STATISTICAL ANALYSIS PLAN

A Phase I Study to Determine the Relative Bioavailability of Various Formulations of GDC-0134 in Healthy Female Subjects of Non-Childbearing Potential

Statistical Analysis Plan Status: Final V1
Statistical Analysis Plan Date: 01 March 2019

Study Drug: GDC-0134

Sponsor Reference Number: GP40957
Covance Study Number: 8398091

Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

E L Warriner — 04 Mar 2019

Emma Warriner, MSc
Statistician

Date

Sarah M Thorn — 04 Mar 2019

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Date

Sponsor approval:

Chen Chen — 03/01/2019

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2 TABLE OF CONTENTS

3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	Analysis Data Model
A_{eu}	amount excreted in urine over a sampling interval
AE	adverse event
AESI	Adverse events of special interest
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
AUC_{0-48}	area under the concentration-time curve from Hour 0 to 48 hours postdose
AUC_{0-t}	area under the concentration-time curve calculated from Hour 0 to the last measurable concentration
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent systemic clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CSR	Clinical Study Report
CV	coefficient of variation
ECG	electrocardiogram
$\%F_{eu}$	percentage of dose excreted in urine over a sampling interval
ICH	International Conference on Harmonisation
λ_z	apparent terminal elimination rate constant
NC	not calculated
NR	no result
PK	pharmacokinetic
QTc	QT correction; QT interval corrected for heart rate
QTcB	QTc calculated using the Bazett correction
QTcF	QTc calculated using the Fridericia correction
SAP	Statistical Analysis Plan
SD	standard deviation
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

t_{max}	time to maximum observed concentration
V_z/F	apparent volume of distribution during the terminal elimination phase
WHO	World Health Organization

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 19 December 2018).

This SAP describes the planned analysis of the safety, tolerability, and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between **Error! Reference source not found.**, Inc. and Covance Clinical Development Services. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Genentech, Inc. and Covance Clinical Development Services and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

The primary objectives of this study are:

- To determine the relative bioavailability of GDC-0134 F16 capsules (newly developed capsule formulation with GDC-0134 malate drug substance) with respect to the current clinical material, GDC-0134 F09 capsules, with a standard meal.
- To determine the relative bioavailability of GDC-0134 F15 capsules (newly developed capsule formulation with GDC-0134 freebase) with respect to the current clinical material, GDC-0134 F09 capsules, under fasted conditions.

The secondary objectives of this study are:

- To determine the safety and tolerability of a single oral dose of GDC-0134 in healthy subjects.
- To characterize the PK of GDC-0134 after oral administration in healthy subjects.

The exploratory objective of this study is:

- To determine urinary elimination of GDC-0134.

6 STUDY ENDPOINTS

6.1 Pharmacokinetic Endpoints

The primary PK endpoints are:

- Maximum observed concentration (C_{max})
- Area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$)

The secondary PK endpoints are:

- Time to maximum observed concentration (t_{max})
- Area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t})
- Apparent terminal elimination rate constant (λ_Z)
- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent systemic clearance (CL/F)
- Apparent volume of distribution during the terminal elimination phase (V_z/F)

The exploratory PK endpoints of this study are:

- Amount excreted in urine over a sampling interval (A_{eu})
- Cumulative amount excreted in urine (Total A_{eu})
- Percentage of dose excreted in urine over a sampling interval ($\%F_{eu}$)
- Cumulative percentage of dose excreted in urine (Total $\%F_{eu}$)
- Renal clearance (CL_R)

6.2 Safety Endpoints

The safety endpoints of this study are:

- Incidence, nature, and severity of adverse events (AEs)

- Changes in vital signs, electrocardiograms (ECGs), physical examination findings, ophthalmology assessment findings, and clinical laboratory results during and following GDC-0134 administration

7 STUDY DESIGN

This will be an open-label, randomized, 2-period crossover study consisting of two parts to determine:

- Part 1 – the relative bioavailability of GDC-0134 F16 capsules and the current clinical material, GDC-0134 F09 capsules;
- Part 2 – the relative bioavailability of GDC-0134 F15 capsules and the current clinical material, GDC-0134 F09 capsules.

Part 1 and Part 2 may occur in parallel or consecutively in either order (Part 1 followed by Part 2, or Part 2 followed by Part 1).

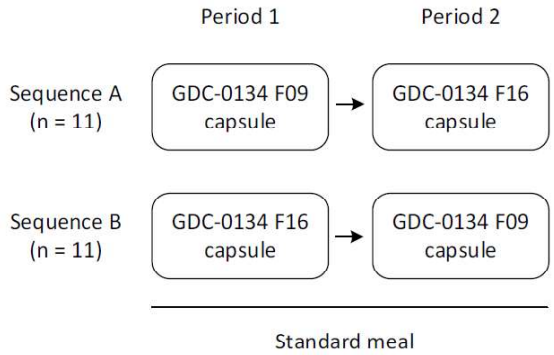
Approximately 22 female subjects of non-childbearing potential (11 per treatment sequence) between 18 and 65 years of age, inclusive, will be enrolled into each part of the study across two clinical research sites.

In Part 1, Periods 1 and 2, eligible subjects will receive 800 mg of either GDC-0134 F16 capsules or the current clinical material, GDC-0134 F09 capsules (Ro 704-0814/F09), orally with a standard meal on Day 1 according to the randomization schedule.

In Part 2, Periods 1 and 2, subjects will receive 800 mg of GDC-0134 F15 or the current clinical material, GDC-0134 F09 capsules, after an overnight fast according to the randomization schedule on Day 1. Subjects will not receive food for 4 hours postdose.

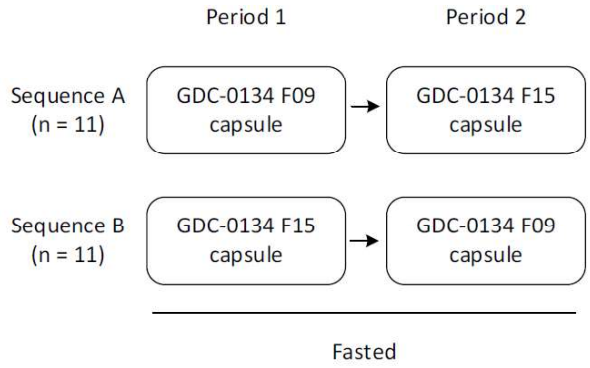
An overview of the study design is provided in **Error! Reference source not found.** and 2:

Figure 1 Study Schematic of Crossover Design – Part 1



Note: F09 capsules = current clinical material of GDC-0134; F16 capsules = newly developed capsule formulation with GDC-0134 malate drug substance

Figure 2 Study Schematic of Crossover Design – Part 2



Note: F09 capsules = current clinical material of GDC-0134; F15 capsules = newly developed capsule formulation with GDC-0134 free base

8 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs for Part 1.

Study Treatment Name	Abbreviation	Treatment Order on TFLs
GDC-0134 F16 capsule fed (Test)	F16 fed	1
GDC-0134 F09 capsule fed (Reference)	F09 fed	2

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs for Part 2.

Study Treatment Name	Abbreviation	Treatment Order on TFLs
GDC-0134 F15 capsule fasted (Test)	F15 fasted	1
GDC-0134 F09 capsule fasted (Reference)	F09 fasted	2

The following is a list of the study treatment sequence abbreviations and ordering that will be used in the baseline TFLs for Part 1.

Study Treatment Sequence	Abbreviation	Treatment Order on TFLs
GDC-0134 F09 capsule fed (Reference)/ GDC-0134 F16 capsule fed (Test)	F09 fed/F16 fed	1
GDC-0134 F16 capsule fed (Test)/ GDC-0134 F09 capsule fed (Reference)	F16 fed/F09 fed	2

The following is a list of the study treatment sequence abbreviations and ordering that will be used in the baseline TFLs for Part 2.

Study Treatment Sequence	Abbreviation	Treatment Order on TFLs
GDC-0134 F09 capsule fasted (Reference)/ GDC-0134 F15 capsule fasted (Test)	F09 fasted/F15 fasted	1
GDC-0134 F15 capsule fasted (Test)/ GDC-0134 F09 capsule fasted (Reference)	F15 fasted/F09 fasted	2

9 SAMPLE SIZE JUSTIFICATION

Twenty-two healthy volunteer female subjects of non-childbearing potential who meet all the protocol inclusion criteria and none of the exclusion criteria will be enrolled into each part of the study.

If the two parts of the study are run sequentially, subjects will be encouraged to participate in both parts. The maximum number of subjects enrolled into the study will be approximately 44.

The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and was not based on power calculations.

10 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug.

The **PK Population** will consist of all subjects who received at least 1 dose of study drug and have at least 1 evaluable postdose PK sample. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median t_{max}.

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

The **All Subjects Population** will be consistent with the Safety Population.

11 STATISTICAL METHODOLOGY

11.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum, and number. For log-normal data (e.g., the PK parameters: AUCs and C_{max}), the geometric mean and geometric coefficient of variation (CV) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed, with the possible exception of missing PK predose concentrations, as detailed in Section 11.4.2.

Data analysis will be performed using SAS® Version 9.4.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

11.1.1 Definition of Baseline and Change from Baseline

Period specific baseline for each parameter is defined as the last value measured prior to dosing in each period, including repeat (vital signs and ECGs) and unscheduled (clinical laboratory parameters) readings (see Section 11.1.2 for definitions of repeat and unscheduled readings).

Mean change from period specific baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

11.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading. Where results are taken in triplicate and repeated, the last 3 readings are used in all subsequent calculations.

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Where results are taken in triplicate, the original reading is defined as the first reading of the triplicate. All results not taken at a scheduled timepoint for other data types (e.g., clinical laboratory parameters) are unscheduled. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 11.1.1).

11.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarized and listed by study part. Subject disposition will be summarized and listed by study part.

11.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version September 2018 Enhanced Dictionary Version B3 format [or higher if version is updated during the study]). Prior and concomitant medications will be listed separately by study part.

11.4 Pharmacokinetic Assessment

11.4.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of GDC-0134 using non-compartmental methods performed using Phoenix WinNonlin (Certara USA, Inc., Version 6.4 or higher):

Parameter	Definition
C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
AUC_{0-48}	area under the concentration-time curve from Hour 0 to 48 hours postdose, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + (C_t/\lambda_z)$ where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant
λ_z	apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (ln)$2/\lambda_z$
CL/F	apparent systemic clearance, calculated as dose/$AUC_{0-\infty}$
V_z/F	apparent volume of distribution during the terminal phase, calculated as $CL/F/\lambda_z$

The following PK parameters will be determined where possible from the urine concentrations of GDC-0134:

Parameter	Definition
A_{eu}	amount excreted in urine over a sampling interval
$\%F_{eu}$	percentage of dose excreted in urine over a sampling interval
Total A_{eu}	cumulative amount excreted in urine
Total $\%F_{eu}$	cumulative percentage of dose excreted in urine
CL_R	renal clearance

Additional PK parameters may be determined where appropriate.

The PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

Concentrations will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

The C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

The A_{eu} for each urine collection interval will be calculated as the product of urine concentration and urine weight (assuming a specific gravity of 1 g/mL); Total A_{eu} will be calculated by summing the A_{eu} values for each collection interval over the 0-12 h, 12-24 h, 24-36 h, and 36-48 h time periods.

The $\%F_{eu}$ will be calculated for each collection interval (i) and the 0-x h time periods (Total $\%F_{eu}$) according to the following formula:

$$\%F_{eu}(i) = \frac{A_{eu}(i)}{dose} \times 100$$

The CL_R will be calculated over 0-48 h according to the following formula:

$$CL_R = \frac{\text{Total } A_{eu\,0-48}}{AUC_{0-48}}$$

11.4.2 Criteria for Handling Concentrations that are Missing or Below the Limit of Quantification in Pharmacokinetic Analysis

- Plasma concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows;
    - Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
    - If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
    - If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
    - If a predose concentration is missing, these values may be set to zero.
- Urine concentrations that are BLQ will be set to zero.

11.4.3 Criteria for the Calculation of an Apparent Terminal Half-Life

11.4.3.1 Number of Data Points

- At least 3 data points will be included in the regression analysis and preferably should not include C_{max}.

11.4.3.2 Goodness of Fit

- When assessing terminal elimination phases, the adjusted coefficient for determination of exponential fit (R^2 adjusted) will be used as a measure of the goodness of fit of the data points to the determined line.

- Regression-based parameters (i.e., λ_z, $t_{1/2}$, $AUC_{0-\infty}$, CL/F, V_z/F) will only be calculated if the R^2 adjusted value of the regression line is ≥ 0.7.

11.4.3.3 Period of Time Estimation

- Apparent terminal elimination half-lives will be estimated over a time period of at least 2 half-lives, where possible.

- Where $t_{1/2}$ is estimated over a time period of less than 2 half-lives, it will be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value should be discussed in the study report.

11.4.3.4 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification, with at least 1 of these concentrations following C_{max}.

- For any partial AUC determination, nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

- The $AUC_{0-\infty}$ values (and related parameters [CL/F, V_z/F]) where the percentage extrapolation is less than 30% will be reported and included in summary and inferential statistics. Any $AUC_{0-\infty}$ values (and related parameters) where the percentage extrapolation is $\geq$30% will be reported but flagged and excluded from summary and inferential statistics.

11.4.3.5 Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

- Positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

11.4.4 Presentation of Pharmacokinetic Data

11.4.4.1 Presentation of Pharmacokinetic Concentration Data

- The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.
    - For the calculation of summary statistics, BLQ values will be set to zero.
    - If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
    - Where there is NR, these will be set to missing.
    - If there are fewer than 3 values in the data series, only the minimum, maximum and number will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
    - If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, minimum and maximum will be presented as zero, and the geometric mean and geometric CV will be denoted as NC.
    - If the value of the arithmetic mean or median is BLQ, it will be presented as zero and the geometric mean and geometric CV will be denoted as NC.

11.4.4.2 Presentation of Pharmacokinetic Parameters

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.
- The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

11.4.5 Pharmacokinetic Statistical Methodology

Descriptive statistics (mean, median, minimum, maximum, SD, geometric mean, and geometric CV) will be calculated for all PK parameters and PK concentration data.

Plasma concentrations of GDC-0134, and derived plasma PK parameters, will be listed and summarized by study part and treatment using descriptive statistics. Individual and mean concentration versus time profiles will be plotted. The primary parameters for analysis will be $AUC_{0-\infty}$ and C_{max} of GDC-0134. A linear mixed model will be applied to analyze the log-transformed primary PK parameters. The model assumes fixed effects for formulation, period, and sequence, and a random effect for subject within sequence. Estimates of geometric mean

ratios on the original scale, together with the corresponding 90% confidence intervals (CIs), will be derived for the comparisons between Test and Reference treatments. All calculations will be performed using SAS® version 9.4 or greater.

Example SAS code that will be used:

```
proc mixed data=xxx;
class treatment period sequence subject;
model lpk = treatment period sequence / ddfm=kr;
random intercept / subject=subject(sequence);
lsmeans treatment / diff cl alpha=0.1;
ods output lsmeans=lsmean diffs=diff;
run;
```

Within-subject CV will be calculated for $AUC_{0-\infty}$ and C_{max} based on the log-normal distribution using the following formula:

$$CV_W(\%) = [\exp(mse) - 1]^{½} \times 100$$

where mse is the residual error from the mixed model.

Residual plots will be produced to assess the adequacy of the model.

The parameter t_{max} will be analyzed nonparametrically using the Wilcoxon signed-rank test. Hodges-Lehmann estimates of the median difference and the corresponding 90% CIs will be calculated for comparison between test and reference treatments.

```
proc univariate data = <data in> cipctldf(alpha = 0.1);
  by parcat1n parcat1 pkday paramn param;
  var ref test dif;
  ods output quantiles = <data out>;
  ods output testsforlocation = <data out>;
run;
(Note: followed by the derivation of Hodges-Lehmann estimates)
```

11.5 Safety and Tolerability Assessments

11.5.1 Adverse Events

A baseline sign and symptom is defined as an AE that starts after the subject has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose. If the start date of an AE is incomplete or missing, it will be assumed to be a TEAE, except if the incomplete start date or the stop date indicates that the event started prior to the first dosing. The AE of special interest (AESI) for this study are defined as follows:

- Clinically significant peripapillary or optic disc swelling on funduscopic examination, as determined by the local site principal investigator/ophthalmologist

- Clinically significant functional visual change from baseline, as determined by the local site principal investigator/ophthalmologist

- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase or aspartate aminotransferase in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law

- Suspected transmission of an infectious agent by the study drug as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. The term applies only when a contamination of the study drug is suspected.

AEs occurring during administration of the Period 1 Day 1 dose up to the dose administration in Period 2 Day 1 will be assigned to Period 1. Any AEs occurring during administration of the Period 2 Day 1 dose and postdose from Period 2 Day 1 to Follow-up will be assigned to Period 2.

All AEs will be listed by study part. The TEAEs will be summarized by study part, treatment, severity rated based on WHO Toxicity Grading Scale, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarized by study part, treatment, and by Medical Dictionary for Regulatory Activities system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of suspected). Any severe or serious AEs or any AESIs or deaths will be tabulated by study part. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

11.5.2 Clinical Laboratory Parameters

All chemistry, hematology, coagulation and urinalysis data outside the clinical reference ranges will be listed by study part, parameter and treatment.

11.5.3 Vital Signs

Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings.

The vital signs data will be summarized by study part and treatment, together with changes from baseline. Figures of mean vital signs and mean change from baseline profiles will be presented by study part and treatment.

11.5.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, and heart rate.

Where ECGs are measured in triplicate (at approximately 2-minute intervals), the mean value will be used in all subsequent calculations.

Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listings.

11.5.5 Ophthalmological Assessments

Ophthalmological assessments include fundoscopic examination, visual acuity assessment, and visual field examination. The ophthalmological data will be listed by study part.

11.5.6 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

Medical history data will be presented.

11.5.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

12 INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the sponsor may choose to conduct interim analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by the sponsor study team personnel.

13 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

14 DATA PRESENTATION

14.1 Insufficient Data for Presentation

Some of the TFLs may not have a sufficient number of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

15 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.