STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1, Open-Label, Multiple Dose Study to Evaluate the Pharmacokinetics of Entospletinib in Subjects with Normal and Impaired Hepatic Function
Name of Test Drug:	Entospletinib
Indication:	Oncology
Sponsor:	Gilead Sciences, Inc.
Protocol No.:	GS-US-339-1631
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Phase of Development:	Phase 1
Lead Biostatistician:	PPD
Lead Pharmacokineticist:	PPD
Analysis Plan Version/Date:	Version 1.0 30 August 2018

CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BLQ	below limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CV	coefficient of variation
CI	confidence interval
CBC	complete blood cell count
C_{max}	maximum concentration
CPT	Child-Pugh-Turcotte
CRF	case report form(s)
CSR	clinical study report
DOB	date of birth
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	Estimated glomerular filtration rate
ENTO	entospletinib
ET	early termination
GLSM	geometric least squares mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HLT	high-level term
HIV	human immunodeficiency virus
INR	International Normalized Ratio
LDL	Low-density lipoprotein
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

SOC	system organ class
TFL	tables, figures, and listings
THC	tetrahydrocannabinol
ULN	upper limit of the normal range
ULOQ	upper limit of quantification
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-339-1631. This SAP is based on the study protocol amendment 4 dated 30 November 2016 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the pharmacokinetics (PK) of Entospletinib (ENTO) and/or its metabolites (if applicable) in subjects with impaired hepatic function (stratified by smoking status, as appropriate) relative to matched, healthy controls

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of administration of ENTO in subjects with normal and impaired hepatic function,

- To evaluate the potential impact of smoking on the PK of ENTO in subjects with moderate hepatic impairment.

1.2. Study Endpoint

The primary endpoints are the PK parameters area under the curve (AUC) and maxium concentration (C_{max}) of ENTO and/or its metabolites (if applicable). The secondary endpoints are the incidences of adverse events and laboratory abnormalities.

1.3. Study Design

This is an open-label, parallel-group, adaptive, multiple-dose, Phase 1 study evaluating the PK of ENTO and/or its metabolites (if applicable) in subjects with impaired hepatic function relative to matched, healthy control subjects.

This study will enroll a minimum of 40 and a maximum of 80 subjects using an adaptive study design that includes up to 3 enrolled cohorts of subjects with hepatic impairment as well as matched healthy controls. Eligible subjects will be male and nonpregnant, nonlactating female subjects, aged ≥ 18 years, 18 ≤ BMI ≤ 40, with either impaired hepatic function of Child-Pugh-Turcotte (CPT) classification A, B, or C or with normal hepatic function. Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years), gender, and BMI (± 20%).

Based on safety and/or PK results from subjects with moderate hepatic impairment (Cohort 1), subjects with severe hepatic impairment (Cohort 2) and/or mild hepatic impairment (Cohort 3) will be enrolled as follows:

Cohort 1 (Moderate Hepatic Impairment) Initial Cohort

Up to 40 subjects: 20 with moderate hepatic impairment (10 smokers [at least 8 evaluable] and 10 non-smokers [at least 8 evaluable]), 20 matched healthy controls (at least 8 evaluable healthy controls matched to smokers with moderate impairment, and at least 8 evaluable healthy controls matched to non-smokers with moderate hepatic impairment).

Adaptive Cohort 2 (Severe Hepatic Impairment)

Up to 20 subjects: 10 with severe impairment, up to 10 matched healthy controls, for 8 evaluable subjects per group. Data from healthy subjects in Cohort 1 who are an appropriate match for a severe hepatic impairment subject may be used.

Adaptive Cohort 3 (Mild Hepatic Impairment)

Up to 20 subjects: 10 with mild impairment, up to 10 matched healthy controls, for 8 evaluable subjects per group. Data from healthy subjects in Cohort 1 or 2 who are an appropriate match for a mild impairment subject may be used.

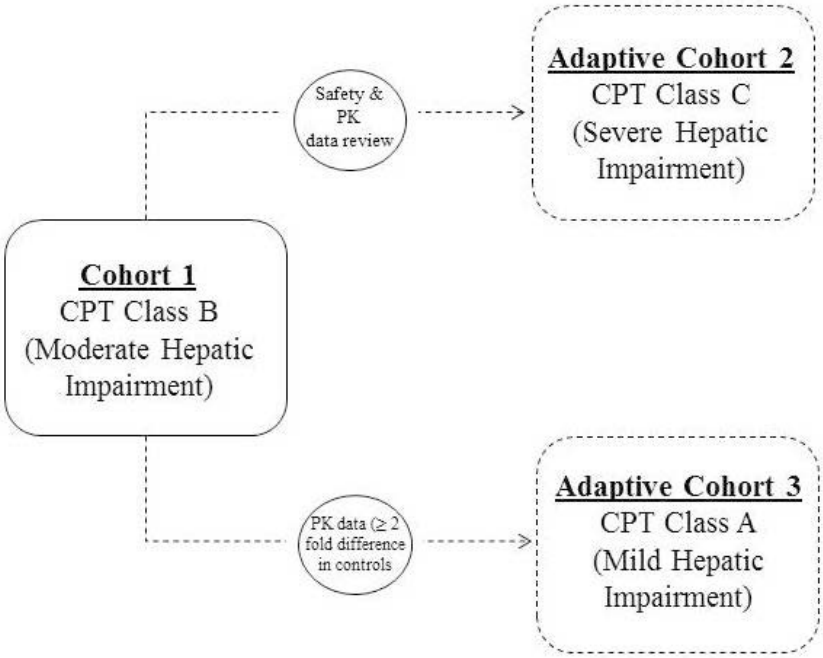
Cohort 1 enrollment of hepatic impairment subjects will be an approximate even distribution of subjects who are active cigarette smokers (at least 10 cigarettes/day) and subjects who are current non-smokers (no use of tobacco, nicotine-containing or tetrahydrocannabinol (THC)-containing products within the last 14 days). Hepatic impairment subjects enrolled in adaptive Cohorts 2 and 3 will be current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days).

Designations of hepatic impairment will be assigned as follows:

- Class A (mild): CPT score 5 to 6
- Class B (moderate): CPT score 7-9
- Class C (severe): CPT score 10-15

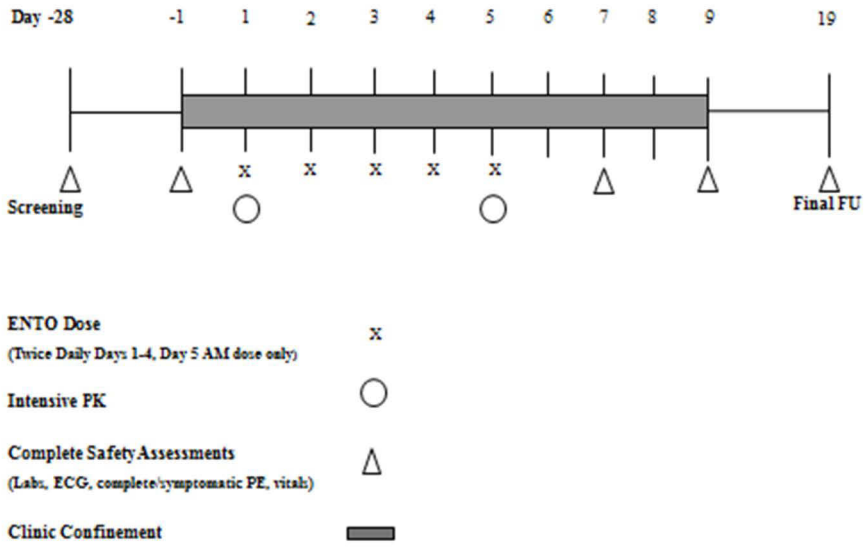
An overview of the study design is shown below in Figure 1-1.

Figure 1-1. Study Design



The study schema for all subjects is shown in Figure 1-2.

Figure 1-2. Study Schema – All Cohorts



1.4. Sample Size and Power

Eight evaluable subjects per hepatic function group (for Cohort 1, it is 8 evaluable subjects per hepatic function group within each smoking status group) will provide ≥ 89% probability for the 90% confidence interval (CI) for the geometric least-squares mean (GLSM) ratio of PK parameters (AUC or C_{max}) for ENTO in the hepatic impairment/dysfunction group(s) versus the appropriate group of matched, healthy controls, to be within limits of 50% to 200%. The calculation assumes an expected ratio of geometric least-squares means of 1.0 in PK parameters and inter-subject standard deviation of 0.455 for the natural logarithm-transformed pharmacokinetic parameters for ENTO. The assumption is based on the data obtained from a prior clinical study of ENTO (Study GS-US-339-0111).

2. PLANNED ANALYSES

2.1. Primary Analysis

The primary analysis objective of this study is to evaluate the multiple-dose PK of ENTO and/or its metabolites (if applicable) in subjects with normal hepatic function, mild hepatic impairment, moderate hepatic impairment, and severe hepatic impairment.

The primary endpoints are the PK parameters AUC and C_{max} of ENTO and/or its metabolites(if applicable).

A parametric (normal theory) analysis of variance (ANOVA) using a linear model will be fitted to the natural logarithmic transformation of PK parameters (AUC_{tau} and C_{max}) for ENTO and/or its metabolites. The 90% confidence intervals (CIs) will be constructed for the GLSM ratios of each of the PK parameters in the hepatic impairment group versus the normal liver function group (see Section 5.2.2).

2.2. Secondary Analysis

The secondary analysis of this study will evaluate the safety and tolerability of ENTO in subjects with normal and impaired hepatic function using the incidence and severity of treatment-emergent adverse events and laboratory abnormalities (see Section 6).

2.3. Changes from Protocol-Specified Analysis

No changes from protocol-specified analyses are planned.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

3.1. Analysis Considerations

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 Enrolled Analysis Set, and sorted by subject identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within subject. The treatment group to which subjects were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.2. Analysis Sets

Analysis sets define which subjects are included in different analyses.

3.2.1. All Enrolled Analysis Set

The all enrolled analysis set will include subjects who were enrolled into the study.

This is the primary analysis set for all listings.

3.2.2. Safety Analysis Set

The safety analysis set will include all randomized subjects who received at least one dose of study drug.

This is the primary analysis set for safety summary tables.

3.2.3. Pharmacokinetic (PK) Analysis Set

The PK analysis sets for ENTO and/or its metabolites will include all enrolled subjects who received at least one dose of ENTO and had at least one evaluable PK concentration data value reported by the PK lab, for each analyte respectively.

This is the primary analysis set for PK summary tables and figures.

3.3. Strata and Covariates

Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years: age ≥ 18), sex, and body mass index (± 20%: 18 ≤ BMI ≤ 40).

3.4. Examination of Subject Subsets

Some baseline variables (i.e., body weight, height, and BMI) will be summarized for males and females separately.

3.5. Multiple Comparisons

All endpoint tests will be done at the significance level of 0.05 with no multiplicity adjustments made for testing.

3.6. Missing Data and Outliers

In general, values will not be imputed for missing laboratory and vital signs data. If the subject is missing a predose value, then the subject will be excluded from the calculation of summary statistics for the predose value and all change from predose values. Similarly, if the subject is missing a postdose value, then the subject will be excluded from the calculation of summary statistics for that postdose and change from predose value (see Section 3.8.2 and Section 3.8.3 for more details).

Missing values will not be imputed for categorical data, such as safety electrocardiogram (ECG).

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the enrollment date will be used instead of the first dosing date of study drug. If only the birth year is collected on the CRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

Pharmacokinetic concentration values that are below the limit of quantification (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as zero at predose and one-half the value of the lower limit of quantitation (LLOQ) at postdose timepoints for determination of summary and order statistics.

For the presentation of summary and order statistics, if at least one subject has a concentration value of BLQ for the timepoint, then the minimum value will be displayed as "BLQ." If more than 25% of subjects have a concentration data value of BLQ for a given timepoint, then the minimum and first quartile (Q1) will be displayed as "BLQ." If more than 50% of the subjects have a concentration data value BLQ for the timepoint, then 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 timepoint, then the minimum, Q1, median, and third quartile (Q3) values will be displayed as "BLQ". If all subjects have concentration data values BLQ for the timepoint, then all summary and order statistics will be displayed as "BLQ". (See Section 5.2.1 for details on the presentation of summary statistics for PK concentration values.)

Exposure parameters selected for statistical analysis will be natural-log transformed (see Section 5.2.2). PK parameter values that are BLQ will be presented as "BLQ" in the parameter data listing. For the purpose of calculation, PK concentration values below the limit of quantitation will be assigned a value of zero for predose and imputed to half of the LLOQ for postdose in determining summary and order statistics.

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation (ULOQ) will be imputed to the value of the lower or upper limit plus or minus 1 significant digit, respectively (e.g., if the results of a continuous laboratory test is < 20 or 2.0, a value of 19 or 1.9, respectively, will be used in computing 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.

The limit of quantification will be used for calculation of descriptive statistics if the datum is reported in the form of "<= x" or ">= x", where x is considered the limit of quantification.

3.8. Visit Windows

3.8.1. Treatment Definitions

Following completion of Screening and Day -1 assessments, eligible hepatic impaired or healthy matched subjects will be enrolled into a cohort and multiple doses of 100 mg BID ENTO (1×100 mg tablet) in the fasted state starting on Day 1 for 5 days.

3.8.2. Definition of Study Day and Predose/Postdose Values

In analyzing safety data (i.e., AEs, laboratory tests, ECG, and vital signs) in this multiple-dose study, Study Day is the number of days relative to the first dosing day of study drug, calculated as:

$$\begin{cases} \text{Visit Date} - \text{First Dosing Date of study drug} + 1, & \text{if Visit Date} \geq \text{Dose Date of study drug;} \\ \text{Visit Date} - \text{First Dosing Date of study drug,} & \text{if Visit Date} < \text{Dose Date of study drug.} \end{cases}$$

Day 1 is defined as the day of the first dose.

Predose value is defined as the last available off-treatment value collected prior to the first dose of study drug.

Postdose value is defined as any value collected after the first dose of study drug and on or before the date of the last dose plus 30 days.

3.8.3. Analysis Windows

In the safety summary tables, postdose laboratory parameters and vital signs will be summarized as follows:

- Only values obtained at the protocol-specified scheduled time points will be included and summarized. Data collected at unscheduled time points will not be included in the summary tables, but will be included in the listings.

- Data collected on early termination visit will be summarized as a separate visit, labeled as "Early Termination Visit."

- Data collected on follow-up visit will be summarized as a separate visit, labeled as "Follow-up Visit."

- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

3.8.4. Selection of Data in the Event of Multiple Records in a Window

If multiple, valid, nonmissing numerical observations exist on the same day, records will be chosen based on:

- For predose, the last available record prior to the time of the dose of the study drug will be selected. If there are multiple records with no time recorded on the same day, the average (arithmetic or geometric mean, as appropriate) will be computed for that day.

- For postdose, use the value for the scheduled visit only. If multiple records are available for a scheduled visit, then the average (arithmetic or geometric mean, as appropriate) will be computed for that day.

If multiple, valid, nonmissing categorical observations exist on the same day, records will be chosen based on:

- For predose, select the last available record prior to the time of first dose of the study drug. 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 (e.g., normal will be selected over abnormal for safety ECG).

- For postdose visit, the most conservative value within that day will be selected (e.g., abnormal will be selected over normal for safety ECG).

4. SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

4.1. Disposition of Subjects

A summary of subject enrollment and disposition will be provided by treatment group. This summary will present the number of subjects enrolled, and the number and percentage of subjects in each of the categories listed below. For the "Dosed" category, the denominator for the percentage calculation will be the total number of subjects enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

- Dosed (Safety Analysis Set)
- PK Analysis Set for each analyte
- Completed study drug
- Did not complete study drug with reason for premature discontinuation of study drug
- Completed the study
- Did not complete the study with reason for premature discontinuation of study

In addition, the total number of subjects who were enrolled, and the number of subjects in each of the disposition categories listed above will be displayed in a flowchart.

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

- Reasons for premature discontinuation of study drug or study

A by-subject listing of subject disposition including cohort, hepatic function group, date of the first/last dose of study drug, study drug completion status, reason for study drug discontinuation, study completion status, reason for study discontinuation, and PK set status (indicating whether or not a subject is included in a PK analysis set) will be provided by subject ID number in ascending order.

4.2. Baseline Characteristics

4.2.1. Demographics and Baseline Characteristics

Subject demographic data (age, sex, race, and ethnicity), baseline characteristics (CPT score, body weight, height, and BMI), and estimated glomerular filtration rate (eGFR) by Cockroft-Gault (CG) method will be summarized using descriptive statistics for the safety analysis set. Eight summary statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum, and

maximum) will be presented for continuous data (age, weight, height, BMI, and eGFR). Age (in years) will be calculated from the date of first study drug dosing if dosed, enrollment if not dosed. The number and percentage will be presented for categorical data (sex, race, ethnicity, and CPT Score). Additionally, body weight, height and BMI will be summarized for males and females separately. Note that the summary of demographics and baseline characteristics will be provided by hepatic function group and smoking status within cohort.

In addition to the summary tables, a listing will be provided for all demographics and baseline characteristics data.

4.2.2. Medical History

Medical history data will be listed only by subject including cohort, hepatic function group, condition or procedure reported term, onset date, ongoing status, and resolution date (if applicable).

Medical history data will not be coded.

4.3. Study Drug and Meal Administration

A listing will be provided to display study drug administration data, including cohort, hepatic function group, study drug dosing date and time, and fasting status.

4.4. Protocol Deviations

A by-subject listing will be provided for those subjects who violated at least 1 inclusion or exclusion criterion, regardless of whether they were exempted or not by the sponsor. The listing will present the entry criterion (or criteria if more than 1 violation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. Any deviations identified will be evaluated to determine if it justifies excluding the subject from any analysis sets.

5. ANALYSIS OF PHARMACOKINETIC DATA

PK parameters will be computed for all subjects in the PK analysis set. The analyte(s) presented in Table 5-1 will be evaluated if data are available.

Table 5-1. Study Treatments and Associated Analytes

Cohort	Treatment	Analyte
1	ENTO 1 × 100 mg BID	ENTO and/or its metabolites (if applicable)
2	ENTO 1 × 100 mg BID	ENTO and/or its metabolites (if applicable)
3	ENTO 1 × 100 mg BID	ENTO and/or its metabolites (if applicable)

The analytes and parameters presented in Table 5-2 will be used to evaluate the objectives of the study.

Table 5-2. Primary and Secondary PK Parameters for Each Analyte

Analyte	Parameters	
	Primary	Secondary
ENTO	AUC_{tau}, C_{tau}, and C_{max}	T_{max}, C_{last}, T_{last}, λ_z, $T_{½}$, CL/F, and V_z/F, and as appropriate, $AUC_{0\text{-}12}$ (Day 1), AUCinf (Day 1), AUC%exp (Day 1)

5.1. Estimation of Pharmacokinetic Parameters

PK parameters will be estimated using WinNonlin® software by application of non-compartmental methods. The linear log trapezoidal rule will be used in conjunction with the appropriate non-compartmental model (usually input Model 200 for oral dosing), with input values for dose, time of dose, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible.

Samples BLQ of the bioanalytical assays that occur prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data. The nominal time point for a key event or dosing interval (τ) may be used to allow for direct calculation of the AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK Scientist on a profile-by-profile basis.

Accurate estimation of several PK parameters, such as λ_z and $T_{½}$, are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK Scientist.

A list of individual data on determination of plasma half-life and corresponding correlation coefficient will be provided including intensive PK sampling day, number of data points in regression, start time, end time, and correlation coefficient.

5.2. Statistical Analysis Methods

PK parameters will be summarized for individual subjects in the PK analysis set (see Section 3.2.3) and summary statistics will be provided for each analyte (when possible) evaluated in the study by hepatic function group and smoking status within cohort.

5.2.1. General Considerations for Statistical Analyses

Nine descriptive statistics (sample size, mean, standard deviation, coefficient of variation [%CV], minimum, median, maximum, Q1, Q3) will be presented for PK concentration data. For concentration values BLQ, the number of subjects with values of BLQ will be presented.

For PK parameter data, the geometric mean, geometric mean 95% CI, and the mean and standard deviation of the natural-log transformed values will be presented in addition to the summaries mentioned above.

The following tables will be provided for each analyte/hepatic function group within cohort:

- Individual subject concentration data and summary statistics
- Individual subject PK parameters and summary statistics

The following figures will be provided for analytes by hepatic function group within cohort:

- Individual subject concentration vs. time–linear and semi-log scale
- Mean (± SD) concentration vs. time–linear and semi-log scale
- Median (Q1, Q3) concentration vs. time–linear and semi-log scale

The following listings will be provided:

- PK sampling details by subject, including differences in scheduled and actual draw times, procedures, and sample ages
- Individual data on determination of plasma half-life and corresponding correlation coefficient

5.2.2. Statistical Comparative Analysis

To evaluate the PK effect of hepatic impairment on ENTO and/or its metabolites (if applicable), the PK parameters (AUC_{0-12} (day 1), AUC_{tau} (day 5), and C_{max} (day 1 and 5), will be compared between impaired hepatic function group (test) vs normal hepatic function group (reference)

within each smoking status group (Cohort 1 only) after natural log transformation. The primary comparison will be based on day 5 PK parameters (AUC_{tau} and C_{max}).

To evaluate the smoking effect on PK of ENTO and/or its metabolites (if applicable), the PK parameters (AUC_{0-12} (day 1), AUC_{tau} (day 5), and C_{max} (day 1 and 5), will be compared between smoking group (test) vs nonsmoking group (reference) within Cohort 1 hepatic impaired subjects after natural log transformation. The primary comparison will be based on day 5 PK parameters (AUC_{tau} and C_{max}).

A parametric (normal theory) ANOVA model will be fitted to the natural log-transformed PK parameter using SAS® PROC MIXED. The model will include hepatic function as a fixed effect. The 2-sided 90% CIs will be constructed for the ratio of geometric least-squares means (impaired hepatic function group /normal hepatic function group).

The following SAS® PROC MIXED code will be used in the comparison analysis described above and the 90% confidence intervals (CIs) will be constructed for the ratio of geometric least-squares means of PK parameters.

```
Proc Mixed method=reml;
*where smoking  status eq "Yes"; Cohort 1 only
*where smoking  status eq "No"; Cohort 1 only
*where hepatic impaired, Cohort 1 only
        class hepgrp;
        *class smoking  status;
        model lnest = hepgrp  / ddfm=kr;
        repeated  / group = hepgrp;
        lsmeans hepgrp / e  diff cl alpha = 0.1;
        estimate 'Impaired  versus Normal'  hepgrp 1 -1 / cl alpha = 0.10;
        *model lnest = smoking  status  / ddfm=kr;
        *repeated  / group = smoking  status;
        *lsmeans smoking_status / e  diff cl alpha = 0.1;
        *estimate 'Smoking vs Nonsmoking HI subjects in Cohort 1'  smoking_status 1 -1 / cl
alpha = 0.10;
    ods output Estimates = LS_Diffs   LSMeans = LS_Means CovParms = MSE;
Run;
```

The ESTIMATE statement will be used to produce the point estimate and 90% CI on natural-log scale for the differences between hepatic function groups/smoking groups. The test/reference comparison ratio and associated 90% CI will be calculated by exponentiation of the natural-log scale point estimate and the corresponding lower and upper limits.

Ninety percent CIs for the GLSM ratio of the test and reference groups will be calculated for each ENTO and/or its metabolites (if applicable) PK parameter in each cohort, consistent with the 2 one-sided t-tests approach {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001, U.S. Department of

Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}. For the comparison between hepatic function groups: if the upper bound of the 2-sided 90% CI of the GLSM ratio for AUC_{tau} and C_{max} (Day 5) is smaller than 2.0, we will reject the hypothesis that subjects with moderate (or mild or severe as applicable) hepatic impairment exhibit average PK parameter (ie, AUC_{tau} and C_{max} [Day 5]) increases of at least 100% for analyte ENTO and/or its metabolites (if applicable) compared with subjects with normal liver function.

The PK parameters $T_{1/2}$, CL/F and V_z/F will be compared between hepatic function groups (for Cohort 1: the comparison between hepatic function groups will be by smoking status groups) using a nonparametric method of Wilcoxon rank sum test. The following SAS® PROC NPAR1WAY code will be used for such nonparametric comparison.

```
proc npar1way wilcoxon;
  class hepgrp;
  var aval;
run;
```

To evaluate the protein binding of ENTO and/or its metabolites, the percent of unbound ENTO and/or its metabolites at T_{max} and another later time point will be summarized by hepatic function group and smoking status group (Cohort 1 only). Protein binding data for individual subject will be presented in a listing.

For subjects hepatic impairment, the relationship between plasma PK exposure parameters AUC_{tau} and C_{max} and overall CPT impairment score will be explored using Spearman correlation analysis and examined graphically. The relationship between the PK parameters (AUC_{tau} and C_{max} on Day 5) and baseline lab tests (albumin, total bilirubin, prothrombin time, and International Normalized Ratio [INR]) will be also explored using Spearman correlation analysis and examined graphically for hepatic impaired subjects and for all subjects by hepatic function group.

6. ANALYSIS OF SAFETY DATA

Safety data (including AEs, laboratory data, vital signs, safety ECG data, and concomitant medications) will be listed and summarized for subjects in the safety analysis set. All safety data collected on or after the date of the first dose of study drug through to the date of the last dose of study drug plus 30 days will be summarized by hepatic function group within cohort. Data for the pretreatment period will be included in data listings.

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

6.1. Adverse Events

6.1.1. Adverse Event Dictionary

AEs will be coded using the current version of MedDRA® (Medical Dictionary for Regulatory Activities). In MedDRA, each verbatim term is mapped to a preferred term (PT) and high level term (HLT), which is then mapped to a system organ class (SOC). Tables and listings will present data at the SOC and PT level.

6.1.2. Adverse Event Severity and Toxicity Grading

Adverse events will be graded by the investigators as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening) according to toxicity criteria specified in the study protocol. The severity grade of AEs for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings.

6.1.3. Relationship of Adverse Events to Study Drug

The investigators will evaluate whether an AE is related to study drug. Related AEs are those for which 'Related' was marked for the question 'Related to the study drug' in the eCRF. Events for which the investigator did not record relationship to study drug will be considered as related to study drug in AE summary tables and will be shown as missing in AE listings.

6.1.4. Relationship of Adverse Events to Study Procedure

The investigators will also evaluate whether an AE is related to study procedure. Related AEs are those for which 'Yes' was marked for question 'Related to the study procedure' in the eCRF. Events for which the investigator did not record relationship to study procedure will be shown as missing in AE listings.

6.1.5. Serious Adverse Events

Serious adverse events (SAEs) are those identified in the eCRF where 'Yes' was marked for the question 'Serious'. Serious AEs are captured in both the eCRF database (clinical database) and the SAE database (managed by Gilead Pharmacovigilance and Epidemiology). The two databases will be reconciled before database finalization.

6.1.6. Treatment-Emergent Adverse Events

6.1.6.1. Definition of Treatment-Emergent

Treatment-emergent AEs are defined as events that meet one of the following criteria:

- Any AEs with onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or
- Any AEs leading to premature discontinuation of study drug

6.1.6.2. 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 date of first dose 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 30 days after the date of the last dose of study drug

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

6.1.7. General Considerations for Analyses

Additional considerations for AE summaries and calculations are as follows when a subject has multiple occurrence of an AE at the level of the PT:

- Multiple events (by PT) will be counted once only per subject
- For summaries by severity grade, the most severe event will be selected per subject

6.1.8. Summaries of Adverse Events

In summary tables, SOC will be presented alphabetically and events within SOC will be presented by decreasing frequency count, based on the total number of events by hepatic function group. For each SOC and PT, the number and percentage of subjects reporting an event will be calculated by hepatic function group.

6.1.9. Additional Analysis of Adverse Events

No additional analyses of AEs are planned.

6.2. Clinical Laboratory Evaluations

A baseline/predose value is defined as the last available measurement obtained prior to administration of the first dose of study drug. In the case where no assessment is available at the baseline visit, the screening assessment will be used. This baseline/predose value will be used as the basis for change from baseline/predose.

A post-dose measurement is defined as any value obtained after the first dose of study drug.

6.2.1. General Considerations for Analyses of Laboratory Data

Listings of laboratory reference ranges and individual subject laboratory results will be provided.

A listing of subjects with graded laboratory results will be provided. This listing will include the complete laboratory test profile for each parameter with a graded result throughout the study.

For summaries of laboratory values (predose, postdose, change from predose), only values obtained at the scheduled visits will be included.

For summaries of laboratory abnormalities, all postdose values will be considered in determining the maximum toxicity grade.

Summaries of clinical laboratory data will be provided for subjects in the safety analysis set. Analysis will be based on values reported in conventional units. No inferential statistics will be provided.

6.2.2. Summaries of Laboratory Results

Chemistry and hematology laboratory tests will be summarized by hepatic function group using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for predose assessments, postdose assessments, and change from predose assessments.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. See Section 3.6 for details on missing data, and see Section 3.8 for details on analysis windows for these data.

6.2.3. Laboratory Abnormality Grades

For specified clinical chemistry, hematology, and urinalysis tests, the criteria described in the study protocol will be used to grade laboratory results as missing (no grade), mild (Grade 1), moderate (Grade 2), severe (Grade 3) or possibly life-threatening (Grade 4). "No Grade" includes all values that do not meet criteria for an abnormality of at least grade one. Some lab tests have criteria for both increased and decreased levels; analysis for each direction (i.e., increased, decreased) will be presented separately.

If there is any lab toxicity grading scale overlapping with normal reference ranges (e.g., Grade 1 scale overlaps with normal reference ranges), lab values within the normal range will still be graded with a footnote indicating the number of graded subjects in such a situation.

Laboratory abnormalities may be reported as an adverse event, and the clinical grading of an event may be different from the quantitative grading depending on the clinical status and underlying conditions.

6.2.4. Treatment-Emergent Graded Abnormalities

A treatment-emergent graded laboratory abnormality is defined as an increase of at least 1 toxicity grade from the predose assessment and occurring after the predose visit and on or before the date of the last dose of the treatment plus 30 days. If the predose assessment is missing, then any abnormality of at least Grade 1 will be considered a treatment-emergent graded laboratory abnormality.

6.2.5. Summaries of Graded Laboratory Abnormalities

The incidence of treatment-emergent graded laboratory abnormalities (number and percentage of subjects) will be presented by hepatic function group. Only the maximum postdose abnormality grade (by each laboratory test or overall as appropriate) observed will be counted. The denominator is the number of subjects with non-missing postdose values in the given analysis window.

6.3. Vital Signs

Each vital signs measurement (including temperature, pulse, systolic blood pressure, diastolic blood pressure, and respiration rate) and weight measurement will be summarized by hepatic function group using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for predose, postdose, and change from predose assessments.

In case of multiple values observed in an analysis window, data will be selected for analysis as described in Section 3.8.3. See Section 3.6 for details on missing data, and see Section 3.8 for details on analysis windows for these data.

A listing of individual subject vital signs will be provided including cohort, hepatic function group, assessment date, temperature, pulse, blood pressures, respiration rate, and weight.

6.4. Electrocardiogram (ECG) Results

Safety ECG results (i.e., normal, not clinically significant abnormal, and clinically significant abnormal) in each postdose visit will be summarized (number) by predose safety ECG result and hepatic function group.

A listing of safety ECG results will be provided including cohort, hepatic function group, assessment date and time, and safety ECG result.

6.5. Prior HIV, HBV and HCV Medications

Only subjects who tested negative for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) surface antigens will be eligible for this study, in addition to meeting other eligibility criteria; therefore, subjects are not expected to have taken any prior HIV or HBV medications. Any prior HCV medications will be documented as part of medical history.

6.6. Concomitant Medications

Concomitant medications (i.e., medications other than study drug that are taken while receiving study drug) will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database.

A listing will be provided for concomitant medications used up to the follow-up visit.

6.7. Other Safety Measures

A listing of any subject pregnancies during the study will be provided. A listing of any subject deaths during the study will be provided. A listing of all comments received during the study will also be provided.

7. REFERENCES

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. January, 2001.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revision 1). March, 2003.

8. SOFTWARE

SAS® (SAS Institute Inc., Version 9.4 Cary, NC) is to be used for all programming of tables, figures, and listings.

WinNonlin® (Pharsight Corporation, Version 6.3, Mountain View, CA) is to be used for all PK analyses.

9. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

10. APPENDICES

Appendix 1. Study Procedures Table – All Cohorts

Study Procedure	Screen[a]	Day -1	Days 1 and 5	Days 2 and 4	Day 3	Days 6 and 8	Day 7	Day 9[b]	Day 19 (±1) FU[c]	ET[d]
Written Informed Consent	X									
Medical History	X									
Complete Physical Exam	X								X	X
Symptom-Driven Physical Examination[e]		X			X		X	X		
Height	X									
Weight	X	X								
Vital Signs[f]	X	X			X		X	X	X	X
HIV-1/HIV-2, HBV, and HCV Serology	X									
Hematology[g]	X	X					X	X	X	X
Serum Chemistry[h]	X	X					X	X	X	X
Genotype Testing for Enzymes and Transporters		X[p]								
Urinalysis	X	X					X	X	X	X
Serum Pregnancy Test[i]	X	X		X[n]				X	X	X
FSH testing[i]	X									
Urine and Alcohol Drug Screen	X	X	X[o]					X	X	X
12-Lead ECG	X	X			X		X	X	X	X
Subject Enrollment[j]		X								
Study Drug Administration			X	X	X					
Intensive Plasma PK[k]			X			X	X	X		
Trough PK[l]				X[l]					X	
Review Study Restrictions										

Study Procedure	Screen[a]	Day -1	Days 1 and 5	Days 2 and 4	Day 3	Days 6 and 8	Day 7	Day 9[b]	Day 19 (±1) FU[c]	ET[d]
Clinic Confinement		X	X	X	X	X	X	X		
Review AEs & Concomitant Medications[m]	X	X	X	X	X	X	X	X	X	X

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drugs.
b Subjects will be discharged from the clinic on *Day 9,* following all morning assessments.
c 14 (±1) days after the last administration of study drug, all subjects will return to the clinic for a follow-up visit.
d Assessments will be performed within 72 hours of early termination from the study.
e Symptom-driven PE's will be performed on Days -1, 3, 7, 9, during confinement as needed, and the follow-up visit.
f Vital signs include blood pressure, pulse rate, respiration rate, and body temperature.
g Hematology: INR, CBC with differential and platelet, neutrophil, and hemoglobin count.
h Fasting serum chemistry: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, α-fetoprotein (at screening only), LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, total cholesterol, HDL, LDL, and triglycerides, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 x ULN).
i All females, except those who are permanently sterile or have medically documented ovarian failure.
j On Day -1, subjects will be enrolled.
k Intensive PK sampling will occur relative to the morning dosing of *ENTO* at the following time points:
Day 1: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 (pre-PM dose) hours postdose
Day 5: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, 84, and 96 hours postdose
l Trough PK sample is taken pre-morning dose on Days 2 and 4 at approximately the same time each day. An additional trough PK sample is taken at the Follow Up visit.
m From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any non-serious adverse events related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF. See Protocol Section 7 Adverse Events and Toxicity Management for additional details.
n Day 4 only
o Day 5 only
p Day -1, before administration of the first dose of study drug, or at any time during clinic confinement