STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Randomized, Open-Label, Active-Controlled Study to Evaluate the Safety and Antiviral Activity of GS-9992 Plus Tenofovir Alafenamide (TAF) for 12 Weeks in Chronic Hepatitis B (CHB) Subjects	
Name of Test Drug:	GS-9992	
Study Number:	GS-US-464-4437	
Protocol Version (Date):	Original:	22 August 2017
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Analysis Plan Author:	PPD	

CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantitation
BMI	body mass index
BPM	beats per minute
CHB	chronic hepatitis B
CI	confidence interval
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FU	follow-up
GLPS	Global Product Safety
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
ID	Identification
IMP	Investigational Medicinal Product
LLT	lower level term
LLOQ	lower limit of quantitation
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NUC	nucleos(t)ide
INR	international normalized ratio
Peg-IFN	pegylated interferon
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RBC	red blood cell

RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TAF	tenofovir alafenamide
TE	treatment-emergent
TFFU	treatment-free follow-up
TFLs	tables, figures, and listings
TND	target not detected
ULN	upper limit of the normal range
WBC	white blood cell
WHO	World Health Organization

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-464-4437. This SAP is based on the study protocol amendment 3 dated 11 March 2019 and the electronic case report form (eCRF). The SAP will be finalized before the final analysis. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of the 12 week treatment regimens of GS-9992 plus tenofovir alafenamide (TAF) or commercially available nucleos(t)ides (NUCs)

- **Groups 1-3 and 5**

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

- **Group 4**

  To evaluate the antiviral activity of 12 weeks of GS-9992 with commercially available NUC(s) in virally suppressed CHB subjects as measured by the proportion of subjects with ≥ 0.5 log10 IU/mL decline from baseline at Week 12 in circulating serum qHBsAg

The secondary objectives of this study are as follows:

- **Groups 1-3 and 5**

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

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

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

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

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

To characterize steady-state pharmacokinetics (PK) of study drugs

To evaluate the change from baseline in hepatitis B virus (HBV) deoxyribonucleic acid (DNA) and qHBsAg in CHB subjects during 12 weeks of GS-9992 plus TAF versus TAF alone and after GS-9992 discontinuation through 48 weeks

- **Group 4**

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

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

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

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

To characterize steady-state PK of study drugs

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

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1.2. Study Design

This is a Phase 2, randomized, open-label, active-controlled study to evaluate the safety and antiviral activity of GS-9992 plus TAF or commercially available NUC in CHB subjects.

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

Groups 1 and 2: Approximately 40 viremic subjects will be randomized in a 3:1 ratio to the following:

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

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

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

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

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

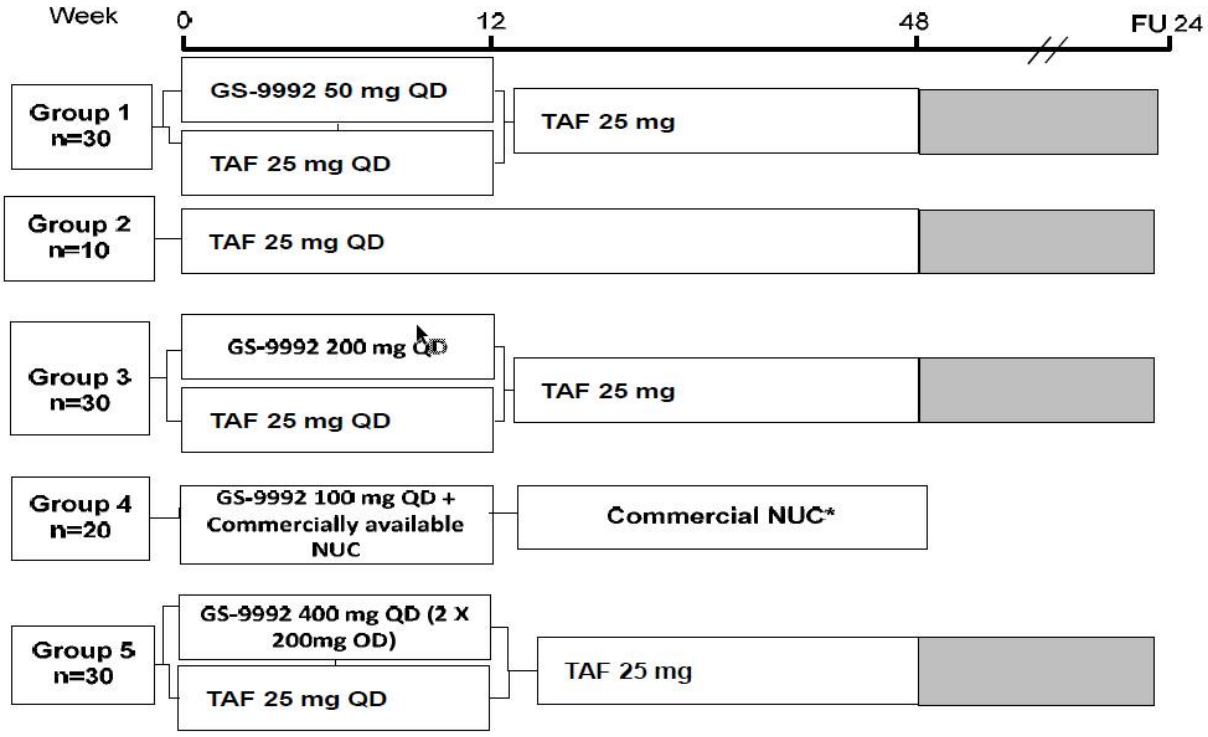
Group 4: Approximately 20 virally suppressed subjects currently being treated with a commercially available NUC(s) for CHB will be administered GS-9992 100 mg tablet once daily one hour before or one hour after a meal for 12 weeks.

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

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

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

Figure 1. Study Schema



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

24 Week Treatment-Free Follow-up (TFFU)

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

- Subjects that discontinue all HBV therapy (eg, GS-9992 and/or TAF or commercially available NUC), for any reason;
- Subjects with HBsAg loss confirmed at least 12 weeks apart should discontinue all HBV therapy following confirmation.

The total time to complete all study visits is up to approximately 79 weeks including the following periods:

- Up to 45 day (6 to 7 weeks) screening period
- A 48-week study period

  Groups 1, 3 and 5: 12 week treatment of GS-9992 plus TAF followed by TAF only treatment

  Group 2: 48 weeks of TAF only treatment

  Group 4: 12 week treatment of GS-9992 plus commercially available NUC followed by NUC only

- Up to 24-week TFFU period

The schedule of assessments is provided as an appendix to the SAP (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. Interim Analysis

After all subjects in Group 3 have completed the study, all the data including Groups 1-4 through TFFU and Group 5 through Week 12 have been cleaned and finalized, the interim analysis of the data will be performed into three parts as follows:

2.1.1. Analysis for 12 Week Regimen

The Analysis for 12 Week Regimen will include data collected through 30 days after the last dose of GS-9992 (Groups 1, 3-5) or 30 days after 12 weeks treatment of TAF (Group 2).

2.1.2. Analysis for 48 Week Regimen

The Analysis for 48 Week Regimen will include data collected to the end of the completion of 48 Week study period.

2.1.3. TFFU Analysis

The TFFU analysis will be conducted for subjects who entered the 24-week TFFU period.

2.2. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed. The final analysis consists of three parts: analysis for 12 Week regimen, analysis for 48 Week regimen, and TFFU analysis.

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 all subjects in the All Randomized/Enrolled Analysis Set and sorted by subject ID, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within the subject. The treatment group to which subjects were randomized (Group 1 and 2) or enrolled (Group 3-5) 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/Enrolled Analysis Set

The All Randomized/Enrolled Analysis Set includes all subjects who were randomized (Group 1 and 2) or enrolled (Group 3-5) in the study. Subjects are grouped within the All Randomized/Enrolled Analysis Set by the treatment group to which they were randomized (Group 1 and 2) or enrolled (Group 3-5).

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized to Groups 1 or 2, or enrolled in Group 3-5, and who took at least 1 dose of any study drug. The study drugs in this study are GS-9992 and TAF. Subjects are grouped within FAS by treatment group to which they were randomized or enrolled.

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 any 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. TFFU Analysis Set

The TFFU Analysis Set includes all subjects who continued in the study following the discontinuation of TAF (Groups1-3, and 5) or commercially available NUC(s) (Group 4), during the Treatment-Free Follow-Up (TFFU) Phase. Subjects are grouped within the TFFU Analysis Set by the treatment group to which they were randomized.

3.1.5. Biomarker Analysis Set

The Biomarker Analysis Set includes all subjects who were randomized to Groups 1 or 2 or enrolled in Group 5, and who took at least 1 dose of any study drug and have at least 1 nonmissing biomarker value for each respective biomarker.

3.2. Subject Grouping

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

3.3. Strata and Covariates

Approximately 40 subjects will be randomly assigned to Group 1 or Group 2 via the interactive voice or web response system (IXRS) in a 3:1 ratio using a stratified randomization schedule. Approximately 30 subjects will be enrolled to Group 3, 20 subjects to Group 4 and 30 subjects to Group 5. Stratification will be based on the following variable:

- HBeAg (positive, negative)

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

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 the presumed prognostic baseline characteristics will not be performed for analysis of 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 (ie, no toxicity grade) for the laboratory abnormality summary.

Both the baseline and post-baseline borderline results for HBeAg, hepatitis B e antibody (HBeAb), HBsAg, and hepatitis B surface antibody (HBsAb) will be imputed following the rules below:

- 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 adverse event (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 (or randomized) subject was not dosed with any study drug, the enrollment (or 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 (eg, 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 Study Day

Study day will be calculated from the first dose date of any study drug and derived as follows:

- For postdose study days: Assessment Date First Dose Date of Any Study Drug + 1
- For days prior to the first dose: Assessment Date First Dose Date of Any Study Drug

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

The last dose date of an individual study drug will be the stop date on the study drug administration eCRF for the record where the "study drug was permanently withdrawn" flag is "Yes".

If the last study drug dosing 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.

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.

- For Groups 1-3 and 5

Data collected up to 3 days after the last dose date of GS-9992 or TAF, whichever comes last, will be considered as on-treatment data whereas data collected afterwards will be considered as posttreatment data.

- For Group 4

Data collected up to 3 days after the last dose date of GS-9992 or 3 days after the subjects have discontinued commercially available NUC(s), whichever comes last, will be considered as on-treatment data whereas data collected afterwards will be considered as posttreatment data.

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 3-1. Analysis Visit Windows for On-treatment qHBsAg, HBV DNA, ddPCR , CCI [redacted] Vital Signs and Safety Laboratory Data

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	8	2	11
Week 2	15	12	22
Week 4	29	23	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	141
Week 24	169	142	211
Week 36	253	212	295
Week 48	337	296	≥ 337

Note: For Group 4, subjects were treated with GS 9992 through Week 12 and continued on NUC afterwards.

Table 3-2. 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

Note: For Group 4, subjects were treated with GS 9992 through Week 12 and continued on NUC afterwards.

Table 3-3. Analysis Visit Windows for On-treatment Electrocardiogram (ECG), and Coagulation

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	≥ 85

Note: ECGs are to be collected at screening, baseline, Week 12 or Early Discontinuation. For purpose of analysis, baseline value will be the last available value prior to the first dose of any study drug. The Early Discontinuation value will be the last available value on or prior to the last dose date of any study drug + 3 days.

Table 3-4. Analysis Visit Windows for On-treatment Creatinine Clearance and Body Weight Data

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	211
Week 48	337	212	≥ 337

Note:
a. For Group 4, subjects were treated with GS 9992 through Week 12 and continued on NUC afterwards.
b. Creatinine clearance data are to be collected at screening, baseline, Week 12, Week 48 or early discontinuation. For purpose of analysis, baseline value will be the last available value prior to the first dose of any study drug. The Early Discontinuation value will be the last available value on or prior to the last dose date of any study drug + 3 days.

Posttreatment data will be mapped to the posttreatment follow-up (FU) analysis windows, which will be defined by FU Day.

- For Groups 1-3

FU Day Assessment Date Last Dose Date of GS-9992 or TAF (whichever comes last)

- For Group 4

FU Day Assessment Date Last Dose Date of GS-9992 or Date Subject Discontinued NUC (whichever comes last)

Posttreatment FU analysis windows are presented in Table 3-5 and Table 3-6.

Table 3-5. Analysis Visit Windows for Posttreatment qHBsAg, HBV DNA, ddPCR, CCI [redacted] Vital Signs and Safety Laboratory Data

Analysis Visit	FU Day	Lower Limit	Upper Limit
FU Week 4	29	4	43
FU Week 8	57	44	71
FU Week 12	85	72	99
FU Week 16	113	100	127
FU Week 20	141	128	155
FU Week 24	169	156	≥ 169

Table 3-6. Analysis Visit Windows for Posttreatment Qualitative HBV Serology

Analysis Visit	FU Day	Lower Limit	Upper Limit
FU Week 12	85	4	127
FU Week 24	169	128	≥ 169

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 any 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 any 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 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) and HBV DNA (IU/mL), HBeAg (IU/mL), HBcrAg (U/mL), HBV RNA (Copies/mL) as 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, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of any 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 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 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 a window are 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

Key study dates (i.e., (first subject screened, first subject enrolled, last subject enrolled/randomized, last subject last visit for the primary endpoint, and last subject last visit for the clinical study report) will be provided. Last subject last visit for the primary endpoint in this study is the last subject who completed Week 12 qHBsAg collection. Last subject last visit for the clinical study report in this study is the last subject who completes TFFU period.

A summary of subject enrollment will be provided by treatment group for each country and investigator within a country and overall. 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.

A similar enrollment table will be provided by randomization stratum, ie, HBeAg status (positive, negative). The denominator for the percentage of subjects in the stratum will be the total number of enrolled subjects. If there are discrepancies in the value used for stratification 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 value of HBeAg 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 treatment group and study overall. This summary will present the number of subjects screened and the number of subjects in each of the categories listed below:

- All Enrolled/Randomized Analysis Set
- Safety Analysis Set
- FAS
- Biomarker Analysis Set
- TFFU Analysis Set
- GS-9992 completion status

    Completed GS-9992

    Prematurely discontinued GS-9992

- Reason for premature discontinuation of GS-9992
- TAF completion status

  Completed TAF

  Prematurely discontinued TAF
- Reason for premature discontinuation of TAF
- TFFU completion status

  On TFFU

  Completed TFFU

  Prematurely discontinued TFFU
- Reason for premature discontinuation of TFFU
- Study completion status

  On Study

  Completed study

  Prematurely discontinued study
- Reason 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 identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reason for premature discontinuation from TFFU
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Lot number and kit ID (if applicable)

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, 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 GS-9992 and TAF 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, Week 1, Week 2, Week 4, Week 8, Week 12 for both GS-9992 and TAF, and additionally Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48 for TAF.

A 3-day window is applied to the last planned on-treatment visit to match with the protocol-specified visit window. Summaries will be provided for each treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

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

$$\text{Total Number of Doses Administered} \left(\sum \text{No. of Doses Dispensed} \right) \left(\sum \text{No. of Doses Returned} \right)$$

4.2.2.1. Prescribed Adherence to GS-9992

The level of prescribed adherence to GS-9992 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 adherence will be expressed as a percentage using the following formula:

$$\text{Adherence to GS-9992 (\%)} = \left(\frac{\text{Total Amount of Study Drug Taken}}{\text{Total Amount of Study Drug Specified by Protocol}} \right) \times 100\%$$

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

For a record where the number of capsules/tablets returned was missing (with "Yes" answered for "Was bottle returned?" question), it is assumed the number of capsules/tablets returned was 0. If the number of capsules/tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, then the capsules/tables will be treated as not taken.

In this study, the total amount of GS-9992 prescribed for 12 weeks would require 168 capsules for Group 1 (dosed with 2 capsules of GS-9992 25 mg QD); 168 tablets for Group 3 (dosed with 2 tablet of GS-9992 100 mg QD); 84 tablets for Group 4 (dosed with 1 tablet of GS-9992 100 mg QD); 168 tablets for Group 5 (dosed with 2 capsules of GS-9992 200 mg QD) respectively.

Descriptive statistics for the level of prescribed adherence to GS-9992 (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (< 80%, ≥ 80 to < 90%, ≥ 90%) will be provided for Group 1, 3 , 4 and 5 by treatment group for the Safety Analysis Set. No inferential statistics will be provided.

4.2.2.2. Adherence to TAF

The level of adherence to TAF will be determined by the total amount of study drug taken relative to the total amount of study drug prescribed, where each total amount is obtained by summing up the corresponding amount at each dispensing period over all evaluable dispensing periods.

The level of adherence will be expressed as a percentage using the following formula:

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

1) 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.

2) 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 capsules/tablets returned was missing (with "Yes" answered for "Was bottle returned?" question); it is assumed the number of capsules/tablets returned was 0. If the number of capsules/tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, then all records for the same dispensing date for that study drug will be excluded from both denominator and numerator calculation.

Descriptive statistics for the level of prescribed adherence to TAF (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (< 80%, ≥ 80 to < 90%, ≥ 90%) will be provided for Group 1, 2 , 3 and 5 by treatment group for the Safety Analysis Set. No inferential statistics will be provided.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number 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 they were exempted by the sponsor or not. 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 treatment group based on All Randomized/Enrolled Analysis Set. A by-subject listing will be provided for those 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 subjects 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 (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for All Randomized/Enrolled 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 or enrollment will be listed with the start and stop dates that they received incorrect study treatment.

A by-subject listing will be provided for subjects with important protocol deviation related to COVID-19. A separate listing will be provided for subjects with non-important protocol deviation related to COVID-19.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, ethnicity and region [South Korea, Hongkong]) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by HBeAg status (positive, negative) and overall for each treatment group and Group 1, 3, and 5 GS-9992 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 (Age : < 50 years, ≥ 50 years; BMI: < 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). 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

- HBV genotype
- cirrhosis (yes, no, indeterminate) and its determination method
- APRI as categories (≤ 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 (≤ 4 log_{10} IU/mL, > 4 log_{10} IU/mL)
- HBV DNA (log_{10} IU/mL) as a continuous variable and as categories (< LLOQ, ≥ LLOQ; and also < 7 log_{10} IU/mL, ≥ 7 log_{10} IU/mL 8 log_{10} IU/mL, ≥ 8 log_{10} IU/mL)
- HBeAb (positive, negative)
- ALT (U/L) as a continuous variable and as categories based on central laboratory normal range (≤ ULN, > ULN 5 × ULN, > 5 × ULN 10 × 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 (≤ ULN, > ULN 5 × ULN, > 5 × ULN 10 × ULN, > 10 ULN)
- current oral nucleoside/nucleotide treatment (Group 4 only)

- previous oral nucleoside/nucleotide treatment experience (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)) × weight (kg) × (0.85 if female)] /
(serum creatinine (mg/dL) × 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 Group 1- 3, and 5 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 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. For Group 4, a separate by-subject listing for current HBV treatment will be provided. The listing will present the current HBV treatment, regimen, and the start date of the current HBV treatment.

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 treatment group. 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 the Primary Efficacy Endpoint

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

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

No statistical hypothesis testing will be performed.

6.1.3. Analysis of the Primary Efficacy Endpoint

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

In addition, the proportion differences (Group 1 Group 2, Group 3 Group 2, Group 5 - Group 2) and the corresponding 2-sided 95% CIs will be reported. CIs of the proportion differences will be calculated by using stratum-adjusted Mantel-Haenszel (MH) proportions {Koch 1989}, stratified by the randomization stratification factor HBeAg status (positive, negative), as follows:

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

where

- $(P_1 \quad P_2)$ $\dfrac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h \quad p_{1h} \quad p_{2h}$ is the proportion difference Groups 1 and 2 in stratum h (h 1 and 2).

- w_h $\dfrac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{1h} and n_{2h} are the sample sizes of Groups 1 and 2 in stratum h.

- SE(P_1 P_2) $\sqrt{\frac{\sum w \left[\frac{p^*_{1h}(1 \quad p^*_{1h})}{n_{1h} \quad 1} + \frac{p^*_{2h}(1 \quad p^*_{2h})}{n_{2h} \quad 1}\right]}{(\sum w_h)^2}}$, where p^*_{1h} $\frac{m_{1h} + 0.5}{n_{1h} + 1}$ and p^*_{2h} $\frac{m_{2h} + 0.5}{n_{2h} + 1}$ and m_{1h} and m_{2h} are the number of subjects with ≥ 0.5 $\log_{10}$ IU/mL decline in HBsAg from baseline at Week 12 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.

6.1.4. Subgroup Analysis of the Primary Efficacy Endpoint

No subgroup analysis 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 Week 12
- Proportion of HBeAg-positive subjects who achieve HBeAg loss and seroconversion through 48 weeks of treatment
- Proportion of subjects who achieve HBsAg loss through 48 weeks of treatment
- Proportion of subjects with drug resistance mutations during 48 weeks of treatment (Group 1 3, and 5)
- Change from baseline in HBV DNA and qHBsAg through 48 weeks of treatment (Group 1 - 3, and 5)
- Change from baseline in qHBsAg through 48 weeks of treatment (Group 4)
- Proportion of subjects experiencing HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL) during 12 weeks of GS-9992 treatment (Group 4)

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.

Lower LOQ (LLOQ) for HBV DNA is defined as 20 IU/mL. LLOQ for qHBsAg is defined as 0.05 IU/mL. LLOQ for qHBeAg is defined as 0.11 IU/mL.

Missing data will be treated as a non-event 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 HBsAg from baseline at Week 12 will be analyzed on FAS similarly to the primary efficacy endpoint. Proportion point estimates and the 2-sided 95% exact CIs will be provided by HBeAg status (positive, negative) and overall for each treatment group. CIs of the proportion point estimates will be constructed based on the Clopper-Pearson method. In addition, the proportion differences (Group 1 Group 2, Group 3 - Group 2, and Group 5 Group 2) and the corresponding 2-sided 95% CIs will be reported. CIs of the proportion differences will be calculated by using stratum-adjusted MH proportions, stratified by HBeAg status (positive, negative).

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 for HBeAg-related serology results.

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) (Group 1- 3, and 5) and qHBsAg (log_{10} IU/mL) by visit (Group 1- 5).

For Group 4, the proportion of subjects who experienced HBV virologic breakthrough (2 consecutive visits of HBV DNA ≥ 69 IU/mL) during 12 weeks of GS-9992 treatment 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.

Imputation rules described in Section 3.6.1 will be used to assign HBeAg and HBsAg status for borderline results. Otherwise, a Missing Excluded analysis will be performed.

Plots of the mean ± SD and median (Q1, Q3) of absolute values and changes from baseline in HBV DNA (Group 1- 3, 5) and qHBsAg will be presented (Group 1-5).

Drug resistance mutations will be analyzed as part of the Virology Study Report.

CCI [redacted]

6.4. Changes From Protocol-Specified Efficacy Analyses

One of the secondary objectives of this study for Groups 1-3 and 5**:**

To characterize steady-state pharmacokinetics (PK) of study drugs

GS-9992 drug development was stopped by Spring Banks and the study team decided not to perform PK analysis and the collected PK samples will be stored.

7. SAFETY ANALYSES

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. System organ class (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 summary presentation.

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

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 data 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 Global Product Safety (GLPS) before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

For the **Analysis for 12 Week Regimen**, treatment-emergent adverse events (TEAEs) are defined as follows:

- For subjects treated with GS-9992 and TAF or commercially available NUC(s) (ie, Group 1, 3 , 4 and 5):

  Any AEs with an onset date on or after the first dose date of any study drug and no later than 30 days after permanent discontinuation of GS-9992

  Any AEs leading to premature discontinuation of any study drug during the first 12 weeks (ie, from Day 1 to Day 84).

- For subjects treated with TAF only (ie, Group 2):

  For those who remained on TAF treatment for the first 12 weeks plus 30 days (ie, from Day 1 to Day 114):

  - Any AEs with an onset date on or after the first dose of TAF and no later than 30 days after the first 12 weeks treatment of TAF (ie, no later than Day 114)

  For those who prematurely discontinued TAF during the first 12 weeks plus 30 days (ie, from Day 1 to Day 114):

  - Any AEs with an onset date on or after the first dose of TAF and no later than 3 days after permanent discontinuation of TAF or up to Day 114, whichever comes earlier
  - Any AEs leading to premature discontinuation of TAF

For the **Analysis for 48 Week Regimen,** TEAEs are defined as follows:

- For subjects treated with GS-9992 and TAF (ie, Group 1 , 3 and 5):

  Any AEs with an onset date on or after the first dose date of any study drug and no later than 3 days after permanent discontinuation of TAF or 30 days after permanent discontinuation of GS-9992, whichever comes last

  Any AEs leading to premature discontinuation of any study drug during the 48 weeks treatment

- For subjects treated with TAF only (ie, Group 2):

  Any AEs with an onset date on or after the first dose date of TAF and no later than 3 days after permanent discontinuation of TAF

  Any AEs leading to premature discontinuation of TAF during the 48 weeks treatment

- Subjects treated with GS-9992 and commercially available NUC(s) (ie, Group 4) are not included in treatment-emergent **Analysis for 48 Week Regimen.**

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 day in the 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 any study drug, will be considered to be treatment emergent in both the Analysis for 12 Week Regimen and Analysis for 48 Week Regimen. 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 any 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.

3 sets of summaries will be generated: (1) all TEAEs for 12 Week Regimen (2) all TEAEs for 48 Week Regimen (Group1-3, and 5). (3) all AEs during TFFU period (AEs that occur during TFFU after Week 48) will be listed, and summary tables will be presented using the TFFU Analysis Set as appropriate.

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT and treatment group:

- TEAEs (with severity)

For the AE categories described below, summaries will be provided by PT and treatment group:

- TEAEs
- TEAEs of Grade 3 or higher
- TE treatment-related AEs
- GS-9992 only TE treatment-related AEs (Group 1, 3-5)
- TE treatment-related AEs of Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of GS-9992
- TEAEs leading to premature discontinuation of TAF
- TEAEs leading to dose modification or temporary interruption of GS-9992
- TEAEs leading to dose modification or 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 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
- SAEs
- All deaths
- AEs leading to premature discontinuation of any study drug
- AEs leading to dose modification or temporary interruption of any 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 inferential statistics will be generated.

7.2.1. Summaries of On Treatment Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided using all available data by treatment group for chemistry (including alanine aminotransferase [ALT], albumin, alkaline phosphatase [ALP], aspartate aminotransferase [AST], creatine kinase, fasting glucose, total bilirubin, fasting total cholesterol, lactate dehydrogenase [LDH]), hematology (including hemoglobin, lymphocytes, neutrophils, white blood cells and platelets), 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 will be defined as the last measurement obtained on or prior to the date/time of first dose of any 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 albumin, ALT, ALP, lipase, estimated creatinine clearance, total bilirubin, triglycerides, total cholesterol, hemoglobin, lymphocytes, neutrophils, platelets, and white blood cells will be plotted using a line plot by treatment group and visit. 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. Summaries of Numeric Laboratory Results during TFFU Period

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided using all available data for chemistry (including albumin, ALT, ALP, AST, total bilirubin, creatine kinase, fasting glucose, fasting total cholesterol and LDH), hematology (including hemoglobin, lymphocytes, neutrophils, white blood cells and platelets), and estimated creatinine clearance calculated by the Cockcroft-Gault method as follows:

- Baseline values
- Value at last on-treatment visit (TFFU baseline)
- Values at each TFFU visit
- Change from TFFU baseline at each TFFU visit

Last on-treatment laboratory value (TFFU baseline) is defined as the last measurement obtained on or prior to the date/time of last dose of any study drug including GS-9992, TAF and NUC treatment. Change from TFFU baseline value to a post treatment visit will be defined as the visit value minus the last on-treatment 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.

Mean ± SD of the observed values for total bilirubin will be plotted using a line plot by HBeAg status and treatment group and visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.3. 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.

7.2.3.1. Treatment-Emergent Laboratory Abnormalities

TE 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 cutoff day defined as follows:

For the **Analysis for 12 Week Regimen**:

- For subjects treated with GS-9992 and TAF or commercially available NUC(s) (ie, Group 1, 3 -5):

  30 days after permanent discontinuation of GS-9992

- For subjects treated with TAF only (ie, Group 2):

  For those who remained on TAF treatment for the first 12 weeks plus 30 days (ie, from Day 1 to Day 114):

  - 30 days after the first 12 weeks treatment of TAF (ie, no later than Day 114)

  For those who prematurely discontinued TAF during the first 12 weeks plus 30 days (ie, from Day 1 to Day 114):

  - 3 days after permanent discontinuation of TAF or up to Day 114, whichever comes earlier

For the **Analysis for 48 Week Regimen**:

- For subjects treated with GS-9992 and TAF (ie, Group 1 , 3 and 5):

  3 days after permanent discontinuation of TAF or 30 days after permanent discontinuation of GS-9992, whichever comes last

- For subjects treated with TAF only (ie, Group 2):

  3 days after permanent discontinuation of TAF

- Subjects treated with GS-9992 and commercially available NUC(s) (ie, Group 4) are not included in treatment-emergent **Analysis for 48 Week Regimen.**

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.

7.2.3.2. Laboratory Abnormalities during TFFU Period

Laboratory abnormalities during TFFU Period are defined as values that increase at least 1 toxicity grade from TFFU baseline at any post treatment time point, up to the end of the study.

7.2.3.3. 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 treatment emergent laboratory abnormalities. Laboratory abnormalities during TFFU period will be summarized using the number and percentage of subjects in the study with the given response at TFFU baseline and each scheduled post treatment visit.

3 sets of summaries will be generated: (1) all TE laboratory abnormalities for 12 Week Regimen (2) all TE laboratory abnormalities for 48 Week Regimen for Groups 1-3, 5. (3) all laboratory abnormalities during TFFU after Week 48 for subjects in the TFFU Analysis Set will be listed, and summary tables will be presented using the TFFU Analysis Set as appropriate.

The following summaries (number and percentage of subjects) for laboratory abnormalities will be provided by lab test and by treatment group; subjects will be categorized according to the most severe postbaseline or post TFFU baseline abnormality grade for a given lab 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 or post TFFU baseline values. A by-subject listing of Grade 3 or 4 laboratory abnormalities, and all graded laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades or abnormal flags displayed.

7.2.4. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for any postbaseline or post TFFU baseline measurements (based on central lab normal range):

1) ALT > 1.5 × nadir and one of the following:

   ALT ≥ 2 × baseline

   ALT ≥ 10 × ULN

   ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN

   ALT ≥ 3 × 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 or post TFFU baseline measurements as follows (based on both central lab and AASLD normal range):

- ALT flare: ALT > 2 × baseline and ≥ 5 × ULN
- AASLD Hepatitis flare: ALT ≥ 3 × baseline and > 100 U/L

2) ALT elevation: ALT > 1.5 × nadir and one of the following:

ALT ≥ 2 × baseline

ALT ≥ 2.5 × ULN and < 5 × ULN

ALT ≥ 5 × ULN and < 10 × ULN

ALT ≥ 10 × ULN

2 sets of summaries will be generated: (1) all liver-related TE laboratory abnormalities and ALT flare/elevation for Week 48 Regimen. (2) all liver-related laboratory abnormalities and ALT flare/elevation during TFFU will be listed, and summary tables will be presented using the TFFU Analysis Set as appropriate.

7.3. Body Weight, Body Mass Index and Vital Signs

Descriptive statistics will be provided by treatment group for vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected 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 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 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 treatment group. 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 dosing 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 by preferred name using the number and percentage of subjects by treatment group. 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 dosing 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.

A shift table of the investigators' assessment of ECG results at Week 12 compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. 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 ECG assessment results will be provided by subject ID number and visit in chronological order.

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

PK samples were collected and stored at Covance. A decision was made that PK analysis will not be performed.

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

12. APPENDICES

Appendix 1. Schedule of Assessments

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

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

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

a. The Early Discontinuation (ED) visit should be performed within 14 days from notification of study discontinuation.
b. Symptom directed physical exam will only be performed when subject is experiencing symptoms.
c. To completed at Treatment Free Follow up Week 4 only: AE review, complete physical examination, and urine pregnancy test.
d. Vital signs include blood pressure, pulse, respiration rate and temperature.
e. QTc interval will be reported using Fridericia's correction: QTcF QT/RR0333. Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording.
f. For female subjects of childbearing potential, the serum pregnancy test will be performed at Screening. Urine test will be performed at all other visits as indicated. Positive urine test will be confirmed with serum test. Pregnancy testing should include prevention counseling.
g. Qualitative HBV serology: (HBeAg [reflex HBeAb if HBeAg is negative] and HBsAg [reflex HBsAb if HBsAg is negative]). Collected every 12 weeks during the study. Post Treatment visit Weeks 12 and 24.
h. PBMCs to be collected at Weeks 4, 8, 12, and 24 only. PBMC sample collection is only required at the sites that have access to PBMC processing laboratory.
i. Weeks 2 and 8 PK samples will be collected between 15 minutes and 4 hours post dose. CCI
j. Single PK sample will be collected at any time on all other Post Day 1 visits CCI . For Group 4, single PK will be collected through Week 12 only.
CCI
l. In the event of a positive result and/or antigen testing for HIV, HDV, or HCV serology, reflex tests will automatically be performed.
m. In clinic dose required for Weeks 2 and 8 single PK samples CCI
CCI
o. HBV genotyping for Groups 1 3 and 5 only, for Group 4 historic genotype should be documented in EDC if available.
p. Serum sample collected will be used for HBV viral sequencing and possible phenotypic analyses for all groups or ddPCR for Group 4.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	21-Sep-2020 16:22:51
PPD	Clinical Research eSigned	23-Sep-2020 20:46:08