GILEAD

STATISTICAL ANALYSIS PLAN

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
Name of Test Drug:	GS-9688
Study Number:	GS-US-389-2025
Protocol Version (Date):	Original: 23 March 2018 Amendment 1: 27 August 2019
Analysis Type:	Week 24 Analysis, Week 48 Analysis, and Final Analysis
Analysis Plan Version:	Version 1.1
Analysis Plan Date:	31 October, 2019
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
AUC	area under the curve
AV	atrioventricular
BLQ	below the limit of quantitation
BMI	body mass index
BPM	beats per minute
C-QT	concentration-QT
CG	Cockcroft-Gault
CHB	chronic hepatitis B
CI	confidence interval
CK	creatine kinase
CLDQ	Chronic Liver Disease Questionnaire
CSR	clinical study report
CV	coefficient of variation
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ET	early termination
FAS	full analysis set
FU	follow-up
GLSM	geometric least-squares means
HBcrAg	hepatitis B core-related antigen
HBV	hepatitis B virus
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HLGT	high level group term
HLT	high level term

HR	heart rate
HRQoL	health-related quality of life
ID	identification
IDRT	internal data review team
INR	international normalized ratio
IXRS	interactive voice or web response system
LDH	lactate dehydrogenase
LLT	lower level term
LOQ	limit of quantitation
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
OAV	oral antiviral
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
Peg-IFN	pegylated interferon
PK	pharmacokinetics
PT	preferred term
PTM	placebo-to-match
PVE	Pharmacovigilance and Epidemiology
Q1	first quartile
Q3	third quartile
qHBsAg	quantitative hepatitis B surface antigen
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SNPs	single nucleotide polymorphisms
SOC	system organ class
TAF	Tenofovir Alafenamide
TE	treatment emergent
TFFU	Treatment free follow up
TFLs	tables, figures, and listings
TLR	toll-like receptor
TND	target not detected
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

WPAI: Hep B   Work Productivity and Activity Impairment Questionnaire: Hepatitis B

PHARMACOKINETIC ABBREVIATIONS

AUC_{0-24}	area under the concentration during 24 hours
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
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
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CL/F	apparent oral clearance after administration of the drug: at steady state: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
τ	The nominal time point for a key event or dosing interval
$t_{1/2}$	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)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve
V_z/F	apparent volume of distribution of the drug

1.   INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-389-2025. This SAP is based on the study protocol Amendment 1 dated 27 August 2019 and the electronic case report form (eCRF). This SAP will be finalized before the Internal Data Review Team Analysis. Any changes made after the finalization of the SAP will be documented in the CSR.

In this SAP, Week 24 analysis and Week 48 analysis will be described in details. For final analysis (treatment free follow up period), data listings will be shown, and summary tables may be presented as appropriate.

1.1.   Study 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 currently not being treated

- To evaluate the antiviral activity of GS-9688 as measured by the proportion of subjects with $\geq 1 \log_{10}$ 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 $\geq 1 \log_{10}$ 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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1.2. Study Design

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

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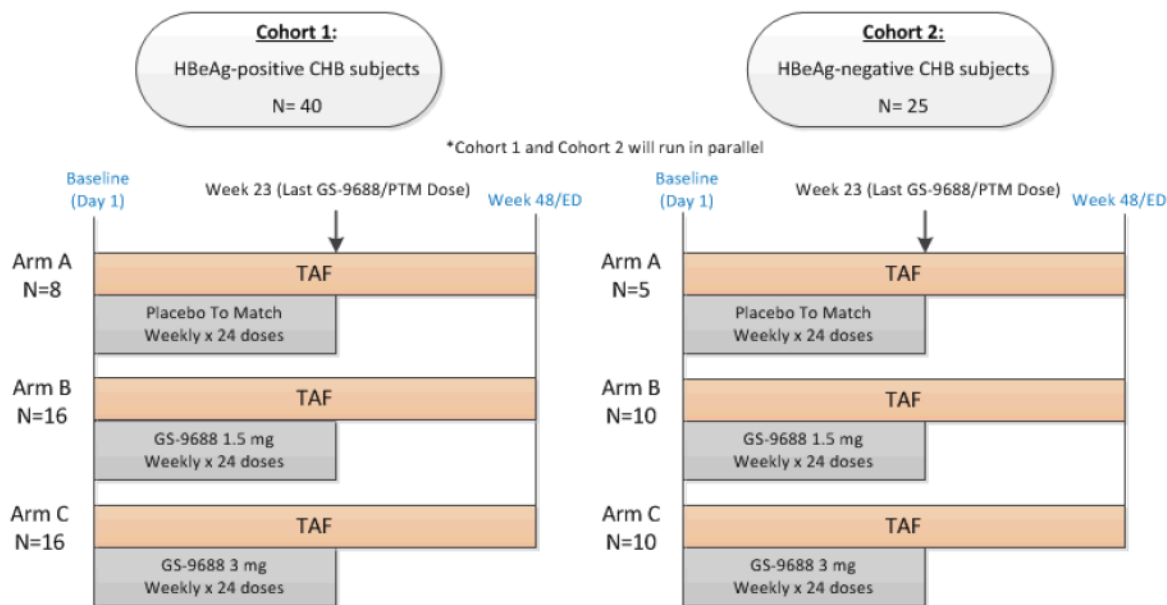
a   At Week 48, per PI's discretion, subjects will be managed in one of two ways:
   1. Continue in the study for 48 weeks following the discontinuation of TAF (TFFU, window of ± 7 days) or until an alternative commercially approved CHB treatment is started, whichever occurs first
   2. Initiate other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

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.

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 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.

The schedule of assessments is provided as an appendix (Appendix 1).

1.3.   Sample Size and Power

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.

2.   TYPE OF PLANNED ANALYSIS

2.1.   Data Monitoring Committee Analysis

An independent, external data monitoring committee (DMC) will review the progress of the study and perform interim reviews of the safety data to protect subject welfare and preserve study integrity. To ensure the best interests of the subjects, the DMC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The initial DMC data review meeting will be conducted 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's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed-upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

2.2.   Internal Data Review Team Analysis

An internal data review team (IDRT), external to the study team, may be unblinded after all subjects have completed Week 12 or prematurely discontinued from the study treatment prior to Week 12. The IDRT will review the unblinded safety, PD and efficacy data in order to guide strategic decisions regarding the future of the program. The IDRT will function independently from all other individuals associated with the conduct of this study, including investigators, Gilead personnel involved in the program, the study management team, and other committees (eg, ethics committees) overseeing the trial.

The IDRT's role and responsibilities and the scope of analysis to be provided to the IDRT are provided in a mutually agreed-upon charter, which defines the IDRT membership, meeting logistics, and meeting frequency.

2.3.   Week 24 Analysis

The Week 24 analysis will be conducted after all subjects have completed Week 24 or prematurely discontinued study treatment prior to Week 24. The study will be unblinded at the time of the Week 24 analysis.

2.4.   Week 48 Analysis

The Week 48 analysis will be performed after all subjects have completed Week 48 or prematurely discontinued study treatment prior to Week 48, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

2.5.   Final Analysis (TFFU)

The final analysis will be conducted for subjects who entered the TFFU period subsequent to study drug discontinuation up to study Week 48 or prematurely discontinued study treatment prior to Week 48.

3.   GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for subjects in the All Randomized Analysis Set and sorted by subject identification (ID) number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order for each subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, if space permits.

3.1.   Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1.   All Randomized Analysis Set

The All Randomized Analysis Set includes all subjects who were randomized in the study. Subjects are grouped within the All Randomized Analysis Set by the treatment group to which they were randomized.

3.1.2.   Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who took at least 1 dose of the study drug. The study drug in this study is GS-9688 or PTM. Subjects are grouped within the FAS by the treatment group to which they were randomized. This is the primary analysis set for efficacy analyses.

3.1.3.   Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of the study drug. Subjects are grouped within the Safety Analysis Set according to the treatment they actually received. This is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes 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. This is the primary analysis set for all PK analyses. Within the PK Analysis Set, those subjects with evaluable PK will be included for parameter estimation.

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3.1.7. TFFU Analysis Set

The TFFU Analysis Set will include all subjects who were randomized into the study, received at least 1 dose of study drug and entered the TFFU period.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set, FAS, or Biomarker Analysis Set, subjects will be grouped according to the treatment to which they were randomized. For analyses based on Safety Analysis Set, PK Analysis Set CCI subjects will be grouped according to the treatment they actually received. The actual treatment received will differ from the randomized treatment only when the actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) with a 1:2:2 in ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- HBeAg (positive, negative)

If there are discrepancies in stratification factor of HBeAg values between the IXRS and the clinical database, the values recorded in the clinical database will be used for analyses.

Safety and efficacy endpoints will be evaluated by baseline HBeAg status and overall for each treatment group.

3.4.   Examination of Subject Subsets

Due to the exploratory nature and the small sample size of this study, subgroup analyses based on presumed prognostic baseline characteristics will not be performed for efficacy endpoints.

3.5.   Multiple Comparisons

Adjustments for multiplicity will not be made because no formal statistical hypothesis testing will be performed in this study.

3.6.   Missing Data and Outliers

3.6.1.   Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

A missing baseline laboratory result will be treated as normal (i.e., no toxicity grade) for the laboratory abnormality summary.

Both baseline and postbaseline borderline results for HBeAg, hepatitis B e antibody (HBeAb), HBsAg, and hepatitis B surface antibody (HBsAb) will be imputed as follows:

- HBsAb/HBeAb borderline → HBsAb/HBeAb negative

- HBsAg/HBeAg borderline → HBsAg/HBeAg positive

For missing last dose date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2.   Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7.   Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth

- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth

- If year of birth is missing, then date of birth will not be imputed

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (e.g., estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

For HBV DNA, if the value in IU/mL is above the upper LOQ, the corresponding diluted HBV DNA value, if available, will be used.

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data, eg, log-transformed data, or nonparametric analysis methods may be used, as appropriate.

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postbaseline time points.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ".

- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ".

- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ".

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ".

- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ".

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8.   Analysis Visit Windows

3.8.1.   Definition of First Dose Day, Last Dose Day, and Study Day

First Dose Date is defined as the minimum of the first dose date of GS-9688 and TAF.

Last Dose Date is defined as the maximum of the last dose date of GS-9688 and TAF. If TAF is ongoing, the last dose of TAF is the maximum of the latest TAF dose date, visit date, vital sign assessment date, and lab date available.

Baseline is defined as the last available observation on or prior to the first dose date.

Study day will be calculated from the first dose date and derived as follows:

- For postdose study days: Assessment Date   First Dose Date of Study Drug + 1

- For days prior to the first dose: Assessment Date   First Dose Date of Study Drug

Therefore, study Day 1 is the day of first dose of either study drug administration.

3.8.2.   Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

Data collected up to the maximum of the last dose date of GS-9688 + 8 days and TAF +3 days will be considered as on-treatment data whereas data collected afterwards will be considered as posttreatment (treatment free follow up period) data. Data from ophthalmology assessment, CCI will be summarized according to the nominal visit as recorded in the database.

On-treatment data will be mapped to the analysis windows defined in Table 3-1, Table 3-2, Table 3-3, and Table 3-4. Table 3-5 showed analysis visit windows for posttreatment period.

Table 3-1.   **Analysis Visit Windows for On-treatment qHBsAg, HBV DNA and Safety Laboratory Data**

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 2	15	2	22
Week 4	29	23	43
Week 8	57	44	67
Week 11	78	68	81
Week 12	85	82	99
Week 16	113	100	127
Week 20	141	128	151
Week 23	162	152	165
Week 24	169	166	183
Week 28	197	184	225
Week 36	253	226	295
Week 48	337	296	≥ 337

Table 3-3.   **Analysis Visit Windows for On-treatment Qualitative HBV Serology**

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	127
Week 24	169	128	211
Week 36	253	212	295
Week 48	337	296	≥ 337

Table 3-4.   **Analysis Visit Windows for On-treatment Vital Signs**

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 1 + 24 hrs	2	2	2
Week 2	15	3	22
Week 4	29	23	43
Week 8	57	44	67
Week 11	78	68	81
Week 12	85	82	99
Week 16	113	100	127
Week 20	141	128	151
Week 23	162	152	165
Week 24	169	166	183
Week 28	197	184	225
Week 36	253	226	295
Week 48	337	296	≥ 337

Posttreatment data will be mapped as follows:

TFFU Day   Assessment Date   Last Dose Date of GS-9688 or TAF (whichever comes last)

Table 3-5.   **Analysis Visit Windows for Posttreatment (Treatment Free Follow Up Period)**

Analysis Visit	TFFU Day	Lower Limit	Upper Limit
TFFU Week 4	29	4	43
TFFU Week 8	57	44	71
TFFU Week 12	85	72	99
TFFU Week 16	113	100	127
TFFU Week 20	141	128	155
TFFU Week 24	169	156	211
TFFU Week 36	253	212	295
TFFU Week 48	337	296	>=337

3.8.3.   Selection of Data in the Event of Multiple Records in an Analysis Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dose date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements will be considered the baseline value.

- For postbaseline values (except for alanine aminotransferase [ALT]):

   The record closest to the nominal day for that visit will be selected.

   If there are 2 records that are equidistant from the nominal day, the later record will be selected.

   If there is more than 1 record on the selected day, the average will be taken except for qHBsAg (IU/mL), HBV DNA (IU/mL), CCI for which the geometric mean will be taken.

- For postbaseline ALT values:

    The record with the largest value within the same analysis window will be selected

    If there is more than 1 record with the largest value, the latest record will be selected.

    If there are multiple largest records with the same time or no time recorded on the same day, any one of these measurements can be selected as the analysis value.

If multiple valid, nonmissing, categorical measurements exist in an analysis window, and a single value is needed, records will be chosen based on the following rules:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected for safety data (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings), and the most conservative value will be selected for efficacy data (eg, negative will be selected over positive for HBeAg and HBsAg, whereas positive will be selected over negative for HBeAb and HBsAb).

- For postbaseline values:

    The most conservative value (eg, abnormal will be selected over normal for safety ECG) within the analysis window will be selected, except for HBV serology (HBsAg, HBsAb, HBeAg, and HBeAb), for which the most favorable value (ie, negative will be selected over positive for HBsAg and HBeAg, whereas positive will be selected over negative for HBsAb and HBeAb) will be selected.

    In the event that more than 1 value within an analysis window is equal, the value collected closest to the nominal day will be selected.

    If there are 2 records that are equidistant from the nominal day, the later record will be selected.

    If there is more than 1 record on the selected day, the latest record will be selected; if these measurements were recorded at the same time or no time recorded, any one of these measurements can be selected as the analysis value.

4.   SUBJECT DISPOSITION

4.1.   Subject Enrollment and Disposition

A summary of subject enrollment will be provided by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo) for each country and investigator within a country. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column. If there are discrepancies in the value used for stratification (ie, HBeAg status) assignment between the IXRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the HBeAg value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo). This summary will present the number of subjects screened, the number of screen failure subjects who were not randomized, the number of subjects who met all eligibility criteria but were not randomized with reasons for subjects not randomized, the number of subjects randomized, and the number of subjects in each of the categories listed below:

*   Safety Analysis Set

*   FAS

*   PK Analysis Set

*   ███████████

*   ███████████

*   Treatment Free Follow Up Analysis Set

*   GS-9688/PTM completion status

    Completed study drug

    Prematurely discontinued study drug

*   Reason for premature discontinuation of GS-9688/PTM

- TAF completion status

    Completed study drug

    Prematurely discontinued study drug

- Reason for premature discontinuation of TAF

- TFFU completion status

    Completed TFFU

    Prematurely discontinued from TFFU

- Reason for premature discontinuation of TFFU

- Study completion status

    Completed study

    Prematurely discontinued study

- Reasons for premature discontinuation of study

For the status of study drug and study completion and the reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-subject listings will be provided by subject ID number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation

- Reasons for premature discontinuation from TFFU

4.2.   Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

4.2.1.   Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dose date minus first dose date plus 1 for TAF and plus 7 for GS-9688, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dose date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: baseline ($\geq$ 1 day), Week 2 ($\geq$ 15 days), Week 4 ($\geq$ 29 days), Week 8 ($\geq$ 57 days), Week 11 ($\geq$ 78 days), Week 12 ($\geq$ 85 days), Week 16 ($\geq$ 113 days), Week 20 ($\geq$ 141 days), Week 23 ($\geq$ 162 days) for GS-9688 and baseline ($\geq$ 1 day), Week 4 ($\geq$ 29 days), Week 8 ($\geq$ 57 days), Week 12 ($\geq$ 85 days), Week 16 ($\geq$ 113 days), Week 20 ($\geq$ 141 days), Week 24 ($\geq$ 169 days), Week 28 ($\geq$ 197 days), Week 36 ($\geq$ 253 days), and Week 48 ($\geq$ 337 days) for TAF.

Summaries will be provided by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo) for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of doses administered will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).

The presumed total number of tablets taken by a subject will be determined by the data collected on the drug accountability eCRF using the following formula:

$$\text{Total Number of Tablets Taken} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets Returned}\right)$$

4.2.2.1. Prescribed GS-9688 Adherence

The level of prescribed adherence to the study drug will be determined by the total amount of study drug taken relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the study.

The level of prescribed adherence of GS-9688 will be expressed as a percentage using the following formula:

$$\text{Prescribed Adherence}(\%) = \left(\frac{\text{Total Amount of Study Drug Taken}}{\text{Total Amount of Study Drug Specified by Protocol}}\right) \times 100\%$$

The number of tablets taken for GS-9688 will be calculated as the recorded sum of tablets taken by a subject. If a subject did not record having taken a tablet during the prescribed treatment period, then the tablet will be treated as not taken.

4.2.2.2.   Adherence to TAF

Adherence (%) of TAF will be calculated as follows:

$$\text{Adherence to TAF (\%)} = \left(\frac{\sum \text{No. of Tablets Taken at Each Dispensing Period}}{\sum \text{No. of Tablets Prescribed at Each Dispensing Period}} \right) \times 100\%$$

Number of **tablets taken at a distinct dispensing period** is calculated as the minimum of (a) the daily number of tablets prescribed for TAF multiplied by *the duration of treatment* at the dispensing period of the same dispensing date, and (b) the number of tablets taken (number of tablets dispensed minus the number of tablets returned). Total number of tablets taken is determined by summing the number of tablets taken from all evaluable dispensing periods.

Number of **tablets prescribed at a distinct dispensing period** is calculated as the daily number of tablets prescribed for TAF multiplied by the duration of treatment at the dispensing period of the same dispensing date. Total number of tablets prescribed is determined by summing the number of tablets prescribed from all evaluable dispensing periods.

The duration of treatment at a dispensing period for a study drug is calculated as the minimum of (a) the last returned date of the same dispensing period for the study drug, (b) date of premature discontinuation of the study drug, and (c) **next dispensing date** of the study drug, minus dispensing date of the study drug.

The next dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

Note: If calculated adherence is greater than 100%, the result will be set to 100%.

For TAF, a record where the number of tablets returned was missing (with "Yes" answered for the question "Was the Bottle Returned?"), it is assumed the number of tablets returned was 0. If the number of tablets dispensed was missing with the missing or unknown bottle status, all records for the same dispensing date for that study drug will be excluded from the calculations for both denominator and numerator.

Descriptive statistics for the level of prescribed adherence to study drug (n, mean, SD, median, Q1, Q3, minimum, and maximum) and the number and percentage of subjects belonging to adherence categories (< 95%, ≥ 95% for GS-9688 and <80%, ≥80% to <90%, ≥90% for TAF) will be provided by HBeAg status (positive, negative) and overall within each treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number (in ascending order) and visit (in chronological order).

4.3.   Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether or not they were exempted by the sponsor. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion and the number of subjects who did not meet specific criteria by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo) based on the All Randomized Analysis Set. A by-subject listing will be provided for subjects who did not meet at least 1 eligibility criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that a subject did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo) for the All Randomized Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

Subjects who received study drug other than their treatment assignment at randomization will be listed with the start and stop dates that they received incorrect study treatment.

5.   BASELINE CHARACTERISTICS

5.1.   Demographics

Subject demographic variables (ie, age, sex, race, ethnicity and region [US, non-US]) will be summarized by HBeAg status (positive, negative) and overall for each treatment group and study overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for age, and using the number and percentage of subjects for age categories (< 50 years, ≥ 50 years), sex, race, ethnicity, and region. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2.   Other Baseline Characteristics

Other baseline characteristics include

- Body weight (kg)

- Height (cm)

- Body mass index (BMI; kg/m^2) as a continuous variable and as categories (< 18.5 kg/m^2, ≥ 18.5 kg/m^2 25 kg/m^2, ≥ 25 kg/m^2 30 kg/m^2, ≥ 30 kg/m^2)

- History of cirrhosis, cirrhosis determination method, and APRI ($<$ 1, $>$1)

- FibroTest score as a continuous variable and fibrosis stage by FibroTest score as a categorical variable (0.00   0.48, 0.49   0.74, 0.75   1.00)

- HBsAg ($\log_{10}$ IU/mL) as a continuous variable and as categories (< 2 $\log_{10}$ IU/mL, ≥ 2 $\log_{10}$ IU/mL   3 $\log_{10}$ IU/mL, ≥ 3 $\log_{10}$ IU/mL   4 $\log_{10}$ IU/mL, ≥ 4 $\log_{10}$ IU/mL)

- HBV DNA ($\log_{10}$ IU/mL) as a continuous variable and as categories (< 7 $\log_{10}$ IU/mL, ≥ 7 $\log_{10}$ IU/mL   8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL)

- HBeAb (positive, negative)

- HBV genotype

- ALT (U/L) as a continuous variable and as categories based on central laboratory normal range ($\leq$ upper limit of normal [ULN], $>$ ULN; $\leq 5 \times$ ULN, $> 5 \times$ ULN; $\leq 10 \times$ ULN, > 10 ULN)

- ALT level as categories based on American Association for the Study of Liver Diseases (AASLD) normal range with the ULN as 25 U/L for female and 35 U/L for male ($\leq$ ULN, $>$ ULN; $\leq 5 \times$ ULN, $> 5 \times$ ULN; $\leq 10 \times$ ULN, > 10 ULN)

- Prior oral nucleoside/nucleotide treatment (yes, no)

- Previous interferon experience to treat HBV (yes, no)

- Duration of being HBV positive (years) as a continuous variable

- Mode of HBV infection

- Estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation (mL/min)

eGFR will be calculated by the Cockcroft-Gault method: $eGFR_{CG}$ (mL/min) [(140 age (years)) $\times$ weight (kg) $\times$ (0.85 if female)] / (serum creatinine (mg/dL) $\times$ 72), where weight is total body mass in kilograms.

These baseline characteristics will be summarized by HBeAg status (positive, negative) and overall for each treatment group and study overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set.

A by-subject listing of baseline characteristics will be provided by subject ID number in ascending order.

A separate by-subject data listing for cirrhosis determination will be provided for all subjects at screening.

A separate by-subject data listing for HBV treatment history will be provided for the Safety Analysis Set. The listing will display the previous HBV treatment experience, previous HBV regimen and treatment, the treatment duration, and the reason for treatment discontinuation for treatment experienced subjects.

5.3.   Medical History

Medical history was collected at screening.

Data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by system organ class (SOC) and preferred term (PT) by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo). Subjects who reported 2 or more medical history items that are coded to the same SOC and/or PT will be counted only once by the unique coded term in the summary. The summary will be provided for the Safety Analysis Set. No formal statistical testing is planned.

A by-subject listing will also be provided.

6.   EFFICACY ANALYSES

6.1.   Primary Efficacy Endpoint

6.1.1.   Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with $\geq 1 \log_{10}$ IU/mL decline in qHBsAg from baseline at Week 24.

6.1.2.   Statistical Hypothesis for Primary Efficacy Endpoint

No statistical hypothesis testing will be performed.

6.1.3.   Analysis of Primary Efficacy Endpoint

The primary efficacy analysis will be performed for the FAS after the last subject has completed Week 24 assessments or prematurely discontinued study drug.

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, point estimates and the 2-sided 95% exact confidence intervals (CIs) of the primary efficacy endpoint will be provided based on the Clopper-Pearson method {Clopper 1934} by HBeAg status (positive, negative) and overall for each treatment group. In addition, point estimates and the 2-sided 95% exact CIs of the proportion difference (1.5 mg   PTM, 3 mg   PTM), will be displayed separately by HBeAg status (positive, negative) for each treatment group. CIs for the proportion differences will be constructed based on the standardized statistic and inverting two 1-sided tests {Chan 1999}.

To compare the GS-9688 1.5 mg dose group and the GS-9688 3 mg dose group with the placebo group for pooled HBeAg positive and negative subjects, the proportion differences (1.5 mg - PTM, 3 mg   PTM) and the corresponding 95% CIs will be calculated using the stratum-adjusted Mantel-Haenszel (MH) method {Koch 1989}, stratified by HBeAg status (positive, negative), as follows:

$$P_1 - P_2 \pm Z_{(1-\alpha/2)} \times SE(P_1 - P_2),$$

where

- $(P_1   P_2)   \frac{\sum w_\square d_\square}{\sum w_\square}$, is the stratum-adjusted MH proportion difference, where $d_\square   p_{1\square} - p_{2\square}$ is the proportion difference of Groups 1 and 2 in stratum h (h   1 and 2).

- $w_\square   \frac{n_{1\square} n_{2\square}}{n_{1\square} + n_{2\square}}$, is the weight based on the harmonic mean of sample sizes for stratum h, where $n_{1\square}$ and n_{2h} are the sample sizes of Groups 1 and 2 in stratum h.

- SE($P_1 - P_2$) $\sqrt{\dfrac{\sum w_h^2\left[\frac{p_{1h}^*(1-p_{1h}^*)}{n_{1h}-1}+\frac{p_{2h}^*(1-p_{2h}^*)}{n_{2h}-1}\right]}{(\sum w_h)^2}}$, where $p_{1h}^* = \dfrac{m_{1h}+0.5}{n_{1h}+1}$ and $p_{2h}^* = \dfrac{m_{2h}+0.5}{n_{2h}+1}$, where m_{1h} and m_{2h} are the numbers of subjects with ≥ 1 $\log_{10}$ IU/mL decline in qHBsAg from baseline at Week 24 in Groups 1 and 2 in stratum h.

- α 0.05 for this study.

- $Z_{(1-\alpha/2)}$ $Z_{0.975}$ 1.96 is the 97.5th percentile of the normal distribution.

If the computed lower confidence bound is less than 1, the lower bound is defined as 1. If the computed upper confidence bound is greater than 1, then the upper bound is defined as 1.

The point estimates and the 2-sided 95% exact CIs based on the Clopper-Pearson method will also be provided for the proportions in each treatment group.

A Forest plot will graphically present the point estimates and the CIs on the proportion difference (1.5 mg PTM, 3 mg PTM) by HBeAg status (positive, negative) and overall for each treatment group.

6.1.4. Subgroup Analysis of Primary Efficacy Endpoint

No subgroup analyses will be performed.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in qHBsAg from baseline at Weeks 4, 8, 12, and 48

- Change from baseline in qHBsAg (log10 IU/mL) at Weeks 4, 8, 12, 24, and 48

- Proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48

- Proportion of subjects who achieve HBsAg loss at Weeks 12, 24, and 48

- Proportion of HBeAg-positive subjects who achieve HBeAg loss and seroconversion at Weeks 12, 24, and 48

- Proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA $\geq$ 69 IU/mL)

- Incidence of drug resistance mutations

HBV Serology definitions:

- **HBsAg loss**: HBsAg changing from positive at baseline to negative at any postbaseline visit.

- **Confirmed HBsAg loss**: HBsAg loss confirmed by any 2 consecutive results.

- **HBsAg loss reversion**: Any postbaseline HBsAg positive result following HBsAg loss.

- **HBsAb seroconversion**: HBsAb changing from negative or missing at baseline to positive at any postbaseline visit.

- **Confirmed HBsAb seroconversion**: HBsAb changing from negative or missing at baseline to positive at any postbaseline visit confirmed by any 2 consecutive results.

- **HBsAb seroreversion**: Any postbaseline HBsAb negative result following HBsAb seroconversion.

HBeAg-related terminology is defined similarly.

The LLOQ for HBV DNA is defined as 20 IU/mL. The LLOQ for qHBsAg is defined as 0.05 IU/mL.

Missing data will be treated as a nonevent unless otherwise specified (eg, no HBsAg loss, no seroconversion, etc.)

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

The proportion of subjects with ≥ 1 $\log_{10}$ IU/mL decline in qHBsAg from baseline at Weeks 4, 8, 12, and 48 will be analyzed using the FAS similarly to the primary efficacy endpoint. Point estimates and 2-sided 95% exact CIs of the proportions will be provided based on the Clopper-Pearson method by HBeAg status (positive, negative) and overall for each treatment group. In addition, point estimates and 2-sided 95% exact CIs of the proportion difference (1.5 mg PTM, 3 mg PTM), will be displayed separately by HBeAg status (positive, negative) and overall for each treatment group.

The proportion of subjects with HBV DNA <LLOQ at Weeks 12, 24, and 48 will be evaluated by HBeAg status (positive, negative) and overall. Proportion point estimates and the 2-sided 95% exact CIs will be calculated based on the Clopper-Pearson method.

A summary table will be provided for HBsAg-related serology results. The proportion of subjects who have ever had HBsAg loss, confirmed HBsAg loss, on-treatment HBsAg loss, posttreatment HBsAg loss (for subjects with positive HBsAg at the end of the on-treatment period), HBsAg loss with HBsAb seroconversion, HBsAg loss with HBsAb seroreversion, and HBsAg loss reversion with or without HBsAb seroconversion will be summarized by HBeAg status (positive, negative) and overall for each treatment group.

Additional summary tables may be provided for the following:

If ≥ 3 subjects achieved HBsAg loss,

- The proportion of subjects with HBsAg loss will be summarized by visit through Week 48;

If ≥ 3 subjects achieved HBsAg loss with HBsAb seroconversion,

- The proportion of subjects with HBsAb seroconversion will be summarized by visit through Week 48

- The proportion of subjects who have ever had HBsAg loss with HBsAb seroconversion, confirmed HBsAb seroconversion, on-treatment HBsAb seroconversion, posttreatment HBsAb seroconversion (for subjects with negative or missing HBsAb at the end of the on-treatment period) will be summarized.

For subjects in the FAS with baseline HBeAg status positive, similar summary tables will be provided.

The proportion of subjects experiencing HBV virologic breakthrough by Week 48 will be evaluated by HBeAg status (positive, negative) and overall for each treatment group for all subjects in the FAS.

Summary statistics will be presented by HBeAg status (positive, negative) and overall for each treatment group for absolute values and change from baseline in HBV DNA ($\log_{10}$ IU/mL) and qHBsAg ($\log_{10}$ IU/mL) by visit through Week 48. Categorical decline tables for qHBsAg ($\log_{10}$ IU/mL) and HBV DNA ($\log_{10}$ IU/mL) will also be presented.

Imputation rules described in Section 3.6.1 will be used to assign HBeAg and HBsAg status for borderline results. A Missing   Excluded approach will be performed.

Plots of the mean ± SD and median (Q1, Q3) of absolute values and changes from baseline in HBV DNA and qHBsAg through Week 48 will be presented by HBeAg status (positive, negative) and overall for each treatment group.

Drug resistance mutations will be analyzed separately from the SAP and will be reported in the CSR.

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6.4. Changes From Protocol-Specified Efficacy Analyses

There are no planned changes from protocol-specified efficacy analyses.

7. SAFETY ANALYSES

Treatment-emergent adverse events (TEAEs) and serious TEAEs will be summarized for the subjects in the Safety Analysis Set. For subjects in the TFFU Analysis Set, by-subject listings will be provided, and summary tables may be presented as appropriate.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. SOC, high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in the summary presentation.

The severity of adverse events will be determined by the investigator as mild, moderate, or severe.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology (PVE) before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

A treatment-emergent AE at 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 will be defined as any AE with an onset date on or after the first dose 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.

7.1.5.2.   Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dose date of study drug, and

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to the cutoff date from TEAE definition in Section 7.1.5.1

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6.   Summaries of Adverse Events and Deaths

AEs will be summarized based on the Safety Analysis Set.

For the **Week 24 analysis**, TEAEs at Week 24 will be summarized as described below. For the **Week 48 analysis**, 2 sets of summaries will be generated: (1) all TEAEs at Week 24 (2) all TEAEs at Week 48. For the **Final analysis**, data listings will be presented, and summary tables may be presented for subjects in the TFFU Analysis Set as appropriate.

A brief high-level summary of TEAEs will be provided by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo) for the number and percentage of subjects who experienced the following: TEAEs, Grade 3 or higher TEAEs, GS-9688/PTM or TAF TE treatment-related AEs, Grade 3 or higher GS-9688/PTM or TAF TE treatment-related AEs, TE SAEs, GS-9688/PTM or TAF TE treatment-related SAEs, AEs leading to premature discontinuation of study drug (GS-9688/PTM or TAF), AEs leading to temporary interruption of study drug (GS-9688/PTM or TAF). Deaths (treatment emergent or non-treatment emergent) observed in the study will also be included in this summary.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT by treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and Placebo) as follows:

- TEAEs (with severity)

- TEAEs with Grade 3 or higher

- TE treatment-related AEs

- GS-9688/PTM TE treatment-related AEs

- TAF TE treatment-related AEs

- TE treatment-related AEs of Grade 3 or higher

- GS-9688/PTM TE treatment-related AEs of Grade 3 or higher

- TAF TE treatment-related AEs of Grade 3 or higher

- TE SAEs

- TE treatment-related SAEs

- GS-9688/PTM TE treatment-related SAEs

- TAF TE treatment-related SAEs

- TEAEs leading to premature discontinuation of GS-9688/PTM

- TEAEs leading to premature discontinuation of TAF

- TEAEs leading to temporary interruption of GS-9688/PTM

- TEAEs leading to temporary interruption of TAF

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order by SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, TEAEs, Grade 3 or higher TEAEs, and treatment-emergent treatment-related AEs will be summarized by PT only, in descending order of total frequency.

In addition to the by-treatment summaries described above, data listings will be provided for the following AEs:

- All AEs, indicating whether the event is treatment emergent

- All AEs of Grade 3 or higher

- All SAEs

- All deaths

- AEs leading to premature discontinuation of study drug

- AEs leading to temporary interruption of study drug

For subjects in the TFFU Analysis Set, by-subject listings will be provided as follows:

- All AEs

- AEs of Grade 3 or higher

- All SAEs

- All deaths

The listings will indicate whether an event is treatment-emergent, and whether the event occurred during TFFU.

7.2.   Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include all available data. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided using all available data by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and Placebo) for chemistry (including ALT, aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase [ALP], creatine kinase [CK], fasting total cholesterol, fasting glucose, international normalized ratio [INR], lactate dehydrogenase [LDH]), hematology (including hematocrit, hemoglobin, lymphocytes, neutrophils, white blood cells [WBC], platelets), creatinine and estimated creatinine clearance calculated by the Cockcroft-Gault method as follows:

- Baseline values

- Values at each postbaseline visit

- Change from baseline at each postbaseline visit

A baseline laboratory value is defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for ALT, total bilirubin, lymphocytes, and neutrophils will be plotted using a line plot by visit and by.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of the last dose of study drug plus 30 days for GS-9688/PTM at Week 24, and 3 days for TAF or 30 days for GS-9688/PTM at Week 48, whichever comes later for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of the analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2.　　　Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit.

For the **Week 24 analysis**, treatment emergent (TE) laboratory abnormalities will be summarized for all TE laboratory abnormalities at Week 24. For the **Week 48 analysis**, 2 sets of summaries will be generated: (1) all TE laboratory abnormalities at Week 24 (2) all TE laboratory abnormalities at Week 48. For the **Final analysis**, data listings will be presented, and summary tables may be presented for subjects in the TFFU Analysis Set as appropriate.

The following summaries (number and percentage of subjects) for laboratory abnormalities will be provided by laboratory test and by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and Placebo); subjects will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Graded laboratory abnormalities

- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values.

By-subject listings of all graded laboratory abnormalities and Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. These listings will include all test results that were collected throughout the study for the laboratory test of interest, with all applicable severity grades and abnormal flags displayed.

7.2.3.　　　Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized by HBeAg status (positive, negative) and for each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo) using the number and percentage of subjects who were reported to have the following laboratory test values for any postbaseline measurements (based on central lab normal range):

- ALT > 1.5 × nadir and one of the following:

  ALT $\geq 2 \times$ baseline

  ALT $\geq 10 \times$ ULN

  ALT $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN

  ALT $\geq 3 \times$ ULN and INR ≥ 1.7

ALT flare, AASLD Hepatitis flare, and ALT elevation will also be summarized using the number and percentage of subjects for any postbaseline measurements (based on both central lab and AASLD normal range):

- ALT flare: ALT $> 2 \times$ baseline and $\geq 5 \times$ ULN

- AASLD Hepatitis flare: ALT increase $\geq 3 \times$ baseline and > 100 U/L

- ALT elevation: ALT $> 1.5 \times$ nadir and one of the following:

    ALT $\geq 2 \times$ baseline

    ALT $\geq 2.5 \times$ ULN and $< 5 \times$ ULN

    ALT $\geq 5 \times$ ULN and $< 10 \times$ ULN

    ALT $\geq 10 \times$ ULN

For the **Week 24 analysis**, all liver-related TE laboratory abnormalities and ALT flare/elevation will be summarized. For the **Week 48 analysis**, 2 sets of summaries will be generated: (1) all liver-related TE laboratory abnormalities and ALT flare/elevation at Week 24 (2) all liver-related TE laboratory abnormalities and ALT flare/elevation at Week 48. For the **Final analysis**, data listings will be presented, and summary tables may be presented using the TFFU Analysis Set as appropriate.

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For the composite criteria of ALT and total bilirubin or INR, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.2.4.   Dose Limiting Toxicities

GS-9688/PTM and/or TAF dosing for a subject will be held or permanently discontinued if the subject experiences at least one of the following dose limiting toxicities (DLTs):

- Confirmed, clinically significant laboratory abnormality (other than ALT) $\geq$ Grade 3

- Confirmed ALT $\geq 10 \times$ ULN

- Confirmed ALT increase (ie, at least 1 grade increase or $2 \times$ previous value) with evidence of worsened hepatic function (eg, total bilirubin > 2 mg/dL above baseline, elevated INR ≥ 1.7 or > 0.5 above baseline, abnormal serum albumin > 1 g/dL decrease from baseline)

- Treatment-related AE $\geq$ Grade 3

"Confirmed" is defined as 2 consecutive results, including retests.

A summary table will be generated, in which each subject will be counted once for any occurrence of a DLT. The denominator will be the number of subjects in the Safety Analysis Set.

GS-9688/PTM and/or TAF dosing will also be held if a subject experiences a confirmed Grade 2 or above neutropenia. A summary table will be provided for the number and percentage of subjects with confirmed Grade 2 or above TEAEs of neutropenia or confirmed Grade 2 or above TE laboratory abnormality of neutrophils.

By-subject listings will also be provided indicating the occurrence of any DLTs or Grade 2 or above neutropenia to support the summary tables.

7.3. Body Weight, Body Mass Index and Vital Signs

Descriptive statistics will be provided by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo)-for body weight, BMI and vital signs as follows:

- Baseline value

- Values at each postbaseline visit

- Change from baseline at each postbaseline visit

A baseline value is defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline at a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and time point in chronological order. A listing of body weight and BMI will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first dose of study drug. Only prior HBV medications will be summarized. A by-subject listing of prior HBV medications will also be provided.

Prior HBV medications will be summarized by preferred name using the number and percentage of subjects by HBeAg status (positive, negative) and for each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo). A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred name in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dose date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized and preferred name using the number and percentage of subjects by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo). A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred name in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dose date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

ECG analysis results are intended to identify meaningful abnormalities. If potential abnormalities of interest are identified, further analyses may be conducted.

Safety ECG data will not be presented in the main body of the CSR since safety ECGs were not assessed in this study other than as part of the screening process for potential new subjects. Time-matched digital 12-lead ECGs will be collected as continuous recordings from Holter monitors, and will be analyzed separately from this SAP for the concentration-QT (c-QT) analysis.

A by-subject listing for safety ECG assessment results will be provided by subject ID number and time point in chronological order.

7.6. Other Safety Measures

Ophthalmic examinations will be performed, including slit lamp and fundoscopic examination with retinal photographs (both eyes). An examination of the full retinal field will be conducted noting changes or abnormalities. Photographs of the retina were to be taken at each exam, and a central vendor was used to assess the retinal photographs. Ophthalmology data will be collected at screening, Week 12, and Week 24. Summaries of ophthalmology data will be based on nominal visits.

A shift table of the overall assessment of ophthalmology results at each visit compared with baseline values will be presented by each treatment group and GS-9688 overall (in the order of 3 mg, 1.5mg, overall GS-9688, and placebo) using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing/unknown. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ophthalmology assessment results will be provided by subject ID number and visit in chronological order.

The shift table will be generated for ophthalmology assessment results from the central reader. The listing will include results from both on-site investigator and the central reader.

7.7. Changes from Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8.   PHARMACOKINETIC ANALYSES

8.1.   PK Sample Collection

Sparse (*pre-identified*) PK plasma sampling will occur for all subjects on Day 1 and Week 23 at predose, 1, 4, and 24 hours postdose and at Week 11 at predose, 1, and 4 hours postdose. 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 predose and any time between 30 minutes to 4 hours postdose.

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The sparse PK sample will not be collected on the day the subject participates in the PK substudy.

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8.1.2.   Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to zero.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

PK parameters such as AUC_{inf}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.1.3. PK Parameters

Table 8-1. Study Treatments and Associated Analyte

Treatment Group	Treatment	Analyte
B	GS-9688 1.5 mg once a week for 24 weeks	GS-9688
C	GS-9688 3 mg once a week for 24 weeks	GS-9688

The analyte and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The primary PK parameters are AUC_{last}, $AUC_{0\ 24}$, AUC_{inf}, and C_{max} of GS-9688. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-2. PK Parameters

Analyte	Parameters
GS-9688	AUC_{last}, AUC_{0-24}, AUC_{inf}, %AUCexp, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, CL/F, V_z/F, and $t_{1/2}$

Individual subject concentration data and individual subject PK parameters for GS-9688 will be listed and summarized using descriptive statistics by dose. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by dose. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual subject PK parameter data.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the LLOQ for postdose time points.

Individual PK parameter data listings and summaries will include all subjects for whom PK parameters can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided by dose:

- Individual subject concentration data and summary statistics

- Individual subject plasma PK parameters and summary statistics

The following figures may be provided by dose:

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)

- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

In addition, a figure may also be provided for individual subject concentration data vs. time (on linear and semilogarithmic scales). Study Day (Day 1, Week 23) will be used to overlay data in these plots.

Individual, mean, and median postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected.

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8.1.4.   Analysis of Dose Proportionality

If data are available, dose proportionality will be obtained by comparing PK parameters across evaluated dose levels.

Day 1 and on Week 23 PK parameters may be pooled to assess dose proportionality across evaluated doses.

Analysis of Variance

An ANOVA model using PROC MIXED will be used to estimate the ratio of the PK parameter at each dose level to the PK parameter at the reference dose. The parameters will be dose-normalized and natural log-transformed prior to analysis. The reference dose is 1.5 mg, determined by the PK scientist. Dose normalization is calculated by dividing each PK parameter value by the ratio of the test dose/reference dose. The ratio of geometric least-squares means (GLSM) and the corresponding 90% CI will be estimated for each PK parameter of interest.

The statistical model will include dose as a fixed effect. The following SAS PROC MIXED code will provide the dose comparison analysis and the 90% CI calculations for the natural log-transformed normalized PK parameters. Similar code will be used for other natural log-transformed normalized parameters and dose levels.

```
PROC MIXED;
CLASS dose;
MODEL lnC_max    dose;
LSMEANS dose/cl alpha  0.10;
ESTIMATE "3 mg vs 1.5 mg" dose -1 1 / cl alpha  0.10;
RUN;
```

The ESTIMATE statement is used to produce the point estimate and corresponding 90% CI of the difference in PK parameters of interest on a logarithmic scale. The test-to-reference ratio and the 90% CI will be calculated by exponentiation of the point estimate and the corresponding lower and upper limits.

A summary table and a listing of SAS analysis output will be provided.

8.2.   PK Analyses Related to Sparse PK Sampling

For PK Analysis Set, sparse (*pre-identified*) PK data will be summarized by time point.

Individual subject concentration data will be listed and summarized using descriptive statistics by dose. Summary statistics (n, mean, SD, percent coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for individual subject concentration data by time point by dose.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the LLOQ for postdose time points.

The following tables will be provided for GS-9688 by dose:

- Individual subject concentration data and summary statistics

For all subjects in the PK Analysis Set, PK sampling details by subject (using concentration data from all sparse CCI plasma PK sampling), including procedures, differences in scheduled and actual draw times, and sample age will be provided in a listing.

9. REFERENCES

Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55 (4):1202-9.

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 1934;26 (4):404-13.

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

10.   SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
31OCT2019	4.1; 4.2.1; 4.3; 5.3; 7.1.6; 7.2.1; 7.2.2.2; 7.2.3; 7.3; 7.4.1; 7.4.2; 7.6	For summaries using Safety Analysis Set (except liver-related abnormality, ALT flare/elevation output, and prior HBV meds), we remove "by HBeAg status".	This is to be consistent with updates from study GS-US-389-2024.
	5.2	Add history of cirrhosis and cirrhosis determination method for baseline characteristics.	
	7.1.6	Remove AEs of Grade 2 or above, treatment-related AEs of Grade 2 or above	
	7.1.6	Update AE tables to keep severity for the TEAE table only.	
	7.6	Shift table of ophthalmology result will only be generated based on central reader, not on-site investigator.	
	6.3.2	Mean ± SD plot will be presented instead of median plot for HBeAg, HBcrAg and HBV RNA.	
	7.2.5	Remove this section as study specific stopping criteria is reviewed by the DMC.	

12.   APPENDICES

Appendix 1.   Schedule of Assessments
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Appendix 1. Schedule of Assessments

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

Study Procedures	Baseline (Day 1)	Day 2 (Day 1 +24hrs)	On Treatment Weeks (±1 Day)									Post GS-9688/PTM Treatment Weeks (±3 Days)					Days (±7 Days)
			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
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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								

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
On Treatment → (Days / Weeks)												**Post GS-9688/PTM Treatment**					**Days**
Windows						(±1 Day)								(±3 Days)			(±7 Days)
Sparse (pre identified) plasma PK sample Collection[j]	X					X				X							
Holter Monitoring[k]	X					X				X							

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
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	

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

Windows	TFFU Week[b] (Study Week)							
	(±7 Days)							
Study Procedures	4 (52)	8 (56)	12 (60)	16 (64)	20 (68)	24 (72)	36 (84)	48 (96)
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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.

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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 ($\leq$ 5 min of dose) through 4 hours, and 24 hours; Week 11 at pre dose ($\leq$ 5 min of dose) through 4 hours

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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.

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