISPOT	enzyme-linked immunosorbent spot assay
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FE	food effect
FIH	first-in-human
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
GLSM	geometric least-squares mean
GLP	Good Laboratory Practice
GSI	Gilead Sciences, Inc.
HAV	hepatitis A virus
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBeAb	hepatitis B e antibody
HBsAb	hepatitis B surface antibody
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HED	human equivalent doses
HEV	hepatitis E virus
HDL	high-density lipoprotein

HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HRQoL	Health Related Quality of Life
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
IgM	immunoglobulin M
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug (application)
IRB	institutional review board
IMRS	Interactive Mobile Response System
IUD	intrauterine device
IWRS	Interactive Web Response System
IXRS	Interactive Response System
kg	kilogram
LDH	Lactic acid dehydrogenase
LDL	low-density lipoprotein
LLT	lower-level term
LLOQ	lower limit of quantitation
MARCO	macrophage receptor with collagenous structure
MCV	mean corpuscular volume
mDC	myeloid dendritic cells
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor
NDA	new drug application
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	Nonsteroidal Anti Inflammatory Drug
OAV	oral antiviral
PBMC	peripheral blood mononuclear cell
PCTFE	Polychlorotrifluoroethylene
PD	pharmacodynamic(s)
PD-1	programmed cell death protein 1

PEG	pegylated interferon-α
PG	Pharmacogenomics
P-gp	p-glycoprotein
PHH	primary human hepatocytes
PI	principal investigator
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
PVC	Polyvinyl chloride
PVE	Pharmacovigilance and Epidemiology
QD	One a day, once daily
qHBsAg	quantitative hepatitis B surface antigen
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
RNA	Ribonucleic acid
SAD	single ascending dose
SADR	serious adverse drug reaction
SAE	serious adverse event
SNP	single nucleotide polymorphism
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide /Vemlidy®
TEAE	treatment-emergent adverse event
TFFU	Treatment Free Follow-Up
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
TG	Triglyceride
TLR	Toll-like receptor
TNF	Tumor necrosis factor
$t_{1/2}$	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)
UGT	UDP glucoronosyl transferase

ULN	upper limit of normal
V_z/F	apparent volume of distribution of the drug
WBC	white blood cell
WHO	World Health Organization
WHV	Woodchuck hepatitis virus
WHsAg	Woodchuck hepatitis surface antigen

1. INTRODUCTION

1.1. Background

Chronic hepatitis B (CHB) is a major public health care issue worldwide and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The hepatitis B virus (HBV) is easily transmissible through perinatal, percutaneous, and sexual exposure {World Health Organization (WHO) 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 {World Health Organization (WHO) 2015, 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 2015, an estimated 654,000 deaths were due to HBV infection and associated complications, placing it among the top 20 causes of mortality worldwide {G. B. D. Mortality Causes of Death Collaborators 2016}.

The loss of HBsAg, accompanied by seroconversion to anti-HBsAg, is the accepted endpoint for anti-HBV therapy endorsed by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver allowing for cessation of therapy {European Association for the Study of the Liver 2017, European Association for the Study of the Liver (EASL) 2012, Lok 2009, Sarin 2015, Terrault 2016}. Clearance of HBsAg has been associated with improvements in liver histology, including the reversal of cirrhosis, a decreased risk of HCC, and prolonged survival, and is considered evidence of a functional cure {Benias 2011, Fattovich 1998, Kim 2013}.

Nucleos(t)ide analogs are the standard-of-care for CHB treatment, providing durable suppression of viral replication that results in long-term clinical benefits with a reduced risk of liver complications {Dienstag 2003, Liaw 2011, Lok 2013}. However, treatment with nucleos(t)ide inhibitors rarely results in clearance of HBsAg and seroconversion to anti-HBsAg {Kwon 2011}. Thus, new treatment options that enhance rates of HBsAg clearance and seroconversion are needed; such treatments will allow patients to discontinue life-long oral antiviral therapy and provide a finite-duration treatment option for a functional cure. A finite therapy is expected to be applicable to a broader population of those chronically infected with HBV, including immunotolerant patients who are currently untreated.

The host immune response to HBV infection plays a pivotal role in whether acute infection is resolved or becomes chronic. Individuals who are able to clear HBV infection spontaneously following an acute infection display a vigorous, polyclonal, HBV-specific $CD8^+$ 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 natural killer (NK) cell antiviral function {Peppa 2010, Rehermann 2005}.

Toll-like receptors (TLRs) are a family of membrane-bound pattern recognition receptors that play a central role in both innate and adaptive immunity by recognition of pathogen-associated molecular patterns from microorganisms {O'Neill 2013}. TLR8 is a transmembrane receptor located in the endosomal membrane of a subset of immune cells and recognizes single-stranded RNA. Published studies have demonstrated that TLR8 activates innate and adaptive effector cell immune responses {Du 2010, Gorski 2006, Jo 2014, Lu 2012, Peng 2005, Wille-Reece 2006}. Activation of TLR8 by a selective, oral, small-molecule agonist with good absorption and high first-pass hepatic clearance to limit systemic activation is therefore a rational approach to safely induce effective antiviral immunity in CHB patients and drive functional cure.

1.2. GS-9688

1.2.1. General Information

GS-9688 is a novel, potent, and selective small molecule agonist of TLR8. GS-9688 directly binds the ectodomain of TLR8 and activates human TLR8 with > 100-fold selectivity over human TLR7. In human peripheral blood mononuclear cells (PBMCs), GS-9688 induces the production of the cellular immune mediator interleukin (IL)-12 and the antiviral cytokines tumor necrosis factor (TNF)-α and interferon (IFN)-γ, but has minimal effects on the levels of IFN-α, a TLR7-induced cytokine. GS-9688 induces cytokine production in myeloid dendritic cells (mDC) and monocytes, but not plasmacytoid dendritic cells; activates natural killer (NK) cells and total $CD8^+$ T cells in vitro in PBMCs isolated from both healthy donors and CHB patients; and increases IFN-γ production and reduces expression of the inhibitory receptor programmed cell death protein 1 (PD-1) by HBV-specific $CD8^+$ T cells. Collectively, these data demonstrate the selectivity and activity of GS-9688 for TLR8 in human primary immune cells.

For further information on GS-9688 refer to the Investigator's Brochure (IB).

1.2.2. Preclinical Pharmacology and Toxicology

GS-9688 has been characterized in repeat-dose oral (once weekly) toxicity studies of up to 26-weeks (27 doses) in mice and 39-weeks (40 doses) in cynomolgus monkeys, genetic toxicology, and phototoxicity studies. The mouse was selected based on its PK properties and previous experience with TLR agonists. In rodents, TLR8 agonists activate TLR7 but not TLR8, and induce a broader immune response than is expected in humans {Hemmi 2002, Liu 2010}. Female mice were used in nonpivotal studies as TLR8 is X-linked {Chuang 2000}; however, no gender-specific toxicities have been observed in repeat-dose toxicity studies with GS-9688. The monkey is the closest pharmacologically relevant species to human for TLR8 activity. Consistent with the intended route of administration in humans, in vivo toxicity studies were conducted by

the oral route of administration. Study designs and parameters evaluated were consistent with accepted principles and practices as outlined by the International Conference on Harmonization (ICH), Organization for Economic Cooperation and Development, and national regulations United States (US) Food and Drug Administration [FDA] and European Community Directives). Unless otherwise noted, all studies were conducted in accordance with US FDA Good Laboratory Practice (GLP) regulations.

In the initial dose range-finding study (2 doses, on Days 1 and 8) studies, mortality in mice was observed following a single dose at 1000 mg/kg due to general debilitation. In the chronic 27 dose study in mice, early mortality was observed in 6 mice administered 30 mg/kg/week, which correlated to an exposure margin of >1400-fold the projected 3 mg clinically efficacious dose.

Ocular

In the 4 week, 5 dose, study in monkeys, early termination (Day 11) of the 300 mg/kg/week group was due to GS-9688-related ocular toxicity and clinical signs of pain/distress associated with these findings. A dose-related bilateral inflammation of the anterior segment of the eyes was observed in 2 of 8 animals in each of the 30 and 100 mg/kg/week groups following ophthalmic evaluation. Changes were partially or completely resolved between each dose at 30 mg/kg/week and in 1 of the 2 animals administered 100 mg/kg/week. In one male at 100 mg/kg/week the inflammatory response progressively worsened and was considered adverse. In the 39 week, 40 dose (30 mg/kg), study in monkeys, 3 of 20 animals administered 30 mg/kg presented with findings consistent with an intraocular inflammatory response. The findings were generally mild, occurred at a low incidence, and/or were self-limiting. In addition, no findings were observed in any animals after the 13-week interim necropsy. The no observed adverse effect level (NOAEL) for ocular findings in the monkey was 30 mg/kg/week. Similar findings have previously been described for another small molecule TLR8 agonist (VTX-2337; motolimod) in non-human primates, but have not been observed clinically {Northfelt 2014}.

No ocular findings were noted in mice at any dose level.

Immunomodulation

Adverse, GS 9688-related, histopathology changes were observed in the kidney, esophagus, thymus, spleen, mesenteric lymph node, mandibular salivary gland, Harderian gland, and/or lacrimal gland of mice administered 30 mg/kg/week in the 27 dose study. Findings with marked severity included: mononuclear cell infiltrates in the kidney, Harderian gland, mandibular salivary gland, and lacrimal gland; fibroplasia in the esophagus; vessel inflammation in the mandibular salivary gland; lymphoid cellularity in thymus and spleen; lymphocyte necrosis in the mesenteric lymph node (males); and moderate and marked severity of chronic progressive nephropathy (CPN) in the kidney. In addition, glomerulonephritis was noted in 2 females. With the exception of CPN, all findings were partially reversed or not observed at the end of the 4-week recovery. As a result of inflammatory findings in the 27 dose study, the NOAEL was 10 mg/kg/week.

In monkeys, multisystemic inflammatory cell infiltrates were noted in the 4-week, 5 dose study in the brain and liver at ≥ 30 mg/kg/week. In the brain, findings of perivascular mononuclear cell infiltrates and/or choroid plexus inflammation at ≥30 mg/kg/week were of increased incidence and/or severity compared with vehicle administered animals. In addition, microgliosis was noted in females administered 100 mg/kg/week. These findings were considered adverse in the monkeys at ≥ 100 mg/kg/week. Inflammatory cellular infiltrates were limited to the liver, gastrointestinal tract, and/or thymus following chronic dosing in the 40 dose study. All changes were considered non-adverse and exhibited reversibility at the end of the recovery phase. Due to the progressive inflammatory infiltrates in the brain at the 100mg/kg/week in the 4-week study and the lack of adverse changes in the 40 dose study, the NOAEL for immumodulation was considered to be 30 mg/kg/week.

GS-9688 is intended for oral administration and evaluation of local tolerance for this route was conducted during the repeat dose studies. There were no treatment-related gastrointestinal effects observed in mice. Emesis was noted at ≥ 10 mg/kg in cynomolgus monkeys; however these observations had no adverse effect on the health of the animals. In addition sporadic findings from male monkeys administered 300 mg/kg/week (terminated early) that were potentially GS-9688 related included occasional fibrin thrombi in the villus lymphatics of the duodenum, jejunum, and/or ileum.

GS-9688 administration is not considered to result in phototoxicity.

At the projected efficacious clinical dose of 3 mg, the anticipated margin of exposure based on the NOAELs in mice and cynomolgus monkey compared to the estimated human exposure $AUC_{0\text{-}24}$ (0.56 ng•h/mL) in virally suppressed CHB subjects is 332- and 64-fold, respectively.

1.2.3. Genotoxicity

GS-9688 was negative in the bacterial reverse mutation (Ames) assay. GS-9688 was considered negative for inducing chromosomal aberrations when tested with and without metabolic activation up to the limit dose level or limits of cytotoxicity. In addition, GS-9688 was negative in the in vivo rat bone marrow micronucleus assay at exposures of up to 5400-fold the human exposure ($AUC_{0\text{-}24}$) of 0.56 ng•h/mL at the projected 3 mg clinically efficacious dose; therefore, GS-9688 was considered non-genotoxic.

1.2.4. Safety Pharmacology

To support the proposed clinical development plan, the nonclinical safety profile of GS-9688 was characterized in studies evaluating the potential pharmacologic effects on specific organ systems. Study designs and parameters evaluated were consistent with accepted principles and practices as outlined by the ICH and the US FDA Center for Drug Evaluation and Research. All studies were conducted in accordance with ICH GLP regulations.

In safety pharmacology studies, there were no clinically-relevant effects on the central nervous and respiratory systems in mice at exposures approximately 2900-fold above the estimated human protein-free C_{max} of 0.015 ng/mL at the projected 3 mg clinical efficacious dose.

In telemetered cynomolgus monkeys, no adverse cardiovascular effects were noted at doses up to 100 mg/kg. A non-dose dependent increase in heart rate (up to 43%) was noted 2-4 hours post dose. These changes in heart rate can be correlated with elevated inflammatory biomarkers associated with TLR8 agonists {Northfelt 2014} and have been associated with increased resting heart rate {Whelton 2014}. Minimal body temperature changes at 100 mg/kg, resulting from a lack of decrease during the post dose dark cycle were noted at 100 mg/kg and are possibly an exacerbation of stress associated with emesis noted at this dose level (2 of 4 animals). Changes were not considered adverse and could potentially be secondary pharmacodynamic effects of TLR8 stimulation with GS-9688. Based on the Day 1 protein-free C_{max} (1.0 ng/mL, males) in the 4-week (5 dose) study in cynomolgus monkeys, the NOAEL dose was at least 67-fold above the estimated human protein-free C_{max} of 0.015 ng/mL at the projected 3 mg dose.

There was no evidence of significant inhibition of the hERG potassium channel current by GS-9688.

Pretreatment with anti-emetic agents (ondansetron or compazine) or a Nonsteroidal Anti-Inflammatory Drug (NSAID) (ibuprofen) did not substantially alter the PD response to GS-9688 in healthy cynomolgus monkeys.

1.2.5. Nonclinical Pharmacology

GS-9688 activates NK cells in vitro in PBMCs from healthy donors and CHB patients. GS-9688 also increases the expression of the activation marker CD40 in human mDCs and monocytes in vitro, suggesting that GS-9688 has the potential to augment antigen-specific CD8+ T cell responses by enhancing antigen presentation. GS-9688 activates total CD8+ T cells in vitro in PBMCs from healthy donors and CHB patients. GS-9688 increases IFN-γ production while reducing expression of PD-1 by HBV-specific $CD8^+$ T cells in vitro, suggesting that GS-9688 has the potential to restore the functionality of HBV specific $CD8^+$ T cells in vivo.

In HBV-infected primary human hepatocytes (PHH), GS-9688 does not have direct antiviral activity, consistent with the lack of TLR8 expression in this cell type. In contrast, cytokines produced by GS-9688-treated PBMCs reduce the levels of HBV DNA, RNA, HBsAg, and hepatitis B e antigen (HBeAg). This antiviral activity is comparable for all HBV genotypes tested (A, B, and D) and in PHH from multiple donors. GS-9688 induced cytokines do not reduce viral cccDNA levels in PHH with established HBV infection, but treatment of PHH prior to HBV infection blocks cccDNA establishment. These data suggest that GS-9688 has the potential to produce cytokines that inhibit established HBV infection and prevent HBV infection of hepatocytes in vivo.

GS-9688 is a selective agonist of woodchuck TLR8. Administration of 3 mg/kg GS-9688 to woodchucks chronically infected with Woodchuck hepatitis virus (WHV) led to a reduction of serum WHV DNA (2.8 to 7.4 $\log_{10}$) and Woodchuck hepatitis surface antigen (WHsAg) (2.2 to > 4.6 $\log_{10}$) in 4 of 6 animals. This response was sustained in 3 animals until the end of the study (24 weeks after the end of treatment). These 3 animals had > 95% reduction in intrahepatic WHV covalently closed circular DNA (cccDNA), DNA, and RNA at the end of the study. These 3 animals also had detectable anti-WHsAg antibodies and an enhanced

WHV-specific T cell response upon GS-9688 treatment. Doses of 3 mg/kg GS-9688 were generally well tolerated in WHV infected woodchucks.

GS-9688 induces a comparable cytokine response in PBMCs from cynomolgus monkeys and humans, albeit with 10-fold lower potency in cynomolgus monkey PBMCs. In healthy cynomolgus monkeys, oral administration of GS-9688 induces dose-dependent induction of serum IL-12p40, as well as whole-blood macrophage receptor with collagenous structure (MARCO) mRNA. The minimum pharmacologically active dose for oral GS-9688 in cynomolgus monkeys is 0.3 mg/kg.

GS-9688 exhibits minimal cytotoxicity (CC50 from 4.6 to > 44 μM) in human MT-4 lymphoblastoid T-cells, hepatoma-derived Huh7 cells, galactose-adapted HepG2 cells, galactose adapted PC-3 prostate cancer cells, normal human fetal lung fibroblast MRC5 cells, primary rat NRVMs, PHHs, and human PBMCs from healthy donors. This corresponds to a selectivity index of 49-fold to > 473-fold relative to the IL-12p40 EC_{50} in PBMCs. GS-9688 did not show any mitochondria-specific inhibition.

Molecular target screening studies showed that GS-9688 had no activity against a panel of 87 receptors, ion channels, and transporters when tested at a concentration of 10 μM.

In summary, the preclinical pharmacology profile of GS-9688 supports its clinical investigation as a novel agent for the treatment of CHB.

1.2.6. Clinical Trials of GS-9688

1.2.6.1. GS-US-389-2021

Study GS-US-389-2021 was a first-in-human (FIH), randomized, blinded, placebo-controlled, single ascending dose study of GS-9688 in healthy male and female subjects. The primary objective of the study was to evaluate the safety, tolerability and PK of escalating doses of GS-9688 as well as evaluate the effect of food on GS-9688 PK. The effect of GS-9688 on PD markers was also explored.

This FIH study comprised four single ascending dose cohorts (each cohort with 12 active/3 placebo) and one food effect cohort that assessed GS-9688 PK administered under fasted and fed conditions (N=12 active subjects). Doses evaluated were 0.5, 1.5, 3, and 5 mg GS-9688 and the food effect cohort evaluated 1.5 mg GS-9688. For all cohorts, subjects were followed for 14 days following the last dose of GS-9688 and evaluated for safety through the reporting of AEs, physical examination and clinical laboratory test findings, and measurement of electrocardiograms (ECGs), vital signs, and ophthalmologic exams.

The treatment was generally safe. There were no Grade 3 or 4 AEs or serious adverse events (SAEs) reported. No significant alterations in vital signs, ECGs, or ophthalmologic exams were noted in any cohort. No individual subject discontinued due to AEs or laboratory abnormalities and most AEs were mild (Grade 1). The single treatment-emergent, treatment-related Grade 2 AE was exacerbation of intermittent diarrhea in one subject who received GS-9688 1.5 mg as a single dose.

There were no Grade 3 or higher laboratory abnormalities in any cohort. In the 0.5 mg single dose cohort, there were 3 treatment-emergent transient Grade 2 lab abnormalities (lipase in a single subject and cholesterol and low density lipoprotein (LDL) in another subject). In the 1.5 mg single dose cohort, there were 2 treatment-emergent Grade 2 lab abnormalities (LDL and cholesterol, all in a single subject). In the 5 mg single dose cohort, there were 2 subjects with treatment-emergent transient Grade 2 ALT elevation and 1 subject with treatment-emergent transient Grade 1 ALT elevation.

PK data following administration of single doses of GS-9688 at 0.5 mg, 1.5 mg, 3 mg and 5 mg under fasted conditions are shown in Table 1-1. GS-9688 was absorbed quickly following single fasted oral doses with the maximum plasma concentrations (C_{max}) occurring between 0.5 and 1.25 hours (median T_{max}). Less than dose proportional increases in exposure were observed between 0.5 and 1.5 mg dose levels; GS-9688 exhibited dose proportional PK between 1.5 mg and 5 mg doses. Median $t_{1/2}$ at 1.5 mg, 3 mg and 5 mg doses was approximately 5 hours.

Table 1-1. GS-US-389-2021: GS-9688 Plasma Pharmacokinetic Parameters by Treatment Following Single-Dose Administration of GS-9688 in the Fasted State (Cohorts 1 to 4) (GS-9688 PK Analysis Set)

	Mean (%CV)			
GS-9688 PK Parameter	**GS-9688 0.5 mg (N = 12)**	**GS-9688 1.5 mg (N = 12)**	**GS-9688 3 mg (N = 12)**	**GS-9688 5 mg (N = 12)**
AUC_{last} (h•pg/mL)	97.4 (44.4)	152.6 (75.8)	494.9 (53.2)	825.3 (37.6)
AUC_{inf} (h•pg/mL)	124.2 (39.4)	160.3 (72.9)	507.5 (52.2)	847.9 (38.0)
Cmax (pg/mL)	36.4 (111.5)	52.9 (83.0)	165.3 (92.6)	258.1 (55.9)
Tmax (h)[a]	0.50 (0.50, 1.00)	0.75 (0.50, 1.00)	0.75 (0.50, 1.01)	1.00 (0.50, 2.25)
t1/2 (h)[a]	11.28 (8.37, 19.94)	4.28 (2.94, 5.03)	4.91 (4.22, 5.55)	5.05 (4.66, 5.81)

a Values are presented as median (Q1, Q3). Means presented are unadjusted arithmetic means. N is the number of subjects in the PK Analysis Set.

PK data summarizing the effect of moderate fat meal on the pharmacokinetics of GS-9688 1.5 mg are shown in Table 1-2.

Food slowed the rate of absorption of GS-9688 (median T_{max}: 05 hours versus 1.5 hours) without a substantial change in bioavailability, as evidenced by comparable plasma exposures (AUC and C_{max}) upon fed and fasted administration. These results suggest that pharmacokinetics of GS-9688 is not substantially altered by food.

Table 1-2. GS-US-389-2021: GS-9688 Plasma Pharmacokinetic Parameters by Treatment Following Single-Dose Administration of GS-9688 in the Fasted and Fed States (Cohort 6) (GS-9688 PK Analysis Set)

GS-9688 PK Parameter	Mean (%CV)	
	GS-9688 1.5 mg Fed (N = 12)	GS-9688 1.5 mg Fasted (N = 12)
AUC_{last} (h•pg/mL)	268.0 (65.0)	220.8 (76.2)
AUC_{inf} (h•pg/mL)	279.0 (62.9)	236.9 (70.2)
C_{max} (pg/mL)	87.2 (83.8)	92.5 (129.9)
T_{max} (h)[a]	1.50 (0.75, 1.75)	0.50 (0.50, 1.00)
$t_{1/2}$ (h)[a]	5.18 (4.00, 5.78)	4.91 (4.66, 6.84)

a Values are presented as median (Q1, Q3). Means presented are unadjusted arithmetic means. N is the number of subjects in the PK Analysis Set.

IL-12p40, IL-1RA, and MARCO gene expression were evaluated as PD markers of GS-9688 pharmacological activity. IL-12p40 and IL-1RA serum concentrations increased after GS-9688 treatment, with peak concentrations occurring approximately 4 hours postdose. Generally, IL-12p40 and IL-1RA concentrations increased with increasing GS-9688 dose. Increases in IL-12p40 and IL-1RA concentrations were smaller following fed-state treatment compared with fasted-state treatment. Whole blood MARCO gene expression following administration of GS-9688 0.5 mg remained generally constant, with a transient dose-dependent decrease in expression 2 hours postdose.

1.2.6.2. GS-US-389-2022

Study GS-US-389-2022 is a randomized, blinded, placebo-controlled, multiple-dose, dose-escalation Phase 1b study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of GS-9688 in Patients with CHB.

This study consisted of four cohorts: Cohort 1 (evaluating 1.5 mg/placebo to match (PTM), n=10), Cohort 2 (evaluating 1.5 mg/PTM, n=9) and Cohort 4 (evaluating 3 mg/PTM, n=10),GS-9688 or placebo to match was administered in the fasted state once a week (every 7 days) for 2 treatment doses; Cohort 5 (evaluating 3 mg/PTM, n=9), GS-9688 or placebo to match was administered in the fasted state once a week (every 7 days) for 4 treatment doses. Cohorts 3 and 6 were not initiated. For Cohorts 1,2, and 4, subjects were followed for up to 28 days and for Cohort 5 subjects were followed for up to 21 days following the last dose of GS-9688 and evaluated for safety by assessment of clinical laboratory tests, electrocardiograms (ECGs), periodic physical examinations including vital signs, ophthalmic examinations, and by documentation of AEs and concomitant medications.

Single and multiple doses of GS-9688 were generally safe when administered to subjects with CHB who were virally suppressed or viremic. Roughly half of subjects (20 of 38 subjects, 52.6%) had at least 1 AE, the majority of these subjects (15 subjects, 75%) reported only Grade 1 AEs. AEs were observed in all treatment groups except for the viremic (2 doses) placebo group.

Across all subjects, the most commonly reported AEs (ie, AEs reported in ≥ 3 subjects overall) were headache, nausea, dizziness, and chills. More AEs were observed in subjects who received GS-9688 3 mg compared with GS-9688 1.5 mg or placebo and more AEs were observed for virally suppressed subjects who received 4 doses of GS-9688 compared with 2 doses.

Six Grade 2 AEs, including headache, cough, herpes virus infection, nausea, and vomiting, were reported for 5 subjects (13.2%) who were virally suppressed (2 subjects, placebo [2 or 4 doses] and 3 subjects, GS-9688 3 mg [4 doses]). Fifteen of 38 subjects (39.5%) had an AE considered related to study drug by the investigator; of these treatment-related AEs, 4 subjects who were virally suppressed (4 doses) had AEs with severity Grade 2 (herpes virus infection [1 subject, placebo], nausea and vomiting [reported in 1 subject, GS-9688 3 mg], headache and cough [1 subject each, GS-9688 3 mg]).

No Grade 3 or 4 AEs, SAEs, AEs that led to discontinuation or interruption of study drug, or deaths were reported.

Overall, 32 of 38 subjects (84.2%) had a graded laboratory abnormality; the majority of these subjects (18 subjects, 56.3%) had only Grade 1 laboratory abnormalities and 36.8% (14 of 38) had Grade 2 laboratory abnormalities, which were observed in all treatment groups. The most frequently reported Grade 2 laboratory abnormalities were increased low-density lipoprotein (LDL) cholesterol and hyperglycemia (5 subjects overall for both). All other Grade 2 laboratory abnormalities were reported for ≤ 2 subjects overall. No Grade 3 or 4 abnormalities were observed.

Two of 8 viremic subjects who received GS-9688 3 mg reported treatment-related Grade 1 AEs of pyrexia; no other notable changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and temperature) or ECGs were reported. One Grade 1 ophthalmic AE of anterior cell trace was incidentally found on eye exam on Day 9 with no other corresponding ophthalmic AE; the AE was considered study drug-related and resolved by Day 21.

Table 1-3 presents GS-9688 plasma PK parameters following multiple-dose administration (2 or 4 doses QW) of GS-9688 1.5 or 3 mg in subjects who were either virally suppressed or viremic in the fasted state.

GS-9688 was rapidly absorbed following single- or multiple-dose administration of GS-9688 1.5 or 3 mg on Day 1 and Day 8. Mean GS-9688 plasma concentrations and exposure (as measured by AUC_{last}, AUC_{inf}, and C_{max}) increased with increasing GS-9688 dose on Day 1 and Day 8. Analysis using the ANOVA model indicated that exposure was approximately dose proportional between the GS-9688 1.5 mg cohort and the pooled GS-9688 3 mg cohorts.

Table 1-3. GS-US-389-2022: Summary Statistics of GS-9688 Plasma Pharmacokinetic Parameters by Treatment Following Single- or Multiple-Dose (2 or 4 Doses QW) Administration of GS-9688 in Subjects Who Were Virally Suppressed or Viremic (PK Analysis Set).

GS-9688 PK Parameter	Mean (%CV)			
	Virally Suppressed (2 Doses)			
	GS-9688 1.5 mg		GS-9688 3 mg	
	Day 1 (N=8)	Day 8 (N=8)	Day 1 (N=7)	Day 8 (N=7)
AUC_{last} (h•pg/mL)	304.9 (35.8)	351.4 (37.7)	624.7 (76.5)	434.0 (44.0)
AUC_{inf} (h•pg/mL)	315.9 (36.1)	364.5 (38.1)	641.5 (74.2)	444.5 (43.5)
C_{max} (pg/mL)	105.4 (32.2)	140.3 (34.2)	266.5 (83.2)	234.8 (68.3)
T_{max} (h)[a]	1.00 (0.75, 1.00)	0.50 (0.50, 1.00)	0.50 (0.25, 2.00)	0.50 (0.50, 0.50)
$t_{1/2}$ (h)[a]	5.63 (5.16, 6.11)	5.54 (4.64, 6.26)	5.26 (3.86, 6.19)	5.32 (4.60, 6.05)
GS-9688 PK Parameter	**Mean (%CV)**			
	Virally Suppressed (4 Doses)		**Viremic (2 Doses)**	
	GS-9688 3 mg		**GS-9688 1.5 mg**	
	Day 1 (N=8)	**Day 8 (N=8)**	**Day 1 (N=8)**	**Day 8 (N=8)**
AUClast (h•pg/mL)	932.4 (53.0)	967.4 (61.1)	944.0 (65.1)	899.9 (61.2)
AUCinf (h•pg/mL)	950.4 (52.5)	986.4 (60.8)	959.5 (64.5)	918.8 (60.9)
Cmax (pg/mL)	627.8 (84.7)	621.0 (71.0)	627.0 (132.3)	433.4 (79.1)
Tmax (h)a	0.75 (0.50, 1.00)	0.50 (0.50, 0.50)	0.38 (0.25, 1.00)	0.50 (0.50, 1.50)
t1/2 (h)a	4.77 (3.96, 5.73)	5.76 (4.69, 6.00)	4.59 (4.15, 5.05)	4.98 (4.60, 5.95)

a Values are presented as median (Q1, Q3). Means presented are unadjusted arithmetic means. N is the number of subjects in the PK Analysis Set.

1.2.6.3. Ophthalmologic Evaluation in GS-US-389-2021 and GS-US-389-2022

Based on nonclinical ophthalmologic finding in monkeys (Section 1.2.2), multiple, sequential ophthalmologic exams were assessed in subjects receiving GS-9688 in GS-US-389-2021 and GS-US-389-2022. In the FIH study in healthy volunteers, GS-US-389-2021, there were 3 treatment-emergent ophthalmologic abnormalities (1 each in 1.5 mg, 3 mg, and placebo groups). The subject receiving 1.5 mg had the abnormality of pupils partially dilated noted on Day 7 and was considered study procedure related; the subject had a corresponding TEAE of visual impairment (with reported term of intermittent visual disturbance) starting on Day 4 and ending on Day 14. It was in the opinion of the onsite ophthalmologist that the visual impairment symptoms were related to the dilated ophthalmic assessments performed during the study. The subject in the 3 mg group had a small conjunctival scar noted on Day 2 exam and the placebo subject had a slight increase in pigment cells in the left eye on Day 7. Neither of these 2 subjects had a corresponding ophthalmologic TEAE.

In study GS-US-389-2022, three treatment-emergent ophthalmic abnormalities were reported, all Grade 1 in severity as follows:

- One subject (GS-9688 1.5 mg [2 doses], virally suppressed) reported Grade 1 eye pruritus starting on Day 13 and ending on Day 26; this was assessed by the clinical investigator as not related to study drug or study procedures. At screening, the subject was noted to have dry eye signs and there were no changes noted on ophthalmologic exams; on the final visit on Day 15, the ophthalmologist noted "punctate epitheliopathy noted in right cornea [that] was seen previously".

- The second subject (GS-9688 3 mg [4 doses], virally suppressed), with a medical history of mild cataract (Listing 16.2.4.3), had a reported AE term of Grade 1 anterior chamber cell trace (Listing 16.2.7.1). At the Day 9 ophthalmologic exam (one day after the second GS-9688 dose), the subject was diagnosed to have trace cells in the anterior chamber, which was evaluated as study drug-related. The subject reported no other corresponding ophthalmologic treatment-emergent AE. The subject was started on fluorometholone acetate drops and the AE was resolved by Day 21 at the time of the next ophthalmologic exam as well as on Day 28.

- The third subject (GS-9688 3 mg [2 doses], viremic) reported Grade 1 dry eye on Day 9 that resolved on Day 10 with no intervention; this AE was considered not related to study drug. There were no changes noted on any ophthalmologic exams.

Ophthalmologic exams for all other subjects in Study GS-US-389-2022 showed no significant abnormalities.

1.2.6.4. GS-US-389-3979

Study GS-US-389-3979 is a Phase 1 study in healthy volunteers to evaluate UDP glucoronosyl transferase (UGT) and cytochrome (CYP) P450 – mediated drug-drug interactions between GS-9688 and probe drugs. The primary objectives were to evaluate the effects of probe inhibitor and inducer on the PK of GS-9688. The secondary objective was to assess the safety of GS-9688 when administered with probe drugs. Exploratory assessment of PD biomarkers was also conducted.

This study consisted of cohort 1 (CYP3A inhibitor - voriconazole 200 mg BID), cohort 2 (UGT inhibitor – probenecid 500 mg BID), cohort 3 (CYP1A2/CYP3A inhibitor – ciprofloxacin 500 mg BID), and cohort 4 (CYP450/UGT inducer – rifampin 600 mg QD). For cohorts 1-3, a dose of 1 mg GS-9688 was given on Day 1 followed by a washout, administration of probe inhibitor on Day 7, and coadministration of 1 mg GS-9688 + probe inhibitor on Day 8. For cohort 4, 2 mg of GS-9688 was administered on Day 1, followed by 600 mg of rifampin on Days 2-7 and administration of GS-9688 + rifampin administered (12 hours after GS-9688 dose) on Day 8. For all cohorts, subjects were followed for 14 days after last dose of study drug and evaluated for safety through the reporting of AEs, physical examination and clinical laboratory test findings, and measurement of ECGs and vital signs.

Safety data from GS-US-389-3979 indicate that GS-9688 was generally safe. There were no SAEs or Grade 4 AEs. There were two discontinuations, both considered study drug related. Both discontinuations were in Cohort 4, one subject with transient neutropenia (Grade 3) and one subject with transient elevated liver function tests (Grade 1 ALT and AST on Day 7). The most common Grade 2 AE observed was nausea in 3 subjects (all in cohort 2) with other Grade 2 AEs observed in one subject each with headache (cohort 1), syncope (cohort 4) and vomiting (cohort 4). Overall, most treatment-emergent treatment-related AEs were Grade 1 with the most common AE being nausea. No Grade 4 laboratory abnormalities were observed and Grade 3 lab abnormalities included creatine kinase (CK) (one subject in cohort 1), LDL (one subject each in cohorts 2 and 4), lipase (one subject in cohort 3), cholesterol (one subject in cohort 4), and neutropenia (one subject in cohort 4, as discussed previously).

PD biomarkers IL-12p40 and IL-1RA showed minimal change (~20-37% increase in cohort 1-3 and ~16% decrease in cohort 4) when GS-9688 was co-administered in the presence of probe inhibitors or inducer compared to administration of GS-9688 alone. PD biomarker levels were similar to those observed in study GS-398-2021. PK data (Table 1-4) for this study showed a 3-fold increase in AUC_{inf} and 8-fold increase in C_{max} in GS-9688 exposure when co-administered with a potent CYP3A4 inhibitor voriconazole. Smaller increases in the systemic exposure of GS-9688 with a pan-UGT inhibitor probenecid or a potent CYP1A2/moderate CYP3A4 inhibitor ciprofloxacin were noted. Co-administration with probenecid showed a 45% and 12% increase in AUC_{inf} and C_{max}, respectively. Co-administration with ciprofloxacin showed a 40% and 77% increase in AUC_{inf} and C_{max}, respectively, likely due to CYP3A inhibition. The coadministration of the inducer rifampin showed a 47% and 50% decrease in AUC_{inf} and C_{max} of GS-9688, respectively.

The data suggest that GS-9688 metabolism is primarily mediated by CYP3A4 with CYP1A2 and UGT playing a less important role. Based on these data, the use of strong inhibitors or inducers of CYP3A with GS-9688 is not currently recommended. GS-9688 may be co-administered with CYP1A2 or UGT inhibitors or inducers.

Table 1-4. GS-US-389-3979: Statistical comparison of GS-9688 Pharmacokinetic Parameters following single dose administration of GS-9688 in the presence of probe drug (Day 8) and GS-9688 alone (Day 1).

Parameter	Cohort 1 (VORI)	Cohort 2 (PBC)	Cohort 3 (CIPRO)	Cohort 4 (RIF)
AUC_{inf}	340.5 (262.3, 442.0)	144.3 (123.8, 168.2)	139.6 (125.2,155.6)	47.0 (39.6,55.6)
C_{max}	801.1 (583.3, 1100.2)	112.8 (94.5, 134.5)	176.77 (142.2,219.8)	50.27 (39.6, 63.8)

Data are: GLSM ratio (90% CI). GLSM = geometric least-squares mean; CI = Confidence Interval
GLSM ratio = Day 8 / Day 1, Day 8 = GS-9688+probe, Day 1 = GS-9688
VORI = voriconazole (200 mg BID), PBC = probenecid (500 mg BID), CIPRO = ciprofloxacin (500 mg BID), RIF = rifampin (600 mg QD).

1.2.6.5. GS-US-389-4564

Study GS-US-389-4564 is a Phase 1 study in healthy volunteers to evaluate the PK, PD, safety, and tolerability of GS-9688 in smoking and nonsmoking subjects.

Nonclinical and clinical DDI data (Study GS-US-389-3979) suggested that GS-9688 metabolism in humans is mediated primarily by oxidation via CYP3A4 with minor contribution of glucuronidation via UGT, and negligible to no contribution by CYP1A2. GS-9688 is also a substrate for human CYP1A1 in vitro (Study AD-389-2035). CYP1A1 is expressed in lung tissue and is known to be induced by smoking {Ding 2003, Kim 2004, Thum 2006}. According to the Centers for Disease Control and Prevention, the prevalence of cigarette smoking among adults in the US has remained approximately 15% to 20% in recent years. Smoking is more prevalent in other regions of the world and in certain ethnic populations, and can be even more prevalent in HBV infected subjects {Yi 2018}. Therefore, it was important to understand the in vivo impact of smoking on GS-9688 PK and provide guidance on GS-9688 administration in smokers.

Subjects were defined as smokers if they consumed ≥ 20 cigarettes per day for at least 6 months prior to enrolling in the study and had a urine cotinine level > 500 ng/mL at screening, and as nonsmokers if they had not smoked during the 6 months prior to dosing and had a urine cotinine level ≤ 20 ng/mL at screening. Following single-dose administration of GS-9688, lower GS-9688 plasma exposures were observed in smoking subjects compared with nonsmoking subjects, as reflected in the 23% and 26% decrease in GS-9688 AUC_{inf} and C_{max}, respectively. The T_{max} and $t_{1/2}$ were similar in smoking and nonsmoking subjects. These data suggest that CYP1A1 does not play an important role in GS-9688 metabolism and are in agreement with the clinical DDI study results (Study GS-US-389-3979).

Mean IL-12p40 and IL-1RA serum concentrations increased following single-dose administration of GS-9688 2 mg, with similar concentration profiles observed in smokers and nonsmokers. Serum concentrations of IL-12p40 and IL-1RA reached peaks at 4 hours postdose and returned to approximate baseline levels 24 hours postdose. There were numerically higher mean concentration ratios for IL-12p40 in smokers and for IL-1RA in nonsmokers at all postdose time points following GS-9688 administration. The variability in the magnitudes of the PD responses, together with the lack of a systematically higher PD response in 1 cohort versus the other, led us to conclude that there was no substantive difference in the PD responses when GS-9688 was administered in smoking and nonsmoking subjects.

GS-9688 was well tolerated by smoking and nonsmoking subjects. There were no SAEs, AEs that led to premature discontinuation of study drug, or deaths reported during this study. All AEs and the majority of graded laboratory abnormalities were Grade 1 or 2 in severity. There were no notable trends in vital signs measurements and no clinically significant ECG abnormalities.

Overall, a slight decrease in GS-9688 plasma exposures and no substantive difference in biomarker responses were observed in smoking subjects compared with nonsmoking subjects. These data suggest a minimal impact of smoking on GS-9688 PK/PD and support GS9688 administration without regard to smoking status.

1.3. Rationale for This Study

1.3.1. GS-9688 for Viremic Subjects with Chronic Hepatitis B Not Currently on Treatment

Given the low rate of HBsAg loss/seroconversion 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/seroconversion with finite treatment duration. The primary objective is to evaluate the safety, tolerability and efficacy of GS-9688 in association with an oral nucleotide HBV polymerase inhibitor, TAF, for the treatment of CHB subjects, and secondary objectives include evaluating the changes in HBV specific immune responses following treatment with GS-9688.

This Phase 2 study will be conducted in viremic CHB subjects not currently on treatment. Subjects with CHB generally have a rapid decline in viremia in response to beginning antiviral treatment. The decrease in viral burden may allow for increased responsiveness to immune stimulation and forms the basis for the design of this study. Of note, only subjects with sufficient hepatic reserve will be included in this study to further maximize safety.

1.3.2. Rationale for the Dose Selection

Selection of the weekly administration of 1.5 mg and 3 mg is based on preclinical data and the safety, tolerability, PK, and PD data from the single ascending dose first in human (FIH) study in healthy volunteers (GS-US-389-2021) and the preliminary data from the ongoing Phase 1b study (GS-US-389-2022) in virologically suppressed (on OAV treatment) patients with CHB.

From available clinical data, a dose of 1.5 mg was chosen as it has resulted in quantifiable and consistent increases in PD biomarkers IL-12 and IL-1RA in both the FIH study and the ongoing Phase 1b study. In the Phase 1b study with CHB subjects, the 1.5 mg dose was well-tolerated and safe as discussed in (Section 1.2.6.2).

The highest GS-9688 dose planned to be developed in clinical studies is 3 mg. This maximum dose has been defined based on the available safety and tolerability data and PK and PD results from the FIH study and the ongoing Phase 1b study. The FIH study GS-US-389-2021 showed that GS-9688 was generally safe with single doses up to 5 mg (Section 1.2.6.1). At the highest dose evaluated, 5 mg, two subjects had a grade 2 laboratory abnormality of elevated ALT. Accordingly, GS-9688 doses of 1.5 mg and 3 mg have been selected for subsequent evaluation. Further, the FIH study showed dose dependent systemic exposure (AUC and Cmax) and PD increases (IL-12p40 and IL-1RA) peripheral cytokine induction with GS-9688 doses ranging from 0.5 mg up to 5 mg. Dosing with food resulted in smaller increases in IL-12p40 and IL-1RA serum concentration compared with fasted state dosing; therefore dosing will be in the fasted state.

In GS-US-389-2022, two or four weekly doses of 1.5 or 3 mg have been evaluated in HBV infected patients. Safety demonstrated that GS-9688 is generally well-tolerated as discussed previously (Section 1.2.6.2). There were no SAEs, no treatment discontinuations due to AEs, and no Grade 3 or higher treatment-emergent laboratory abnormalities in either cohort. Similar to

data from the FIH study, data shows evidence of biological activity with dose dependent induction of IL-12p40 and IL-1RA and PK data shows a similar profile in patients compared to healthy volunteers in the FIH study, with minimal to no accumulation with time (Section 1.2.6.2).

Thus, based on preclinical data, safety and tolerability and available PD and PK data from both the FIH study and Phase 1b trial, GS-9688 doses of 1.5 mg and a maximal dose of 3 mg is supported to explore safety, tolerability and efficacy in viremic CHB patients not currently on treatment.

1.3.3. Rationale for Treatment Duration

As no reductions in HBsAg levels were anticipated or observed with 2 once-weekly doses, longer treatment duration of 24 weeks is being explored. This duration is based on nonclinical data with GS-9688 that demonstrated efficacy in the woodchuck animal model of CHB. In this model, 8-12 weeks of exposure induced persistent reduction in WHsAg to undetectable levels in a subgroup of animals with response rate increasing over time. Given the preclinical efficacy data that suggests longer treatment duration may be required to achieve higher rates of antiviral response, this study will evaluate a 24 week treatment duration.

More frequent observation and safety labs at the start of treatment, along with clear management of dose limiting toxicities (Section 7.6.2) will allow an adequate assessment of safety with repeated dosing and a rigorous evaluation of efficacy based on reductions in serum HBsAg levels.

1.4. 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.

1.4.1. 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

1.4.2. 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 (OAV) 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 1-5. 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 OAV 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 1-5. 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 1-6 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 1-6. 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 1-7. 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 1-7. 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 1-5 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 1-8 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 1-8. 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 1-9 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 1-9. 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 1-10 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 1-10. 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 1-11 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 1-11. 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' means 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.

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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.

1.5. Risk/Benefit Assessment for the Study

GS-9688 is being developed to provide patients with CHB with a finite duration, curative treatment option and for beneficial antiviral response without inducing a significant systemic immune response. Published studies have demonstrated that TLR8 activates innate and adaptive effector cell immune responses {Du 2010, Gorski 2006, Jo 2014, Lu 2012, Peng 2005, Wille-Reece 2006}. Activation of TLR8 by a selective, oral, small-molecule agonist with good absorption and high first-pass hepatic clearance to limit systemic activation is therefore a rational approach to safely induce effective antiviral immunity in CHB patients and drive functional cure.

The loss of HBsAg with seroconversion is the gold standard endpoint for anti-HBV therapy and allows for cessation of treatment {European Association for the Study of the Liver 2017, Liaw 2012, Sarin 2015, Terrault 2016}. 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 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 after multiple 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 with seroconversion are needed. Through effects on both innate and adaptive immune effectors (including HBV-specific T cells), agonist-induced activation of TLR8 may provide a novel component of treatment for patients with chronic HBV infection.

In human studies, dose escalation in healthy volunteers demonstrated dose-dependency of AEs with the highest evaluated dose of 5 mg demonstrating significant increases in nausea and vomiting and with several subjects experiencing transient ALT elevations at the highest dose. Importantly, at doses of 1.5 and 3 mg evaluated in the Phase 1b study in CHB patients (GS-US-389-2022), rates of nausea, vomiting, and laboratory abnormalities have been limited. Nonclinical data in cynomolgus monkeys suggest that vomiting AEs are sporadic with no persistence and no morbidity or mortality associated with vomiting was noted. Currently, it is not known if there will be any treatment effects associated with longer treatment duration.

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 7.6.2 and 7.9. Based on safety data from 3 clinical trials (completed or ongoing), a number of dose limiting toxicities (DLTs), including ALT elevation and neutropenia, are identified that would determine if treatment should be discontinued in a patient. In addition, risk will be further minimized with the inclusion of a data safety monitoring committee that will periodically evaluate the safety of the entire study and verify independently if the benefits of the trial continue to outweigh any risks observed. In summary, the goal of the GS-9688 program is to address a major unmet need for CHB patients, namely to enhance rates of serum HBsAg loss with seroconversion with a finite duration treatment regimen. Study GS-US-389-2025 will investigate the efficacy of 24 doses of GS-9688 at two dose levels (1.5 and 3 mg) administered weekly, in association with TAF administered daily, to viremic CHB patients not currently on treatment.

The risks of treatment with GS-9688 in pregnancy have not been evaluated. Pre-clinical data has shown that the potential for GS-9688 to affect the PK of other drugs via CYP450, or UGT enzymes or drug transporter (p-glycoprotein [P-gp]/ Breast Cancer Resistance Protein [BCRP]) is low. Oral contraceptives are mainly metabolized by CYP450 enzymes and may be substrates for P-gp/BCRP. If females are using hormonal agents for contraception, the likelihood for substantial changes in safety and/or efficacy of the contraceptive via drug-drug interaction (DDI) is low. Please refer to the current Investigator's Brochure for additional information about GS-9688.

Based on in vitro data and preliminary data from the DDI study (GS-US-389-3979), GS-9688 is mainly metabolized by CYP450 enzymes. In this study, the inhibition or induction of CYP3A showed a decrease in GS-9688 exposure, thus drugs that are known to be potent CYP3A inhibitors/inducers of CYP3A are prohibited in this study.

Further, pre-clinical data showed that GS-9688 is unlikely to be a perpetrator of DDIs (based on inhibition and induction studies of CYP450 enzymes and drug transporters). OAVs used in the treatment of HBV are not metabolized CYP450 enzymes. Thus, it is not expected that GS-9688 will result in DDIs with OAVs used to treat HBV.

Based on available information, the benefit/risk balance for this study is 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 as follows:

- To evaluate the safety and tolerability of multiple oral doses of GS-9688 at Week 24 in CHB adult subjects who are viremic and not currently not being treated
- To evaluate the antiviral activity of GS-9688 as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from baseline in serum quantitative hepatitis B surface antigen (qHBsAg) at Week 24

The secondary objectives of this study are as follows:

- To evaluate the antiviral activity of GS-9688 at Weeks 4, 8, 12 and 48 as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from baseline in serum qHBsAg
- To evaluate the change in serum qHBsAg ($\log_{10}$ IU/mL) from baseline to Weeks 4, 8, 12, 24 and 48
- To evaluate the proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48
- To evaluate the proportion of subjects with HBsAg loss at Weeks 12, 24 and 48
- To evaluate the proportion of subjects with Hepatitis B e-Antigen (HBeAg) loss and seroconversion at Weeks 12, 24 and 48
- To characterize the PK of GS-9688
- To evaluate the proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL)
- To evaluate the incidence of drug resistance mutations


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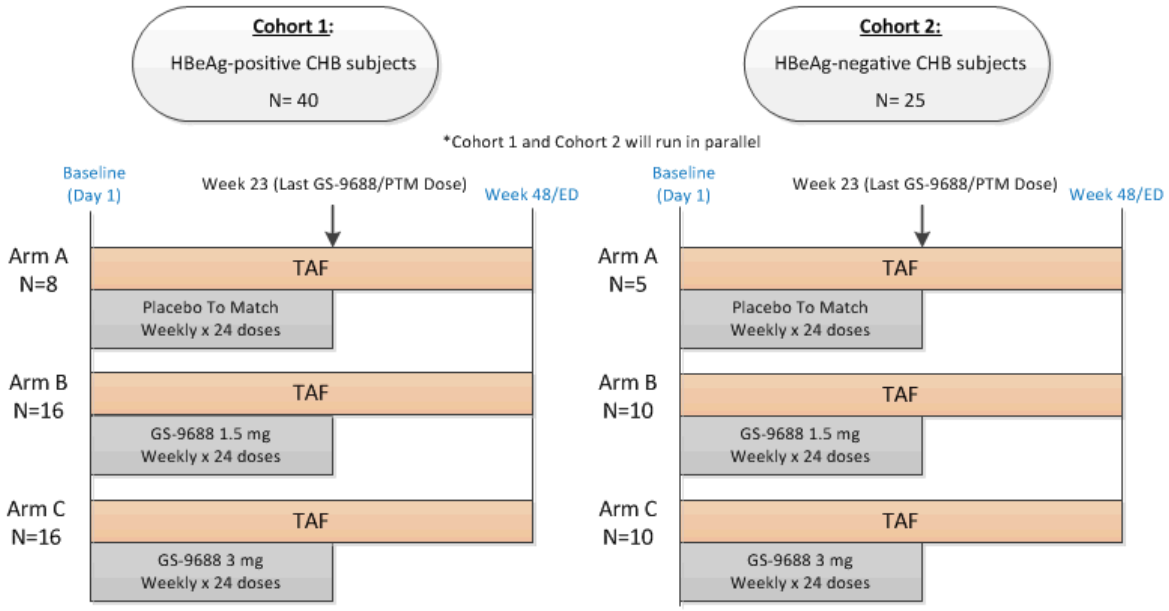
3. STUDY DESIGN

3.1. Study Design

This is a multicenter, randomized, double-blinded, placebo-controlled Phase 2 study of GS-9688/PTM in viremic adult CHB subjects not currently on OAV treatment.

Figure 3-1. Study Schema



a At Week 48, per PI's discretion, subjects will be managed in one of two ways:
1. Continue in the study for 48 weeks following the discontinuation of TAF (TFFU, window of ± 7 days) or until an alternative commercially approved CHB treatment is started, whichever occurs first
2. Initiate other standard of care CHB therapy with Week 48 representing the last study visit

3.2. Study Treatments

Approximately 65 viremic subjects who are not currently being treated for CHB will be enrolled into two cohorts within this study that will run in parallel.

- Cohort 1 (n = 40): HBeAg-positive CHB subjects
- Cohort 2 (n = 25): HBeAg-negative CHB subjects

Within each cohort, subjects will be randomized in a 1:2:2 in ratio to one of the three treatment arms (A: B: C) for weekly dosing of GS-9688/PTM for 24 doses.

All subjects will also be treated with TAF 25 mg oral daily for the duration of the study, 48 weeks, in addition to the following treatments:

Treatment Arm A: Approximately 8 subjects in Cohort 1 and approximately 5 subjects in Cohort 2 will be administered placebo-to-match (PTM) orally on the same day once a week (every 7 days) for 24 doses

Treatment Arm B: Approximately 16 subjects in Cohort 1 and approximately 10 subjects in Cohort 2 will be administered GS-9688 1.5 mg orally on the same day once a week (every 7 days) for 24 doses

Treatment Arm C: Approximately 16 subjects in Cohort 1 and approximately 10 subjects in Cohort 2 will be administered GS-9688 3 mg orally on the same day once a week (every 7 days) for 24 doses

All GS-9688 study drug doses will be administered in fasted state.

After the 24th dose (Week 23 visit), GS-9688/PTM will be discontinued. Subjects will continue being treated with TAF and will be followed until Week 48/ED. The total study duration for each subject will be 48 weeks with up to an additional 48 weeks if continued into the Treatment Free Follow-up (TFFU) phase. Subjects should take TAF and other commercially available medications no earlier than 2 hours after GS-9688/PTM dosing. Ondansetron dosing is allowed around GS-9688/PTM dosing; dosing of other antiemetics should be discussed with the Gilead MM for approval.

Following completion of the 48-week study period the Investigators will be responsible for assessing the need to continue study subjects on treatment for CHB. At Week 48, at Principal Investigator (PI) discretion, subjects will be managed in one of two ways:

1) Continue in the study for 48 weeks following the discontinuation of TAF (Treatment Free Follow-Up, TFFU, window of ± 7 days) or until an alternative commercially approved CHB treatment is started, whichever occurs first

2) Initiate other standard of care CHB therapy immediately at end of study.

At the PI's discretion, subject(s) in the TFFU phase may initiate other standard of care CHB therapy at any time per local treatment guidelines. If a subject initiates other standard of care CHB therapy for their CHB, TFFU visits will continue for 2 more TFFU visits or until the end of the TFFU phase (Week 96), whichever comes first.

The primary analysis will occur after all subjects have completed Week 24 assessment post last dose of GS-9688/PTM or prematurely discontinued with the primary endpoints being the safety and tolerability of GS-9688, as well as assessment of the antiviral activity of GS-9688 at Week 24 as measured by the proportion of subjects with ≥1 $\log_{10}$ (IU/mL) decline from baseline in serum qHBsAg.

The study will be unblinded to appropriate Gilead Sciences Inc., (GSI) study team personnel at the time of primary analysis (Week 24 assessment). An Internal Data Review, external to the study team, may be unblinded at Week 12 assessment visit to review the unblinded safety and efficacy data in order to guide strategic decisions regarding the future of the program. Investigators and subjects will remain blinded through Week 48.

3.3. Duration of Treatment

The total study duration for each subject will be 48 weeks with up to an additional 48 weeks if continued into the TFFU phase. Cohort 1 and 2 consist of 24 doses (Week 23) of treatment of GS-9688 study drug/PTM, and 48 weeks of TAF treatment.

3.4. Pharmacokinetic Assessment

Sparse (*pre-identified*) PK plasma sampling will occur on Day 1 and Week 23 at pre-dose, 1, 4, and 24 hours post-dose and at Week 11 at pre-dose, 1, and 4 hours post-dose. Sparse (*timed*) plasma PK samples will be obtained on any two of the following visits: Weeks 2, 4, 8, 12, 16, and/or 20 at pre-dose and any time between 30 minutes to 4 hours post-dose. See details in Section 6.8.

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[redacted]

3.7. End of Study

The end of this study will be the last subject's last completed study visit at Week 48. If the subject enrolls in the TFFU phase, the subject will be observed for up to an additional 48 weeks (Week 96).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A total of approximately 65 subjects will be enrolled in the study, aged 18-65 years inclusive, with CHB and not currently on OAV treatment.

4.2. Inclusion Criteria

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

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

2) Adult male and non-pregnant, non-lactating female subjects, 18-65 years of age inclusive based on the date of the Screening visit.

3) Documented evidence of chronic HBV infection (e.g., HBsAg positive for more than 6 months) with detectable HBsAg levels at Screening.

4) Females of childbearing potential (as defined in Appendix 3) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline prior to enrollment.

5) Male and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.

6) Screening HBV Deoxyribonucleic acid (DNA) ≥ 2000 IU/mL.

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

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

4.3. Exclusion Criteria

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

1) 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 3 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

2) Received a commercially available HBV OAV treatment(s) (tenofovir alafenamide, tenofovir disoproxil fumarate, entecavir, adefovir dipivoxil, lamivudine, telbivudine, either as single agents or in combination) within the 3 months prior to screening.

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

4) Subjects meeting any of the following laboratory parameters at screening:

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

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

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

d) Alanine aminotransferase (ALT) >5x ULN

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

f) Albumin < 3.5 g/dL

g) Direct bilirubin >1.5x ULN

h) Platelet Count < 100,000/μL

i) Estimated creatinine clearance (CrCl) < 60 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the screening evaluation, i.e.,

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

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

5) Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV)

   - Subjects who are HCV Ab positive, but have a documented negative HCV RNA, are eligible

6) Prior history of hepatocellular carcinoma (HCC) (e.g., as evidenced by prior imaging) or screening alpha-fetoprotein (AFP) ≥ 50 ng/mL without imaging to rule out HCC.

7) 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.

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

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

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

11) Received solid organ or bone marrow transplant.

12) Use of another investigational agent within 90 days of screening, unless allowed by the Sponsor.

13) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance.

14) Known hypersensitivity to study drugs or formulation excipients.

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

16) Female subjects unwilling to refrain from egg donation and in vitro fertilization during and until at least 30 days after the last study drug dose.

17) Male subjects unwilling to refrain from sperm donation during and until at least 90 days after the last study drug dose.

18) Use of any prohibited concomitant medications as described in Section 5.5 and Table 5-1.

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment. Subjects will be assigned a screening number at the time of consent.

All screening procedures must be completed and reviewed by the investigator for eligibility prior to the administration of the first dose of study drug on Day 1. Once informed consent is obtained subjects will be randomized in a 1:2:2 ratio to receive either PTM, blinded GS-9688 1.5 mg, or GS-9688 3 mg. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. If necessary, replacement subjects may be enrolled after discussion and approval from sponsor. A new unique subject number will be assigned to the replacement subject.

The randomization will be performed via an Interactive Mobile Response System (IMRS) or 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.

Investigators and subjects will remain blinded through Week 48 except in instances of emergency treatment unblinding.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the Interactive Response System (IXRS) for that subject. In the event of a system or technology failure, the IXRS provider should be contacted via phone. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

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

In addition, Gilead Pharmacovigilance and Epidemiology (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of GS-9688/PTM and TAF

5.2.1. Formulation

5.2.1.1. GS-9688

GS-9688 is provided as 1.5 mg strength tablets. GS-9688 tablets are round, plain-faced, film-coated white tablets. In addition to the active ingredient, GS-9688 tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, crospovidone, and magnesium stearate. The white tablet film-coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol (PEG) 3350, and talc.

PTM GS-9688 tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The white tablet film-coating contains polyvinyl alcohol, titanium dioxide, PEG 3350, and talc. PTM GS-9688 tablets are identical in size, shape, color and appearance to the active GS-9688 tablets.

5.2.1.2. Vemlidy (TAF Tablets)

Vemlidy (TAF) 25 mg tablets contain 28 mg of tenofovir alafenamide fumarate, which is equivalent to 25 mg of TAF. 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

All study drugs are to be distributed to centers in participating countries and shall be labeled to meet applicable requirements of the local regulations.

5.2.2.1. GS-9688

GS-9688 1.5 mg tablets and PTM tablets are packaged in clear Polyvinyl chloride (PVC) / Polychlorotrifluoroethylene (PCTFE) film blister strips and sealed with aluminum foil lidding material. Each blister strip contains 4 round tablets sealed with an aluminum push through lidding material. GS-9688 active and placebo blister strips in the quantity needed for a 4 week supply of GS-9688 (i.e., 2 strips/8 ct) are placed into a paperboard child resistant wallet system in accordance with the dosage strategy.

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, aluminum-faced liner.

5.2.3. Storage and Handling

To ensure the stability and proper identification, study drugs 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.

5.2.3.1. GS-9688

The recommended storage condition for GS-9688 active and PTM tablets packaged in blister strips/wallet system is as follows: "Store below 30°C." Storage conditions are specified on the label. Until dispensed to the subjects, all study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

5.2.3.2. 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.

5.3. Dosage and Administration of GS-9688/PTM and TAF

Approximately 65 viremic subjects who are not currently being treated for CHB will be enrolled into two cohorts depending on HBeAg status.

- Cohort 1 (n = 40): HBeAg-positive CHB subjects
- Cohort 2 (n = 25): HBeAg-negative CHB subjects

5.3.1.1. GS-9688

Within each cohort, subjects will be randomized in a 1:2:2 in ratio to one of the three treatment arms (A: B: C) for weekly dosing of GS-9688/PTM for 24 doses. Study drug will be taken orally at approximately the same time on the same day once a week (every 7 days). All GS-9688 study drug doses will be administered in fasted state.

Treatment Arm A: Approximately 8 subjects in Cohort 1 and approximately 5 subjects in Cohort 2 will be administered placebo-to-match (PTM) orally on the same day once a week (every 7 days) for 24 doses

Treatment Arm B: Approximately 16 subjects in Cohort 1 and approximately 10 subjects in Cohort 2 will be administered GS-9688 1.5 mg orally on the same day once a week (every 7 days) for 24 doses

Treatment Arm C: Approximately 16 subjects in Cohort 1 and approximately 10 subjects in Cohort 2 will be administered GS-9688 3 mg orally on the same day once a week (every 7 days) for 24 doses

5.3.1.2. TAF

All subjects will also be treated with TAF 25 mg oral at approximately the same time daily with food or, in jurisdictions in which TAF has been approved, consult the local prescribing information for TAF dose recommendations with concomitant medications for 48 weeks. For Baseline through Week 23, TAF dosing will be no earlier than 2 hours post GS-9688/PTM weekly dose.

5.4. Fasting State Dosing

GS-9688/PTM will be orally administered at approximately the same time, on the same day, once weekly, following an overnight fast (no food or drinks, except water, for at least 8 hours with no food or drinks, including water, for the 1 hour before dosing). After dosing, subjects will continue to fast (no food or drinks, including water) for 2 hours. After 2 hours postdose, water is allowed and after 4 hours postdose, patients are allowed to eat any food or drinks. Subjects should take their other prescribed medications no earlier than 2 hours after GS-9688/PTM dosing or, if medications require dosing with food, no earlier than 4 hours after GS-9688/PTM dosing. Ondansetron dosing is allowed around GS-9688/PTM dosing; dosing of other antiemetics should be discussed with the Gilead MM for approval.

5.5. Concomitant and Prohibited Medications

Concomitant medications taken within 30 days prior to Screening, up to and including 30 days after the last administration of study drug need to be recorded in the source documents and eCRFs. Further, any concomitant medications taken during TFFU should also be recorded in the source documents and eCRFs.

Data from the drug-drug interaction study GS-US-389-3979 indicate that CYP3A plays a major role in GS-9688 metabolism and therefore the administration of potent CYP3A inhibitors/inducers is not permitted in this study (see Section 1.2.6.4).

During treatment with GS-9688/PTM, use of the following medications on Table 5-1 are prohibited for a minimum of 21 days prior to the Baseline/Day 1 visit through the last dose of GS-9688/PTM study treatment plus 7 days (except where noted).

This is not an exhaustive list of agents. Any medications not in Table 5-1 should be reviewed with the Sponsor prior to randomization and during the study treatment period with GS-9688/PTM.

Table 5-1. List of Agents Disallowed while on GS-9688/PTM treatment (+7 days)

Drug Class	Agents Disallowed
Acid Reducing Agents[a]	Proton-Pump Inhibitors, H2-Receptor Antagonists, Antacids, Sucralfate
Antibiotics	clarithromycin, rifabutin, rifampin, rifapentin, telithromycin, troleandomycin
Anticonvulsants	carbamazepine, enzalutamide, oxcarbazepine, phenobarbital, phenytoin
Antidepressants	Nefazodone
Antifungals	fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
Antiviral	VIEKIRA PAK (ombitasvir/paritaprevir/ritonavir & dasabuvir), telaprevir, danoprevir, boceprevir
Cardiac Medications	Mifefradil
Diuretics	Conivaptan
GI Motility Agents[b]	Cisapride, metoclopramide, domperidone, mosapride citrate, pruclopride, itopride hydrochloride, levosulpiride
Hematologic stimulating agents	erythropoiesis-stimulating agents; granulocyte colony stimulating factor [GCSF]; and thrombopoietin [TPO] mimetics
Herbal/Natural Supplements	St. John's Wort, Echinaccea. Milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Other	Avasimive, enzalutamide, idelalisib, lumacaftor, nitotane

a Proton pump inhibitors can be taken up to 7 days before study drug dosing (Day 1). H2 receptor antagonists can be taken up to 3 days before study drug dosing (Day 1). Antacids that directly neutralize stomach pH (e.g., Tums, Maalox) are permitted but may not be taken within 4 hours (before or after) study drug administration.
b GI motility agents are prohibited starting 2 days prior to GS-9688/PTM dosing and for the 24 hours postdose

During treatment with TAF (alone or with GS-9688/PTM), use of the following medications listed below and on Table 5-2 are prohibited for a minimum of 21 days prior to the Baseline/Day 1 visit through Week 48/ED:

- Investigational agents or devices for any indication
- Agents that reduce renal function or compete for active tubular secretion with tenofovir (e.g., cidofovir, acyclovir, valacyclovir, ganciclovir, famciclovir, valganciclovir, high dose or multiple NSAIDS, probenecid).
- Nephrotoxic agents (e.g., aminoglycosides, amphoterecin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Systemic chemotherapeutic agents, systemic corticosteroids (except short-term use of prednisone as a steroid burst [≤ 1 week of use], immunosuppressant, or immunomodulating agents

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

Table 5-2. Disallowed Concomitant Medications while on TAF

Medication Class	Prohibited Medications
Anticonvulsants	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin: may lower concentration of TAF and/or TFV
Antimycobacterials	Rifapentine, Rifabutin, Rifampin
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)

Subjects who are currently taking other prescription or non-prescription medications may still be randomized into the study if, in the judgment of the Sponsor and the Investigator, the medication will not interfere with the study procedures or compromise subject safety, efficacy, and/or pharmacokinetic assessments. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication. For subjects requiring treatment with a concomitant medication (including treatment of an adverse event) after starting study drug, the subject's continued participation in the study should be re-evaluated by the investigator, in consultation with the Gilead Medical Monitor (or designee) on an ongoing, case-by-case basis.

Vitamins, acetaminophen, ibuprofen and hormonal contraceptive medications are allowed during the study period. The investigator is authorized to administer acetaminophen or ibuprofen for the treatment of minor ailments occurring on study without prior consultation with the Gilead Medical Monitor. Acetaminophen is the preferred agent, followed by ibuprofen. The Gilead Medical Monitor should be consulted before administering acetaminophen at doses > 2 g/day and ibuprofen as a single dose of >200 mg or >400 mg/day.

5.6. Other Protocol Restrictions

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

- Subjects will be required to refrain from consumption of grapefruit juice, grapefruits, Seville oranges and Seville orange juice 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.

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

5.7. Accountability for GS-9688/PTM and TAF

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

GS-9688/PTM and TAF accountability records will be provided to each study site to:

- Record the date received and quantity of IMP tablets.
- Record the date, subject number and the IMP blister pack/bottle number dispensed.
- Record the date, quantity of used and unused IMP tablets returned, along with the initials of the person recording the information.

5.8. Investigational Medicinal Product Return or Disposal

At the beginning of the study, the study monitor will evaluate the study centers 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 sites 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 bottles and blister packs 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 (Window of -30 Days)

Subjects will be screened within 30 before randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain Informed Consen[redacted]
- Review of inclusion/exclusion criteria
- Obtain medical history (including HBV disease and treatment history)
- Review concomitant medications
- Complete Physical examination (including weight, height, and BMI)
- Vital Signs (blood pressure, heart rate, respiration rate and body temperature)
- Safety laboratory tests (serum chemistry, hematology, and coagulation)
- 12-lead ECG (Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Ophthalmologic exam (Days -10 to -1)

- Qualitative HBV serology (HBeAg [reflex Hepatitis B e-Antigen (HBeAb) if HBeAg is negative] and HBsAg [reflex Hepatitis B surface Antigen (HBsAb) if HBsAg is negative])
- HBV DNA levels and resistance surveillance sample
- HBV Genotyping by history (if known) and laboratory testing
- Quantitative HBsAg
- HCV, HDV and HIV Ab testing (with reflex testing performed if positive)
- FibroTest
- AFP (Imaging test required to rule out HCC for subjects with AFP $\geq$ 50 ng/mL)
- Urinalysis and urine drug screen
- For all female subjects of child-bearing potential, serum beta human chorionic gonadotropin (β-hCG)
- For female subjects post-menopausal for less than two years, serum follicle-stimulating hormone (FSH) testing (if FSH < 40 mIU/mL a serum pregnancy test will be required)
- 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 30 days after screening for randomization 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 (CRF/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 CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Randomization/ Baseline Assessments

All Day 1 (Baseline) tests and procedures must be completed in a fasted state prior to the receipt of the first dose of study drug.

- Review of inclusion/exclusion criteria and confirm medical history
- Complete pre-dose physical examination (includes weight, height, BMI)
- Review concomitant medications and adverse events (AEs)

- Vital Signs (blood pressure, heart rate, respiration rate and body temperature)
- Safety laboratory tests (serum chemistry, hematology, and coagulation)
- Urinalysis
- FibroTest
- Serum β-hCG, for all female subjects of child-bearing potential
- Urine Pregnancy Test, for all female subjects of child-bearing potential
- HBV DNA and resistance surveillance
- Quantitative HBsAg
- Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative])

[redacted]

- Whole blood gene expression (Paxgene RNA) samples on Day 1 Pre-dose, 1 + 4 hours
- PBMC samples will be collected on Day 1 Pre-dose, 1 + 4 hours
- Sparse (*pre-identified*) PK plasma sampling
- Holter Monitoring:

  Day 1: Pre-dose (≤ 5 minutes of dose) through 4 hours, and 24 hours

[redacted]

[redacted]

- Randomization
- In clinic GS-9688/PTM study drug dosing. Study drug will be taken orally at approximately the same time on the same day once a week (every 7 days) for 24 doses.
- TAF is to be dosed at approximately the same time daily with food or, in jurisdictions in which TAF has been approved, consult the local prescribing information for TAF dose recommendations with concomitant medications. Baseline dosing will be no earlier than 2 hours post GS-9688/PTM weekly dose
- Drug Administration of GS-9688/PTM
- Dispense study drugs as directed by IWRS
- Instruct the subject on the packaging, storage, and administration of both study drug GS-9688/PTM and TAF
- Observe the subject taking the first dose of study drug

6.3. Treatment Assessments (All Visits Have Window of ± 1 Days)

All On-Treatment Assessments (Day 2 through Week 23 +24 hours) must be obtained in a fasted state prior to taking study drug unless otherwise indicated:

- Complete pre-dose physical examination (includes weight, height, BMI, vital signs, concomitant medications and adverse events [AEs]) on Weeks 2, 4, 8, and 12.
- Symptom directed physical exam (includes weight) on Day 2, Weeks 11, 16, 20, 23 and 23 + 24 hours.
- Ophthalmologic exam on Week 12 (Days -4 to +10)
- Review concomitant medications and AEs
- Vital Signs (blood pressure, heart rate, respiration rate and body temperature)
- Safety laboratory tests (serum chemistry, hematology, and coagulation) on Weeks 2, 4, 8, 11, 12, 16, 20, and 23
- Urinalysis on Weeks 2, 4, 8, 11, 12, 16, 20, and 23

- Serum β-hCG, for all female subjects of child-bearing potential on Weeks 4, 8, 12, 16, and 20
- Urine Pregnancy Test, for all female subjects of child-bearing potential on Weeks 2 and 11
- HBV DNA and resistance surveillance on Weeks 2, 4, 8, 11, 12, 16, 20, and 23
- Quantitative HBsAg on Weeks 2, 4, 8, 11, 12, 16, 20, and 23
- Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) on Week 12

[redacted]

- Whole blood gene expression (Paxgene RNA) samples on Days 1 + 24 hours (Day 2) and Weeks 11 Pre-dose, 11+4 hours, 12, 23, 23 +4 hours, and 23 + 24 hours
- PBMC samples will be collected on Days 1 + 24 hours (Day 2) and Weeks 11 Pre-dose, 11 + 4 hours, 12, 23, 23 + 4 hours, and 23 + 24 hours

[redacted]

- Sparse (*pre-identified*) PK plasma sampling will occur on Week 23 at pre-dose, 1, 4, and 24 hours post-dose and Week 11 at pre-dose, 1, and 4 hours post-dose.
- Sparse (*timed*) plasma PK samples will be obtained on any two of the following visits: Weeks 2, 4, 8, 12, 16, and/or 20 at pre-dose and any time between 30 minutes to 4 hours post-dose.
- Holter Monitoring:

  Week 11: Pre-dose (≤ 5 minutes of dose) through 4 hours

  Week 23: Pre-dose (≤ 5 minutes of dose) through 4 hours, and 24 hours

[redacted]

- In clinic GS-9688 study drug dosing on Weeks 2, 4, 8, 11, 12, 16, 20, and 23. Self/Home GS-9688 study drug dosing on Weeks 1, 3, 5, 6, 7, 9, 10, 13, 14, 15, 17, 18, 19, 21, and 22. Study drug will be taken orally at approximately the same time on the same day once a week (every 7 days) for 24 doses.

- TAF is to be dosed at approximately the same time daily with food or, in jurisdictions in which TAF has been approved, consult the local prescribing information for TAF dose recommendations with concomitant medications. Day 2 through Week 23, TAF dosing will be no earlier than 2 hours post GS-9688/PTM weekly dose.

- Dispense GS-9688 and TAF on Weeks 4, 8, 12, 16, 20

- Perform study drug accountability on both GS-9688/PTM and TAF

6.4. Post GS-9688/PTM Treatment Assessments (All Visits Have Window of ± 3 Days except Week 24 ± 1 Day)

Post GS-9688/PTM treatment assessments include the following, performed in a fasted state at all visits from Week 24 through Week 48, or in event of ED, unless specifically noted:

- Complete physical examination (includes weight, height, BMI)

- Ophthalmologic exam on Week 24 (-4days to +10 days)

- Review concomitant medications and AEs

- Vital Signs (blood pressure, heart rate, respiration rate and body temperature)

- Safety laboratory tests (serum chemistry, hematology, and coagulation)

- Urinalysis

- FibroTest on Weeks 24 and 48/ED

- Serum β-hCG, for all female subjects of child-bearing potential

- HBV DNA levels and resistance surveillance samples

- Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]) on Weeks 24, 36, and 48/ED

- Quantitative HBsAg

- [redacted]

- [redacted]

[redacted]

- Whole blood gene expression (PAXgene RNA) samples on Weeks 24 and 48/ED
- PBMC samples will be collected on Weeks 24 and 48/ED

[redacted]

- Dispense TAF on Weeks 24, 28, and 36.
- Perform TAF study drug accountability

If a subject chooses to terminate the study anytime during the post GS-9688/PTM period, all subjects should complete all of the above assessments at the ED visit.

6.5. Treatment Free Follow-Up (TFFU) after ED

Subjects who ED will be followed every 4 weeks for 24 weeks or until initiation of alternative CHB therapy, whichever comes first.

6.5.1. TFFU after ED Visit Assessments (± 7 Days)

The following evaluations will be performed at follow up visits for subjects when they discontinue TAF unless otherwise specified. For more details, refer to Appendix 2**.**

- Review of AEs and concomitant medications
- Symptom-directed physical examination
- Vital Signs (blood pressure, heart rate, respiration rate and body temperature)
- Serum pregnancy test (for all female subjects of child-bearing potential)
- Urinalysis
- Safety laboratory tests (serum chemistry, hematology, and coagulation)
- HBV DNA levels and resistance surveillance
- Quantitative HBsAg

[redacted]

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

6.6. TFFU Post Study Completion (Week 48)

Following completion of the 48-week study period the Investigators will be responsible for assessing the need to continue study subjects on treatment for CHB. At Week 48, at PI discretion, subjects will be managed in one of two ways:

1) Continue in the study for 48 weeks following the discontinuation of TAF (Treatment Free Follow-Up, TFFU, window of ± 7 days) or until an alternative commercially approved CHB treatment is started, whichever occurs first. These subjects will be followed every 4 weeks for the first 24 weeks and thereafter at Week 36 and 48 or until initiation of alternative CHB therapy, whichever comes first.

2) Initiate other standard of care CHB therapy immediately at end of study.

6.6.1. TFFU Post Study Completion Visit Assessments (± 7 Days)

The following evaluations will be performed at follow up visits for subjects when they discontinue TAF unless otherwise specified. For more details, refer to Appendix 2.

- Review of AEs and concomitant medications
- Symptom-directed physical examination
- Vital Signs (blood pressure, heart rate, respiration rate and body temperature)
- Serum pregnancy test (for all female subjects of child-bearing potential)
- Urinalysis
- Safety laboratory tests (serum chemistry, hematology, and coagulation)
- HBV DNA levels and resistance surveillance
- Quantitative HBsAg
- [redacted]
- Qualitative HBV serology (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative])
- [redacted]
- [redacted]
- Whole blood gene expression (PAXgene RNA) samples

- PBMC samples

[redacted]

At the PI's discretion, subject(s) in the TFFU phase may initiate other standard of care CHB therapy at any time per local treatment guidelines. If a subject initiates other standard of care CHB therapy for their CHB, TFFU visits will continue for 2 more TFFU visits or until the end of the TFFU phase (Week 96), whichever comes first.

6.7. Unscheduled Visits

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

6.8. Pharmacokinetic Assessments

- **Sparse (*pre-identified*) plasma PK Collection:**

  Day 1: Pre-dose, 1, 4 and 24 hours post-dose

  Week 11: Pre-dose , 1, and 4 hours post-dose

  Week 23: Pre-dose , 1, 4 and 24 hours post-dose

- **Sparse (*timed*) plasma PK Collection (Any 2 of the 2 collections below):**

  Week 2: Pre-dose and any time between 30 minutes to 4 hours post-dose

  Week 4: Pre-dose and any time between 30 minutes to 4 hours post-dose

  Week 8: Pre-dose and any time between 30 minutes to 4 hours post-dose

  Week 12: Pre-dose and any time between 30 minutes to 4 hours post-dose

  Week 16: Pre-dose and any time between 30 minutes to 4 hours post-dose

  Week 20: Pre-dose and any time between 30 minutes to 4 hours post-dose

CCI [redacted]

[redacted]

CCI [redacted]

6.9. Pharmacodynamic Assessments

[redacted]

- **Whole blood gene expression (Paxgene RNA) samples:**

  Days 1: Pre-dose, 4 hours and 24 hours post-dose

  Weeks 11: Pre-dose and 4 hours post-dose

Week 12: Pre-dose

Week 23: Pre-dose, 4 hours and 24 hours post-dose

Week 24

Week 48/ED

TFFU: Weeks 4, 8, 12, 16, 20, 24, 36, and 48

- **PBMC:**

Days 1: Pre-dose, 4 hours, and 24 hours post-dose

Week 11: Pre-dose and 4 hours post-dose

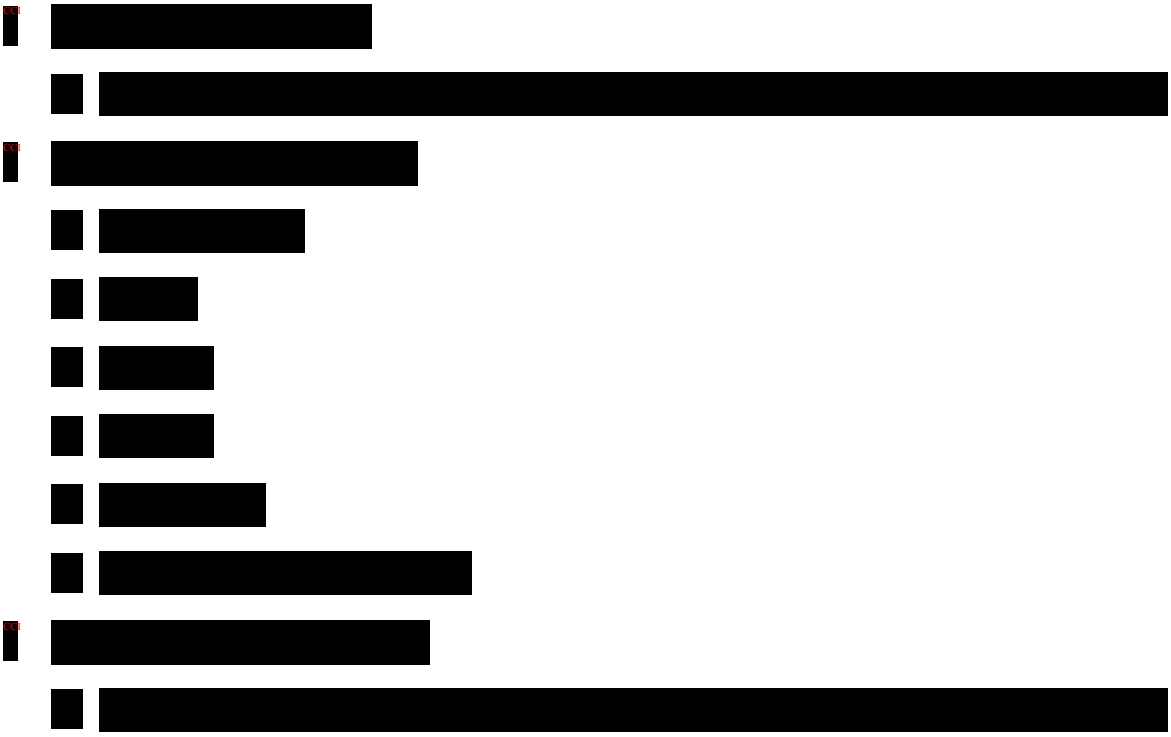
Week 12 Pre-dose

Week 23: Pre-dose, 4 hours, and 24 hours post-dose

Week 24

Week 48/ED

TFFU: Weeks 4, 8, 12, 16, 20, 24, 36, and 48



CCI [redacted]

6.10. Safety Assessments

Assessment of AEs and concomitant medications will continue throughout the duration of the study, including TFFU. Laboratory analyses, physical examinations including vital signs, and ECGs/ Holter monitoring will be performed at defined intervals throughout the study.

Safety Assessments will be performed through the study as outlined in Appendix 2.

6.10.1. Electrocardiogram Assessment

Subjects should rest quietly in the supine position for a minimum of 10 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 prior to any blood draw 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.

6.10.2. Holter Monitoring

For the purposes of this study, time-matched digital 12-lead ECGs will be collected as continuous recordings. ECGs may be extracted from recorded data at a later time.

Holter recording will be obtained via continuous 12-lead digital recorder. Baseline and on-treatment ECGs for all treatments will be measured from the same lead for each subject (lead II, when possible). Triplicate ECGs will be extracted at various time points for each pre-determined time point as indicated below:

- **Holter Monitoring**

  Day 1: Pre-dose (≤ 5 minutes of dose) through 4 hours, and 24 hours

  Week 11: Pre-dose (≤ 5 minutes of dose) through 4 hours

  Week 23: Pre-dose (≤ 5 minutes of dose) through 4 hours, and 24 hours

During ECG sampling, subjects will rest in a supine position for 10 minutes before and during the 5-minute window for each pre-determined ECG acquisition time point. ECGs should be collected in a calm, relaxed environment. Environmental distractions (including TV, radio, video games, and conversation) and the use of electronic devices (including cell phones, tablets, and laptops) during both the pre-ECG rest and the ECG recording period must be avoided.

All ECG acquisitions will be carried out before blood sample collections at that time point.

6.10.3. Physical Examination

Physical examinations conducted throughout the study will be either a complete physical examination or symptom directed physical examination, as outlined in Appendix 2.

The complete physical examination conducted at screening will also include the following assessments:

Review medical history, including history of allergies, prior and current use of ,cigarettes, tobacco, or any smoking products, alcohol and illegal drug use, and prior (within 30 days) and current medication use.

6.10.4. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and oral temperature. Subject body weight will also be assessed at all visits with a complete PE. Refer to Appendix 2 for more information.

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

6.10.5. Clinical Laboratory Tests/Assessments for Safety Evaluations

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

6.10.5.1. 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 INR)

- Chemistry (fasting):

  Alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein (HDL), LDL, triglycerides (TG), total protein, albumin, lactic acid dehydrogenase (LDH), 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 × ULN)

- Serum pregnancy test (females of childbearing potential only)

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

- HIV, HDV, and HCV testing (screening only)

- HBV Viral Parameters:

  Qualitative HBV Serology, HBV DNA levels, HBV Resistance Surveillance, Quantitative HBsAg, CCI [redacted]

6.10.5.2. Urine Samples

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

6.10.6. Creatinine Clearance

Weight will be collected at screening and upon admission calculate creatinine clearance (CrCl) for inclusion criteria.

Estimated CrCl < 60 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the screening evaluation, i.e.

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

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

6.10.7. Ophthalmic Examination

Ophthalmic Examinations will be performed to assess ophthalmologic findings, including slit lamp and fundoscopic examination with retinal photographs (both eyes). An examination of the full retinal field should be conducted noting changes or abnormalities. Photographs of the retina must be taken at each exam and filed in the subject's source medical records. A central vendor will be used to assess the retinal photographs. Refer to Appendix 2 for ophthalmic examination collection time points.

A procedural window will be given to accommodate ophthalmic assessments. Refer to Section 6 and Appendix 2 for details.

6.10.8. 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 7.1 for more information regarding AEs and Section 5 and Table 5-1 for more information about concomitant medications.

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6.12. Assessments for Premature Discontinuation from Study

If a subject discontinues study treatment 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 procedures until stabilization per the investigator.

If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. Evaluations indicating abnormal results believed to be possibly or probably related to study treatment at the ED visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

6.13. Criteria for Discontinuation of Study Treatment

Discontinuation of dosing for individual subjects will be governed by pre-specified stopping rules for safety and tolerability.

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management Section 7.6 of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest

- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3
- Investigator discretion
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Continuation of dosing will be suspended if three or more Grade 3 or two or more Grade 4 treatment-emergent, drug related AEs or laboratory abnormalities occur. Decisions to reinitiate continuation of dosing will be made by the Sponsor 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 study drugs will be followed for 24 weeks or until the initiation of alternative CHB therapy, whichever comes first.

6.14. Resistance Surveillance

Sequence analysis of the HBV genome will be attempted for all viremic subjects (HBV DNA >69 IU/mL) at Week 48 or at early discontinuation (with at least 24 weeks of TAF treatment). Additionally, any patient that experiences virologic breakthrough (confirmed HBV DNA ≥69 IU/mL after having been <69 IU/mL or confirmed HBV DNA ≥1 $\log_{10}$ IU/mL increase from nadir) will be evaluated by sequence analysis of the HBV pol/RT.

As it may not be known at the time of the visit whether a patient is viremic or if it will be their last study visit, a separate serum sample for potential resistance surveillance will be collected at each study visit.

6.15. End of Study

The end of this study will be the last subject's last completed study visit observed at Week 48. If the subject enrolls in the TFFU phase, the subject will be observed for up to an additional 48 weeks (Week 96).

6.16. Post Study Care

Once a subject has completed their study participation, the long-term care of the participant will remain 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 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 7.10.1)
- 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 CRF.

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 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

AE severity should be recorded and graded according to the modified GSI Grading Scale for Severity of AEs and Laboratory Abnormalities (Appendix 4). 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.

The distinction between the seriousness and the severity of an adverse event should be noted.

Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events.

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.

7.3. 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 (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study treatment, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug(s) and report to the eCRF database as instructed. Further, any AEs occurring during TFFU should also be reported, regardless of cause or relationship.

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.

7.3.2. 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 CRF/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.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study drug(s), regardless of causality, should also be reported.

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 CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there 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 (previously Gilead DSPH):	Fax: E-mail:	PPD 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 CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local 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 as applicable.

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

Laboratory abnormalities without clinical significance 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, modification or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the modified GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as described in Appendix 4. The GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities has been modified to be more appropriate for healthy volunteers and patients with inflammatory diseases (e.g. rheumatoid arthritis, asthma, psoriasis). 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 detailed in Appendix 4.

- All Grade 3 or greater AEs and laboratory abnormalities will be reviewed by the Sponsor to determine if the event is at least possibly treatment-related to determine if the study drug should be held or discontinued
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).
- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose that is dependent upon discussion with the Gilead Sciences Medical Monitor.
- Administration of study drug may be discontinued due to a clinical or laboratory event. The Gilead Medical Monitor should be consulted prior to dose discontinuation of study drug unless the investigator believes that immediate action is warranted to ensure the continued safety of subject.
- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

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7.6.2. Management of GS-9688/PTM Dose Limiting Toxicities

In the event of any DLT, the investigator should discuss with the Gilead Medical Monitor the subject's status until the DLT has resolved.

GS-9688/PTM dosing for a subject will be held if the subject experiences at least one of the following DLT:

- A confirmed, clinically significant lab abnormality (other than ALT) ≥ Grade 3 considered drug-related by the investigator or Sponsor
- Dose-limiting ALT flare defined as confirmed ALT ≥ 10x ULN (to be confirmed within 3 days from receipt of initial laboratory results)

If a subject experiences any of the above DLT, then GS-9688/PTM will be held until repeat labs demonstrate that the lab abnormality returns to ≤ Grade 2 levels. Once the lab abnormality returns to ≤ Grade 2, GS-9688/PTM can be restarted with medical monitor approval. Subjects who experience a dose interruption DLT will continue to be monitored at least once a week, or more frequently as clinically needed, until resolution.

GS-9688/PTM dosing for a subject will be permanently discontinued if the subject experiences at least one of the following DLTs:

- A confirmed ALT increase (i.e. grade shift or 2x previous value) with evidence of worsened hepatic function (e.g. Total Bilirubin > 2mg/dL above BL, elevated INR ≥ 1.7 or > 0.5 over BL, abnormal serum albumin > 1g/dL decrease from BL)
- Prolonged (2 sequential), confirmed, clinically significant lab abnormality (other than ALT) ≥ Grade 3 considered drug-related by the investigator
- Any confirmed recurrence of study drug-related Grade 3 or 4 clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of study drug.
- A confirmed ≥ Grade 3 AE (excluding ALT) considered drug-related by the investigator

Subjects who experience a permanent discontinuation DLT will be monitored at least once a week, or more frequently as clinically needed, until resolution.

7.6.3. TAF Dose Modification and Monitoring

Post GS-9688/PTM treatment plus 7 days, based on the results of the confirmatory tests listed in Section 7.6.1, the following treatment modifications for TAF are recommended:

Table 7-1. 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.

The Gilead Medical Monitor should be consulted prior to study drug modification or discontinuation when medically feasible.

7.6.4. Management of Neutropenia

If a subject experiences Grade 2 or higher neutropenia while participating in the study, they should return to the study site the following week (within 7 days) for retest and result confirmation from the central lab. If Grade 2 or higher neutropenia is confirmed, GS-9688/PTM dosing should be held until the retest results are available and subject followed weekly until neutrophils improves to < Grade 2. At that time, with Gilead medical monitor approval, GS-9688/PTM may be rechallenged.

If study drug is re-challenged following a return to < Grade 2, GS-9688/placebo dosing should continue as per the original treatment schedule. If any scheduled dosing of GS-9688/placebo is missed due to a Grade 2 neutropenia event, it should be captured in the source documentation and appropriate CRF.

7.6.5. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.6.6. Grades 3 and 4 Laboratory Abnormality or Clinical Event

For a Grade 3 and 4 clinical event or clinically significant Grade 3 and 4 laboratory abnormality (with the exception of asymptomatic Grade 3 or 4 cholesterol and triglyceride increases or CK elevations unrelated to study drug, or hematuria due to menses) confirmed by repeat testing (preferably within 3 calendar days after receipt of the original test results), study drug 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 3 and 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

7.7. Other Criteria for Discontinuation of Study Drug

- Discontinuation of dosing for individual subjects will be governed by pre-specified stopping rules for safety and tolerability.

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management Section 7.6 of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Subject requests to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3
- Investigator discretion
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB or IEC
- Continuation of dosing will be suspended if three or more Grade 3 or two or more Grade 4 treatment-emergent, drug related AEs or laboratory abnormalities occur. Decisions to reinitiate continuation of dosing will be made by the Sponsor 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 disease will be managed according to local standard of care if subjects are discontinued from the study. Subjects that discontinue all study drugs will be followed for 24 weeks or until the initiation of alternative CHB therapy, whichever comes first.

An independent, external Data Monitoring Committee (DMC) will review the progress of the study and perform safety data review after 20 subjects have completed randomization. Subsequent meetings may be held approximately every 3 months until the last subject enrolled has completed the study drug dosing period. The DMC will provide recommendations as needed regarding study conduct and the need for additional meetings or an alternative meeting schedule. The DMC will be immediately notified in the event of any dose limiting toxicities (DLT) or virologic study stopping criteria.

7.8. Subject Withdrawal Criteria

Discontinuation of dosing for individual subjects will be governed by pre specified stopping rules for safety and tolerability. A subject will be withdrawn from study if they experience one of the following:

- A confirmed, clinically significant treatment-emergent ≥ Grade 3 adverse event or laboratory abnormality (with the exception of asymptomatic Grade 3 or 4 cholesterol and TG increases or CK elevations unrelated to study drug, or hematuria due to menses), considered treatment-related, defined by the GSI Grading Scale (Appendix 4). Subjects should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. Grade 3 and 4 laboratory abnormalities that are not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- A clinically significant ECG measurement (e.g., a change from baseline QTcF value of > 60 msec, 2nd or 3rd degree heart block, or pronounced QRS widening) by confirmed measurement as described in Section 6.10.1.

7.9. Study Specific Stopping Criteria

7.9.1. Laboratory Abnormalities and Treatment-Emergent Adverse Events

If 3 or more subjects in any cohort experience the same or similar Grade 3 or Grade 4 treatment-emergent adverse event or confirmed laboratory abnormality (with the exception of asymptomatic Grade 3 or 4 cholesterol and TG increases), unless there is a clear and obvious physiologic explanation for the events (e.g., blood in urine occurring in a menstruating female, CK elevation after strenuous exercise, or TG elevation that is non fasting, etc.), then a review of all safety data generated in subjects dosed to date will be initiated. For individuals already on study drug, the decision whether or not to complete the full course of study medication will be made by the sponsor with disclosure of new information to the study subject(s).

7.9.2. Virologic Criteria

If 2 or more subjects in a treatment arm experience an increase in HBV DNA of ≥ 69 IU/mL on two consecutive visits, unless there is a clear and obvious explanation for the events (e.g. nonadherence to OAV), then a review of all safety data generated in subjects dosed to date will be initiated. During this time, further enrollment into that treatment arm will be held and not

reopened for enrollment until the decision to reinitiate dosing is made by the Sponsor with input from the DMC upon review of all safety data generated by subjects dosed to date. For individuals already on study drug, the decision whether or not to complete the full course of study medication will be made by the Sponsor. Disclosure of this new information will be provided to the study subject(s).

7.10. Special Situations Reports

7.10.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs 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.

Infant exposure from breastfeeding that is associated with an AE.

7.10.2. Instructions for Reporting Special Situations

7.10.2.1. 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 CRF/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 Section 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 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.10.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. 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 CRF/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 as follows:

- To evaluate the safety and tolerability of multiple oral doses of GS-9688 at Week 24 in CHB adult subjects who are viremic and not currently not being treated
- To evaluate the antiviral activity of GS-9688 as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from baseline in serum qHBsAg at Week 24

The secondary objectives of this study are as follows:

- To evaluate the antiviral activity of GS-9688 at Weeks 4, 8, 12 and 48 as measured by the proportion of subjects with ≥1 $\log_{10}$ IU/mL decline from baseline in serum qHBsAg
- To evaluate the change in serum qHBsAg ($\log_{10}$ IU/mL) from baseline to Weeks 4, 8, 12, 24 and 48
- To evaluate the proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48
- To evaluate the proportion of subjects with HBsAg loss at Weeks 12, 24 and 48
- To evaluate the proportion of subjects with HBeAg loss and seroconversion at Weeks 12, 24 and 48
- To characterize the PK of GS-9688
- To evaluate the proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL)
- To evaluate the incidence of drug resistance mutations

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8.1.2. Primary Efficacy Endpoint

The **primary efficacy endpoint** is:

- Proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in serum qHBsAg from baseline at Week 24

8.1.3. Secondary Efficacy Endpoints

The **secondary efficacy endpoints** are:

- Proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in serum qHBsAg from baseline at Weeks 4, 8, 12 and 48
- Change in serum qHBsAg ($\log_{10}$ IU/mL) from baseline at Weeks 4, 8, 12, 24 and 48
- Proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48
- Proportion of subjects with HBsAg loss at Weeks 12, 24 and 48
- Proportion of subjects with HBeAg loss and seroconversion at Weeks 12, 24 and 48
- Proportion of subjects with virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL)
- Proportion of subjects with drug resistance mutations

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 randomized subjects who took at least 1 dose of the study drug. Subjects will be analyzed according to the randomized treatment assignment. In this study, the study drugs are GS-9688/PTM and TAF.

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 the study drug. Subjects will be analyzed according to the treatment actually received.

8.2.1.3. Pharmacokinetics

The PK analysis set will include all randomized subjects who took at least 1 dose of the study drug and have at least 1 nonmissing concentration value reported by the PK laboratory.

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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. For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at pre-dose and one-half of the LLOQ for post dose time points.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized by treatment group and overall for each cohort 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, HBsAg (log_{10} IU/mL), HBV DNA (log_{10} IU/mL), HBV genotype, ALT and additional endpoints as necessary.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy analysis will be performed in FAS after the last subject has completed Week 24 assessments or discontinued GS-9688 or placebo prematurely.

The proportion of subjects with ≥ 1 log_{10} IU/mL decline in qHBsAg from baseline at Week 24 will be evaluated. To compare the GS-9688 1.5 mg dose group and the GS-9688 3 mg dose group to the placebo group for HBeAg positive and negative subjects separately, the 95% confidence intervals (CI) on the proportion difference (1.5 mg – PTM, 3 mg – PTM) will be constructed, by baseline HBeAg status (positive, negative), based on the standardized statistic and inverting 2 1-sided tests.

In addition, by combining the HBeAg positive and negative subjects, the 2-sided 95% CI of the proportion difference (1.5 mg – placebo, 3 mg – placebo) will be constructed by using stratum-adjusted Mantel-Haenszel proportions, stratified by 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 for each cohort.

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

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 for each cohort.

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

8.6. Safety Analysis

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of GS-9688/PTM will be summarized by treatment group according to the study drug received for primary analysis at Week 24. Safety data will continue to be collected for TAF up to 48 weeks plus 3 days and will be summarized by treatment group according to the GS-9688/PTM study drug received. All safety data collected during the study will be included in data listings.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Clinical and laboratory 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.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent +AE at primary analysis (Week 24) will be defined as any AE with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the GS-9688/PTM; or any AE leading to premature discontinuation of study drugs. A treatment-emergent AE at Week 48 analysis will be defined as any AE with an onset date on or after study drugs start date and no later than 3 days after permanent discontinuation of TAF or 30 days after GS-9688/PTM, whichever comes later; or any AE leading to premature discontinuation of study drugs.

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

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs

- All treatment-related SAEs
- All AEs leading to temporary interruption of the study drug
- All AEs leading to premature discontinuation of the 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 the corresponding change from baseline will be summarized by treatment group at each measured study visit.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 4 (GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities) for analysis purpose.

Treatment emergent lab abnormalities will be defined as values that increase by at least one toxicity grade from baseline at any time post baseline up to the date of the last dose of GS-9688/PTM plus 30 days at primary analysis (Week 24), and up to the date of the last dose of TAF plus 3 days or up to the last dose of GS-9688/PTM plus 30 days, whichever comes later at Week 48 analysis. Incidence of treatment-emergent laboratory abnormalities will be summarized by treatment group.

Values for missing safety laboratory data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

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

8.6.4. Other Safety Evaluations

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

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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.

8.10. Data Monitoring Committee

An independent, external DMC will review the progress of the study and perform safety data review after 20 subjects have completed randomization. Subsequent meetings may be held approximately every 3 months until the last subject enrolled has completed the GS-9688/PTM study drug dosing period. The DMC will provide recommendations as needed regarding study conduct and the need for additional meetings or an alternative meeting schedule. The DMC will be immediately notified in the event of any DLT or virologic study stopping criteria.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

8.11. Internal Data Review Team

The study will be unblinded to appropriate GSI study team personnel at the time of primary analysis (Week 24 assessment). An Internal Data Review, external to the study team, may be unblinded at Week 12 assessment visit to review the unblinded safety and efficacy data in order to guide strategic decisions regarding the future of the program. Investigators and subjects will remain blinded through Week 48 except in instances of emergency treatment unblinding (See Section 5.1.1).

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), 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. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. 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 (ICF), and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval letter from the IRB has been documented and sponsor has also provided a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval.

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 IRB/IEC-approved ICF for documenting written informed

consent. Each ICF 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 IRB/IEC local requirements. The consent form will inform subjects about PG testing and sample retention, and whether they will receive clinically relevant PG analysis results.

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 date 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, IRB/IEC/EC 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 or in accordance with local regulations. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRF, the study drug, 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, CRF and query forms, IRB/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, date 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 AEs 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 ED, 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 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 GSI. The investigator must notify GSI before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, GSI 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 GSI 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 will be completed by an authorized study staff member whose training for this function is completed in EDC. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF 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. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical

data management plan), 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. The eCRF capture the data required per the protocol schedule of events and procedures. 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). 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. Study Drug 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 IRB/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 IRB/IEC and regulatory authorities in accordance with local requirements and receive documented IRB/IEC and regulatory authority approvals before modifications may be implemented.

9.2.2. Study Report and Publications

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

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 CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of GSI 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 GSI medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or GSI 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, 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.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-center Study to Evaluate the Safety, Tolerability and Antiviral Activity of GS-9688 in Viremic Adult Subjects with Chronic Hepatitis B who are not currently on Treatment

GS-US-389-2025, Amendment 1, 27 August 2019

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

PPD

PPD

8-27-19
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 Tables

Part A. Study Procedures Required at Screening Visit

Screening Study Procedures – Window (-30 days)
Obtain written Informed Consent
Review of Inclusion/Exclusion Criteria
Medical History (including HBV disease and treatment history)
Review AEs & concomitant medications
Complete Physical Exam (Including Height, Weight and BMI)
Vital Signs (blood pressure, heart rate, respiration rate and body temperature)
Safety Labs (hematology, serum chemistry, and coagulation)
12-Lead ECG
Ophthalmologic exam (Window Days -10 to -1)
Qualitative HBV Serology Qualitative (HBV serology consists of HBeAg and HBsAg and reflex HBeAb and reflex HBsAb at Screening and all visits indicated in Part B)
HBV DNA levels
HBV Resistance Surveillance
HBV Genotyping (By history if known and laboratory testing)
Quantitative HBsAg
HCV, HDV and HIV Ab testing (In the event of a positive result and/or antigen testing for HIV, HDV, or HCV serology, reflex tests will automatically be performed)
FibroTest
Alpha Fetoprotein
Urinalysis for urine drug screen, alcohol , and urine pregnancy testing
Serum Pregnancy Test (for all female subjects of child-bearing potential)
Follicle-stimulating Hormone (FSH, for female subjects post-menopausal for less than two years)

Part B. Study Procedure Table (On and Post GS-9688/PTM Treatment Assessments)

	On Treatment											Post GS-9688/PTM Treatment					
	Days		Weeks														Days
Windows			(±1 Day)										(±3 Days)				(±7 Days)
Study Procedures	**Baseline (Day 1)**	**Day 2 (Day 1 +24hrs)**	**2**	**4**	**8**	**11**	**12**	**16**	**20**	**23**	**23+24 hrs**	**24**	**28**	**36**	**48**	**ED[a]**	**TFFU after ED**
Review of inclusion/exclusion criteria and confirm medical history	X																
Complete Physical Exam (including weight, height, BMI)	X		X	X	X		X					X	X	X	X	X	
Symptom Directed Physical Exam		X				X		X	X	X	X						X
Ophthalmologic exam[c]							X					X					
Review AEs & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (blood pressure, heart rate, respiration rate and body temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Labs (Hematology, Serum Chemistry, and Coagulation)	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X
Urinalysis	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X

	On Treatment											Post GS-9688/PTM Treatment					
	Days		Weeks														Days
Windows			(±1 Day)										(±3 Days)				(±7 Days)
Study Procedures	**Baseline (Day 1)**	**Day 2 (Day 1 +24hrs)**	**2**	**4**	**8**	**11**	**12**	**16**	**20**	**23**	**23+24 hrs**	**24**	**28**	**36**	**48**	**ED[a]**	**TFFU after ED**
FibroTest	X											X			X	X	
Serum Pregnancy Test[d]	X			X	X		X	X	X			X	X	X	X	X	X
Urine Pregnancy Test[d]	X		X			X											
HBV DNA levels, HBV Resistance Surveillance, Quantitative HBsAg	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X
Qualitative HBV Serology	X						X					X		X	X	X	X
CCI																	
CCI																	
CCI																	
CCI																	
Whole Blood gene expression biomarkers[g]	X	X				X	X			X	X	X			X	X	
PBMC Collection[h]	X	X				X	X			X	X	X			X	X	
Sparse (*timed*) plasma PK sample Collection[i]			X	X	X		X	X	X								

	On Treatment											Post GS-9688/PTM Treatment					
	Days		Weeks														Days
Windows			(±1 Day)										(±3 Days)				(±7 Days)
Study Procedures	**Baseline (Day 1)**	**Day 2 (Day 1 +24hrs)**	**2**	**4**	**8**	**11**	**12**	**16**	**20**	**23**	**23+24 hrs**	**24**	**28**	**36**	**48**	**ED[a]**	**TFFU after ED**
Sparse (*pre-identified)* plasma PK sample Collection[j]	X					X				X							
Holter Monitoring[k]	X					X				X							
CCI																	
CCI																	
Randomization	X																
In Clinic GS-9688 Dosing & Accountability[m]	X		X	X	X	X	X	X	X	X						X	
TAF Dispensation and Accountability	X			X	X		X	X	X			X	X	X		X	
CCI																	
CCI																	

Part C. Study Procedure Table (Treatment Free Follow-up Post Study Completion)[n]

	TFFU Week[b] (Study Week)							
Windows	(±7 Days)							
Study Procedures	**4 (52)**	**8 (56)**	**12 (60)**	**16 (64)**	**20 (68)**	**24 (72)**	**36 (84)**	**48 (96)**
CCI								
Symptom Directed Physical Exam	X	X	X	X	X	X	X	X
Vital Signs (blood pressure, heart rate, respiration rate and body temperature)	X	X	X	X	X	X	X	X
Safety Labs (Hematology, Serum Chemistry, and Coagulation)	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X	X	X	X	X	X	X	X
Qualitative HBV Serology	X	X	X	X	X	X	X	X
HBV DNA levels, HBV Resistance Surveillance, Quantitative HBsAg	X	X	X	X	X	X	X	X
CCI								
CCI								
PBMC Collection[h]	X	X	X	X	X	X	X	X
Whole Blood gene expression biomarkers[g]	X	X	X	X	X	X	X	X
CCI								
Review AEs & Concomitant Medications	X	X	X	X	X	X	X	X

a The ED visit should be performed within 1 week if ED occurs before Week 24; after week 24 ED should be performed within 2 weeks from notification of study discontinuation.
b Subjects will be followed every 4 weeks for the first 24 weeks and thereafter at Week 36 and 48 or until the initiation of alternative CHB therapy, whichever comes first.
c Ophthalmologic exam windows per visit: Screening (Days -10 to -1), Week 12 and Week 24 (-4 days to +10 days)
d For female subjects of childbearing potential, the pregnancy test will be performed at all study visits as indicated. Positive urine test will be confirmed with serum test. Pregnancy testing should include prevention counseling.
[redacted]
[redacted]
g Whole blood gene expression (Paxgene RNA) samples collected on Days 1 pre-dose and 1+4 hours, 1 + 24 hours post-dose, and on Weeks 11 pre-dose, 11+4 hours post-dose, 12 pre-dose, 23 pre-dose, 23 + 4 hours , 23 + 24 hours post-dose, PT Week 24, 48/ED, and TFFU Week 4, 8, 12, 16, 20, 24, 36, and 48.
h PBMC samples collected on Days 1 predose and 1+4 hours, 1 + 24 hours post-dose, and on Weeks 11 pre-dose, 11+4 hours post-dose, 12 pre-dose, 23 pre-dose, 23 + 4 hours, 23 + 24 hours post-dose, PT Week 24, 48/ED, and TFFU Week 4, 8, 12, 16, 20, 24, 36, and 48.
i Sparse (*timed*) plasma PK samples will be obtained on any two of the following visits: Weeks 2, 4, 8, 12, 16, and/or 20 at pre-dose and any time between 30 minutes to 4 hours post-dose.
j Sparse (*pre-identified*) PK plasma sampling will occur on Day 1 and Week 23 at pre-dose, 1, 4, and 24 hours post-dose and at Week 11 at pre-dose, 1, and 4 hours post-dose.
k Holter Monitoring to be collected prior to blood collection on Day 1 and Week 23 at pre-dose (≤ 5 min of dose) through 4 hours, and 24 hours; Week 11 at pre-dose (≤ 5 min of dose) through 4 hours
[redacted]
m In addition to the clinic GS-9688 study drug dosing, self/home GS-9688 study drug dosing will be on Weeks 1, 3, 5, 6, 7, 9, 10, 13, 14, 15, 17, 18, 19, 21, and 22
n At Week 48, at PI discretion, following the discontinuation of TAF (window of ± 7 days), the subject will be followed every 4 weeks for the first 24 weeks and thereafter at Week 36 and Week 48 (TFFU phase). At the PI's discretion, subject(s) in the TFFU phase may initiate other standard of care CHB therapy at any time per local treatment guidelines. If a subject initiates other standard of care CHB therapy for their CHB, TFFU visits will continue for 2 more TFFU visits or until the end of the TFFU phase (Week 96), whichever comes first.

Appendix 3. 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. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b) Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception with GS-9688/PTM

The risks of treatment with GS-9688 during pregnancy have not been evaluated. The reproductive and developmental toxicity studies with GS-9688 have not been conducted to date. Drug-drug interaction (DDI) with hormones used for contraception is not available. Therefore, the use of hormonal contraception with GS-9688 is not recommended. Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable, highly effective contraceptive methods. Pregnancy tests will be performed regularly throughout this study. Please refer to the latest version of the IB for additional information.

b) Study Drug Effects on Pregnancy and Hormonal Contraception with 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 orembryo-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.

c) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective 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 at the baseline/Day-1 visit prior to randomization/enrollment. Female subjects must agree to 1 of the following from screening until 30 days following the end of relevant systemic exposure:

- 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 with a failure rate of < 1% per year

  Tubal sterilization

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure to GS-9688/PTM or 7 days after the last dose of TAF, whichever comes later.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the end of relevant systemic exposure. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the end of relevant systemic exposure.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

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 (90 days for female partners of male subjects) of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study, including TFFU, 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 7.10.2.1.

Appendix 4. 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 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate **Adult and Pediatric ≥ 4 Years** **Pediatric < 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN NA	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L 11.0 mEq/L to <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L 8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L < 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Adult** LDL (Fasting) **Pediatric >2 to <18 years**	130 to 160 mg/dL 3.35 to 4.15 mmol/L 110 to 130 mg/dL 2.84 to 3.37 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L >130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L > 190 mg/dL >4.92 mmol/L	NA NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA 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)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than 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 (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (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 [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hour	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hours.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle 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 (eg, status epilepticus), or difficult to control (eg, 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 (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5-20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (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 [eg, tube feeding or total parenteral nutrition]

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

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

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

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic 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 (eg, septic shock)

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