Official Title: A RANDOMIZED, OPEN-LABEL, TWO-TREATMENT, TWO-PERIOD, TWO-WAY CROSSOVER STUDY TO INVESTIGATE THE BIOEQUIVALENCE OF ENTRECTINIB POLYMORPH FORMS A AND C UNDER FASTED CONDITIONS IN HEALTHY SUBJECTS

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STATISTICAL ANALYSIS PLAN

A RANDOMIZED, OPEN-LABEL, TWO-TREATMENT, TWO-PERIOD, TWO-WAY CROSSOVER STUDY TO INVESTIGATE THE BIOEQUIVALENCE OF ENTRECTINIB POLYMORPH FORMS A AND C UNDER FASTED CONDITIONS IN HEALTHY SUBJECTS

Statistical Analysis Plan Status: Final V1
Statistical Analysis Plan Date: 31 January 2019

Study Drug: Entrectinib

Sponsor Reference No.: GP41049
Covance Study No: 8397015

Clinical Phase I

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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:

[redacted], MSc — 01 Feb 2019
Statistician — **Date**

[redacted], BS — 01 Feb 2019
Pharmacokineticist — **Date**

Sponsor approval:

[redacted] — 01 Feb 2019
Statistician — **Date**

2 TABLE OF CONTENTS

3 ABBREVIATIONS

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

ADaM	Analysis Data Model
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve 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
C_{max}	maximum observed concentration
CSR	Clinical Study Report
C_t	last measurable concentration
CV	coefficient of variation
CV_W	within-subject coefficient of variation
ECG	electrocardiogram
ICH	International Conference on Harmonisation
λ_z	apparent terminal elimination rate constant
MR_{AUC}	metabolite ratio based on $AUC_{0-\infty}$
NC	not calculated
NR	no result
PK	pharmacokinetic
QTcB	QTc calculated using the Bazett correction
QTcF	QTc calculated using the Fridericia correction
R	Reference formulation
R^2	adjusted coefficient for determination of exponential fit
SAP	Statistical Analysis Plan
T	Test formulation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

t_{max}	time to maximum observed concentration
t_{last}	time of last measurable concentration
$t_{1/2}$	apparent terminal elimination half-life
V_z/F	apparent volume of distribution during the terminal elimination phase

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1 dated 05 November 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 Genentech, 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 EC Biometrics 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 CSRs."[1,2]

5 STUDY OBJECTIVES

5.1 Primary objective

The primary objective of this study is:

- To demonstrate bioequivalence between entrectinib polymorph Forms A and C under fasted conditions in healthy adult male and female subjects.

5.2 Secondary objective

The secondary objective of this study is:

- To explore the safety and tolerability of a single 200-mg oral dose of entrectinib polymorph Forms A and C in healthy adult male and female subjects.

6 STUDY ENDPOINTS

6.1 Primary Endpoints

The primary endpoints are:

- The geometric mean ratios and associated 90% confidence intervals (CIs) of entrectinib and M5 metabolite PK parameters area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t}) and maximum observed concentration (C_{max}).

6.2 Secondary Endpoints

The secondary endpoints are:

- Incidence and severity of adverse events (AEs) and incidence of abnormalities in laboratory safety tests, 12-lead electrocardiograms (ECG) and vital sign measurements.

7 STUDY DESIGN

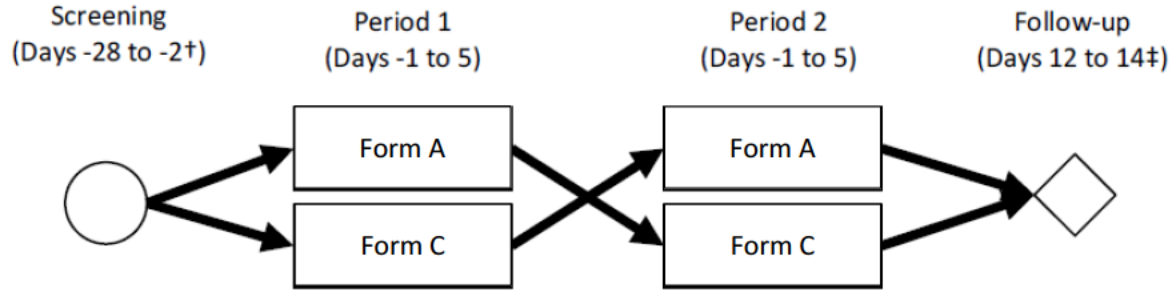
This is a randomized, open-label, 2-treatment, 2-period, 2-way crossover study to demonstrate bioequivalence between entrectinib polymorph Forms A and C administered under fasted conditions in healthy male and female subjects. In each treatment period, subjects will receive a single 200-mg oral dose of entrectinib while fasted. It is planned that a total of 28 subjects will receive the following 2 treatments in a randomized sequence:

Treatment A: Single 200-mg oral dose of entrectinib F06 capsule formulation Form A (Reference formulation [R])

Treatment C: Single 200-mg oral dose of entrectinib F06 capsule formulation Form C (Test formulation [T])

An overview of the study design is provided in Figure 1.

Figure 1 Overview of Study Design



* Minimum 14 days between study drug administrations in Periods 1 and 2.
† Relative to study drug administration in Period 1.
‡ Relative to study drug administration in Period 2.

Potential subjects will be screened to assess their eligibility to enter the study within 27 days (Days -28 to -2) prior to study entry. Replacement subjects may be enrolled, only if deemed necessary by the Sponsor, to ensure that 26 subjects complete the study (have evaluable PK data for both Periods 1 and 2).

Eligible subjects will be admitted to the study site on the day prior to entrectinib dosing (Check-in [Day -1] of Period 1) to collect baseline data and to familiarize the subjects with study procedures that will be used during the rest of the study. On Day 1 of Period 1, subjects will be randomly assigned to 1 of 2 treatment sequences (i.e., TR or RT) according to a pre-specified randomization scheme based on the order of study enrollment. The assigned treatments will be administered under fasted conditions on Day 1 of each period. Doses of entrectinib will be separated by a washout period of at least 14 days.

8 TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment Order on TFLs
Single 200-mg oral dose of entrectinib F06 capsule formulation Form C (Test)	Form C	1
Single 200-mg oral dose of entrectinib F06 capsule formulation Form A (Reference)	Form A	2

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

Study Treatment Sequence	Abbreviation	Treatment Sequence Order on TFLs
Single 200-mg oral dose of entrectinib F06 capsule formulation Form C (Test) /Single 200-mg oral dose of entrectinib F06 capsule formulation Form A (Reference)	Form C / Form A	1
Single 200-mg oral dose of entrectinib F06 capsule formulation Form A (Reference) /Single 200-mg oral dose of entrectinib F06 capsule formulation Form C (Test)	Form A / Form C	2

9 SAMPLE SIZE JUSTIFICATION

A total of 28 subjects will be enrolled to ensure that 26 subjects complete the study and have evaluable PK data from both treatment periods.

In a previous study (Study RXDX-101-15), the within-subject coefficients of variation (CV) for entrectinib area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} following administration of a single dose of entrectinib were estimated to be 20% and 16%, respectively. Assuming a true ratio of 1.05 between the geometric means of Test and Reference treatments, and a within-subject CV of 21%, 26 evaluable subjects are needed to ensure there is

at least 90% probability that the 90% CI for the treatment ratios fall within the no-effect boundaries of 0.80 and 1.25 for each of the 2 primary PK parameters ($AUC_{0-\infty}$ and C_{max}).

10 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug and have at least 1 postdose safety assessment.

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 time to maximum observed concentration.

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, median, minimum, maximum, and number. For log-normal data (e.g. the PK parameters: area under the concentration-time curves [AUCs] and C_{max}) the geometric mean and geometric CV will also be presented. For categorical data, frequency count 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.

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. 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. Subject disposition will be summarized and listed.

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.

11.4 Pharmacokinetic Assessment

11.4.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of entrectinib and M5 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
t_{last}	time of last measurable concentration
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 (wherever possible), where $t_{1/2}$ = natural log(ln)$2/\lambda_z$
CL/F	apparent systemic clearance, calculated as dose/$AUC_{0-\infty}$ (entrectinib only)
V_z/F	apparent volume of distribution during the terminal elimination phase, calculated as CL/F/λ_z (entrectinib only)
MR_{AUC}	metabolite ratio based on $AUC_{0-\infty}$ (M5 only)

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}, t_{max}, and t_{last} 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 metabolic ratios (MR_{AUC}) will be calculated as follows:

$$MR_{AUC} = \frac{AUC_{0-\infty}\ \text{metabolite}}{AUC_{0-\infty}\ \text{parent drug}}$$

The AUC_{0-t} or other common partial area may be used to determine metabolite ratios (MR_{AUC}) if $AUC_{0-\infty}$ cannot be reliably calculated for the majority of subjects.

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

- 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.

11.4.1.2 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

Number of Data Points

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

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, MR_{AUC}) will only be calculated if the R^2 adjusted value of the regression line is ≥ 0.7.

Period of Estimation

- The time period used for the estimation of $t_{1/2}$, where possible, will be over at least 2 half-lives.
- Where an elimination half-life is estimated over a time period of <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.

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 (where applicable), 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, MR_{AUC}]) where the percentage extrapolation is less than 30% will be reported. Any $AUC_{0-\infty}$ values (and related parameters) where the percentage extrapolation is ≥30% will be reported and flagged but excluded from descriptive statistics.

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.
- If a PK profile has a quantifiable predose value that is >5% of its respective C_{max} value, all concentrations and PK parameters for the given PK profile may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

11.4.2 Presentation of Pharmacokinetic Data

11.4.2.1 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 <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). A BLQ is considered a value.
    - If all the values are BLQ, then the arithmetic mean, arithmetic standard deviation, median, min and max 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.

11.4.3 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 3 concentrations, and/or 3 concentrations if the last is C_{max}.

11.4.4 Pharmacokinetic Statistical Methodology

Descriptive statistics (mean, median, minimum, maximum, standard deviation, geometric mean, and geometric CV will be calculated for all PK parameters and PK concentration data. Plasma concentrations of entrectinib and its active metabolite M5, and derived plasma PK parameters, will be listed and summarized by treatment using descriptive statistics. Individual and mean concentration versus time profiles will be plotted.

The primary parameters for bioequivalence testing will be C_{max} and AUC_{0-t} of entrectinib. Statistical analysis for M5 primary parameters, C_{max} and AUC_{0-t} will be provided as supportive evidence. For each analyte, if t_{last} notably varies between the treatments, then AUC calculated over a common partial area may be included in the statistical analysis. If $AUC_{0-\infty}$ is reliably calculated, this will be used for analysis. A linear mixed model[5] will be applied to analyze the log-transformed (base e)[4] primary PK parameters. The model will include fixed effects for treatment, 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% CIs, will be derived for the comparisons between Test and Reference treatments. Bioequivalence will be concluded if the 90% CIs for the treatment ratios fall within the no-effect boundaries of 0.80 and 1.25 for AUCs and C_{max}[3].

An example of the SAS code that will be used (assuming trtmnt coding is 1= Form A, 2= Form C) is as follows:

```
proc mixed data=xxx;
class sequence subject period trtmnt;
model l_pk = sequence period trtmnt / ddfm=kr;
random intercept / subject=subject(sequence);
estimate 'Test - Ref' trtmnt -1 1 / cl alpha=0.1;
lsmeans trtmnt;
run;
```

where l_pk is the log-transformed (base e) PK parameter.

Within-subject coefficients of variation (CV_W) will be calculated for AUCs 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.

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.

Any AEs occurring during administration of the Period 1 Day 1 dose up to the dose administration in Period 2 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. The TEAEs will be summarized by treatment, severity rated based on National Cancer Institute Common Terminology Criteria for Adverse Events, 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 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 AEs of special interest (AESIs) or deaths will be tabulated. 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, and urinalysis data outside the clinical reference ranges will be listed by parameter and treatment.

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

11.5.3 Vital Signs

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

The vital signs data will be summarized by treatment, together with changes from baseline. Figures of mean vital signs and mean change from baseline profiles will be presented by 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 Bazett correction (QTcB), the QT interval calculated using the Fridericia correction (QTcF), the PR, RR, and QT intervals, QRS duration, and heart rate.

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

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

An outlier analysis will be performed including all individual postdose measurements (not the mean data), including all repeat and unscheduled readings. The frequency of subjects with a maximum increase from baseline in QTcB and QTcF intervals will be summarized for each treatment according to the following categories: >30, >60, and ≤30 ms. All incidences of >30 and >60 ms will be flagged on the listing. In addition, the frequency of subjects with QTcB and QTcF postdose values will be summarized for each treatment, according to the following categories: >450, >480, >500, and ≤450 ms. All incidences of >450, >480, and >500 ms will be flagged on the listing.

11.5.5 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.

11.5.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

12 INTERIM ANALYSES

Interim statistical analyses will be performed on the PK parameter results (Table 14.2.1-1 only).

13 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

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

14 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers 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 AEs 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.

3. Statistical Approaches to Establishing Bioequivalence. Rockville, MD: US Dept of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER); January 2001.

4. Keene ON. The log transformation is special. Statistics in Medicine 1995; 14: 811-819.

5. Brown H, Prescott R. Applied Mixed Models in Medicine. Wiley, 1999; Ch 7.