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STATISTICAL ANALYSIS PLAN ADDENDUM FOR TFFU ANALYSIS

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 Virally-Suppressed Adult Subjects with Chronic Hepatitis B
Name of Test Drug:	Selgantolimod
Study Number:	GS-US-389-2024
Protocol Version (Date):	Original: 15 January 2018 Amendment 1: 13 March 2018 Amendment 2: 15 February 2019 Amendment 2.1: 27 August 2019
Analysis Type:	TFFU (Treatment-Free Follow-Up) Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	11 September 2020
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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1. INTRODUCTION

This statistical analysis plan (SAP) addendum provides the list of additional tables, figures, and listings (TFLs) to be used in final clinical study report (CSR) for Study GS-US-389-2024 during the treatment-free follow-up (TFFU) phase. The detailed statistical methods and data presentations for the Week 24 and Week 48 analysis were defined in the SAP for Study GS-US-384-2024, and the Week 24 and Week 48 analyses were previously completed and will not be repeated. This SAP addendum is based on the study protocol Amendment 2.1 dated 27 August 2019. The SAP addendum will be finalized before data finalization. Any changes made after the finalization of the SAP addendum will be documented in the final CSR.

2. TYPE OF PLANNED ANALYSIS

2.1. TFFU Analysis

The TFFU analysis will be conducted for subjects who entered the 48-week TFFU period. 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 TFFU analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR TFFU ANALYSES

Subject disposition will be summarized in All Screened Subjects, adverse events (AE) and laboratory abnormalities will be summarized using TFFU Analysis Set. By-subject listings will be presented for subjects in the TFFU 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.

Data will be listed according to the nominal visit as recorded in the database during TFFU period.

The list of TFLs for TFFU analysis is displayed in Appendix 1.

3.1. TFFU Analysis Set

The TFFU Analysis Set includes all subjects who continued in the study following the discontinuation of oral antiviral (OAV) during the TFFU Phase.

4. SUBJECT DISPOSITION

4.1. Subject Disposition

The key study date last subject last visit for the clinical study report will be provided. The last subject last visit for the clinical study report in this study is the last visit of the last subject who completed TFFU period.

A summary of subject disposition will be provided by HBeAg status (positive, negative) and overall for each treatment group and the study overall. 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
- Full Analysis Set (FAS)
- TFFU Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Study completion status at Week 48

  Completed Week 48

  Prematurely discontinued before Week 48
- Reason for premature discontinuation of Study at Week 48
- TFFU completion status

  Completed TFFU

  Prematurely discontinued from TFFU
- Reason for premature discontinuation of TFFU
- Completed study
- Did not complete the study with 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.

5. EFFICACY ANALYSES

Plots of the mean (standard deviation,SD) of absolute values and changes from baseline in qHBsAg (log10 IU/mL) and HBV DNA (log10 IU/mL) till the end of study will be presented.

Qualitative HBsAg, HBsAb, HBeAg and HBeAb; quantitative HBV Viral Parameters (HBV DNA, HBV RNA, HBcrAg, HBeAg and HBsAg, log10 Scale) will be listed using TFFU Analysis Set.

Health-related quality of life (HRQoL) surveys will be listed using TFFU Analysis Set. A by-subject listing for SF-36 scores, Chronic Liver Disease Questionnaire (CLDQ , overall score) and Work Productivity and Activity Impairment Questionnaire: Hepatitis B (WPAI: Hep B; including percent overall work impairment, percent activity impairment) after obtaining properly transformed scores will be provided by subject ID number and visit in chronological order.

6. SAFETY ANALYSES

6.1. Adverse Events and Deaths

6.1.1. Adverse Event Dictionary

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

6.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to the 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.

6.1.3. 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 Gilead Global Product Safety (GLPS) SAE database before database finalization.

6.1.4. Summaries of Adverse Events and Deaths

AEs will be summarized based on the TFFU Analysis Set.

A brief high-level summary of AEs will be for the number and percentage of subjects who experienced the following: any AE, any AE of Grade 3 or above, any AE of Grade 2 or above, any SAE. All deaths observed in the study will also be included in this summary.

The following data listings will be provided for the subjects in the TFFU Analysis Set:

- All AEs
- SAEs
- Deaths

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

6.2. Laboratory Evaluations

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.

The observed values for ALT will be plotted using a line plot by visit till the end of the study using TFFU Analysis Set.

6.2.1. Laboratory Abnormalities during TFFU Period

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

6.3. Vital Signs

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

6.4. 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.

6.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first dose of study drug.

6.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug.

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. SOFTWARE

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

8. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

9. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Table Number	Title	Analysis Set
15.8.1.1	Key Study Dates	All Screened Subjects
15.8.1.3	Subject Disposition	All Screened Subjects
15.11.2.1.1.3	Adverse Events: Overall Summary During TFFU Period	TFFU Analysis Set
15.11.6.4.6	Laboratory Abnormalities During TFFU Period	TFFU Analysis Set

Figure Number	Title	Analysis Set
15.9.2.5.1	HBsAg (log10 IU/mL) by Visit	TFFU Analysis Set
15.9.2.5.3.2	Change from Baseline in HBsAg (log10 IU/mL) by Visit	TFFU Analysis Set
15.9.2.5.4	HBV DNA (log10IU/mL) by Visit	TFFU Analysis Set
15.9.2.5.5	Change from Baseline in HBV DNA (log10IU/mL) by Visit	TFFU Analysis Set
15.11.1	ALT (U/L) by Visit	TFFU Analysis Set

Listing Number	Title	Analysis Set
16.2.1.3	Subject Disposition	TFFU Analysis Set
16.2.4.4.1	Prior and Concomitant Medications	TFFU Analysis Set
16.2.6.3	HBV Serology: HBsAg and HBsAb	TFFU Analysis Set
16.2.6.4	HBV Serology: HBeAg and HBeAb	TFFU Analysis Set
16.2.6.7	Quantitative HBV Viral Parameters (HBV DNA, HBV RNA, HBcrAg, HBeAg and HBsAg, log10 Scale)	TFFU Analysis Set
16.2.7.1.2	All Adverse Events	TFFU Analysis Set
16.2.7.3	Deaths	TFFU Analysis Set
16.2.7.4.2	Serious Adverse Events	TFFU Analysis Set
16.2.8.1.1.1	Hematology Results (Part I): Hematocrit, Hemoglobin, and Platelets	TFFU Analysis Set
16.2.8.1.1.2	Hematology Results (Part II): WBC, Neutrophils, and Lymphocytes	TFFU Analysis Set
16.2.8.1.2.1	Chemistry Results (Part I): ALT, AST, Direct Bilirubin, Indirect Bilirubin and Total Bilirubin	TFFU Analysis Set
16.2.8.1.2.2	Chemistry (Part II): Albumin, Calcium, Creatine Kinase, Creatinine, and Cockcroft-Gault Creatinine Clearance	TFFU Analysis Set
16.2.8.1.2.3	Chemistry (Part III): Alkaline Phosphatase, LDH, Glucose , Total Protein, and Uric Acid	TFFU Analysis Set
16.2.8.1.3.1	Coagulation: International Normalized Ratio (INR) and APTT	TFFU Analysis Set
16.2.8.1.3.2	Urinalysis (Part I): Urine Blood, Bilirubin,, Glucose, Ketones, and Leukocyte Esterase	TFFU Analysis Set
16.2.8.1.3.3	Urinalysis (Part II): Nitrite, pH, Protein, Urobilinogen, and Specific Gravity	TFFU Analysis Set
16.2.8.1.4	Graded Laboratory Abnormalities	TFFU Analysis Set
16.2.8.1.5	Grade 3 or 4 Laboratory Abnormalities	TFFU Analysis Set
16.2.8.2.1	Vital Signs	TFFU Analysis Set
16.2.8.4	Pregnancy Report	TFFU Analysis Set
16.2.8.5	Comments	TFFU Analysis Set
16.2.9.1	SF-36 Quality of Life Questionnaire	TFFU Analysis Set
16.2.9.2	CLDQ Quality of Life Questionnaire	TFFU Analysis Set
16.2.9.3	WPAI: Hep B Quality of Life Questionnaire	TFFU Analysis Set

Appendix 2. Study Procedure Table (Treatment Free Follow-up)

Windows	TFFU Week (Study Week) (±7 Days)							
Study Procedures	**4 (52)**	**8 (56)**	**12 (60)**	**16 (64)**	**20 (68)**	**24 (72)**	**36 (84)**	**48 (96)**
Health Related Quality of Life Surveys			X			X		X
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[c]	X	X	X	X	X	X	X	X
HBV DNA levels, HBV Resistance Surveillance, Quantitative HBsAg	X	X	X	X	X	X	X	X
Quantitative HBCrAg, Quantitative HBeAg, HBV RNA	X	X	X	X	X	X	X	X
CCI								
PBMC Collection[l]	X	X	X	X	X	X	X	X
CCI								
Whole Blood gene expression biomarkers[m]	X	X	X	X	X	X	X	X
CCI								
Review AEs & Concomitant Medications	X	X	X	X	X	X	X	X

a Ophthalmologic Exam window at Screening will be (Days 10 to 1) ,Weeks 12 and 24 (Days 4 to +10)
b In the event of a positive result and/or antigen testing for HIV, HDV, or HCV serology, reflex tests will automatically be performed

c Qualitative HBV serology consists of HBeAg and HBsAg and reflex HBeAb and reflex HBsAb

[redacted]

f Holter Monitoring to be collected prior to blood collection on Day 1 and Week 23 at pre dose (≤ 5 min of dose) through 4 hours, and 24 hours; Week 11 at pre dose (≤ 5 min of dose) through 4 hours

g 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

h 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.

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.

[redacted]

k Serum/plasma PD biomarkers will be collected on Day 1 and Week 23 at pre dose, 4 and 24 hours post dose; Weeks 2, 8, 12, 16, 20, 24 and 28 pre dose; and Week 11 pre dose and 4 hours pose dose.

l PBMC samples collected on Days 1 and 1+4 hours, 1 + 24 hours, and on Weeks 11, 11+4 hours, 12, 23, 23 + 4 hours, 23 + 24 hours, 24, 48/ED, and during TFFU. See also footnote d for collection of Leukapheresis samples in lieu of PBMC samples

m Whole blood gene expression (Paxgene RNA) samples collected on Days 1 and 1+4 hours, 1 + 24 hours, and on Weeks 11, 11+4 hours, 12, 23, 23 + 24 hours, 24, 48/ED, and during TFFU

n 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

o At Week 48, at PI discretion, if a subject discontinues OAV treatment, 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 restart commercially available CHB OAV treatment at any time per local treatment guidelines. If a subject restarts OAV 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.

GS-US-389-2024 SAP Addendum for TFFU Analysis v 1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	09-Sep-2020 15:59:40
PPD	Project Team Leader eSigned	12-Sep-2020 02:35:47