Statistical Analysis Plan I4V-MC-JAGU A Bioequivalence and Food Effect Study in Healthy Subjects Comparing Baricitinib Suspension and Commercial Tablet Formulations

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STATISTICAL ANALYSIS PLAN

A Bioequivalence and Food Effect Study in Healthy Subjects Comparing Baricitinib Suspension and Commercial Tablet Formulations

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t_{last}, where t_{last} is the last time point with a measurable concentration
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) derived by extrapolation
BQL	Below the lower limit of quantitation
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent clearance
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
SAP	Statistical Analysis Plan
SD	Standard deviation
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Apparent terminal half-life

t_{max}	Time of maximum observed drug concentration
TF	Test formulation
WHO	World Health Organization
V_z/F	Apparent volume of distribution during the terminal phase
V_{ss}/F	Apparent volume of distribution at steady state

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 28 September 2016).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (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 and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. 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 signed off prior to first dose administration 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 Eli Lilly and Company and Covance EC Biometrics and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

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

4. STUDY OBJECTIVES

4.1 Primary Objective

To determine if 4 mg of baricitinib administered in a single dose of the suspension formulation (2 mL of 2 mg/mL suspension), with or without water, is bioequivalent (with 0.80, 1.25 as the bioequivalence boundaries) to 4 mg of baricitinib administered as a single 4 mg tablet.

4.2 Secondary Objectives

The secondary objectives are:

- To evaluate the tolerability of baricitinib given as a single dose when administered to healthy adult subjects.
- To compare the relative bioavailability of the suspension formulation administered with and without water.
- To determine the effect of a high-fat, high-calorie meal on the PK of baricitinib when administered as a single 4 mg dose of the suspension formulation.

5. STUDY DESIGN

This is a 2-part, open-label, randomized, crossover study in healthy subjects.

Part A will be a 3-period, randomized, crossover study to evaluate the bioequivalence of 4 mg baricitinib administered as a single dose of the suspension formulation, with and without water, and 4 mg of baricitinib administered as a single 4 mg tablet with water.

Subjects in Part A will be randomly allocated to 1 of 3 treatment sequences (Table 1). Approximately 8 subjects may be allocated to each treatment sequence. Subjects will receive single oral doses of baricitinib on 3 separate occasions, separated by washout periods of at least 72 hours. Each subject will receive the following:

- a single 4 mg (2 mL × 2 mg/mL) dose of baricitinib suspension formulation administered without water (T1), in the fasted state
- a single 4 mg (2 mL × 2 mg/mL) dose of baricitinib suspension formulation administered with 240 mL water (T2), in the fasted state
- a single 4 mg (1 × 4 mg) dose of baricitinib commercial tablet formulation administered with 240 mL water (R), in the fasted state

Table 1. Treatment Sequences in Part A of Study I4V-MC-JAGU

Sequence	Period 1	Period 2	Period 3
1	T1	T2	R
2	T2	R	T1
3	R	T1	T2

Abbreviations: R = 4 mg dose of baricitinib commercial tablet formulation administered with 240 mL water; T1 = 4 mg dose of baricitinib suspension formulation administered without water; T2 = 4 mg dose of baricitinib suspension formulation administered with 240 mL water.

Part B will be a 2-period, randomized, crossover study to determine the effect of a high-fat, high-calorie meal on the PK of baricitinib administered as a single dose of the suspension formulation. Subjects who participate in Part A of the study will not participate in Part B.

Subjects in Part B will be randomly allocated to 1 of 2 treatment sequences (Table 2). Subjects will receive single oral doses of baricitinib on 2 separate occasions, separated by a washout period of at least 72 hours. Whether or not these doses are administered with water (i.e. what the Part B suspension test formulation [TF] will be) will be decided after an interim analysis of the data from Part A of the study. Each subject will receive the following:

- a single 4 mg (2 mL × 2 mg/mL) dose of baricitinib TF administered after a high-fat, high-calorie meal
- a single 4 mg (2 mL × 2 mg/mL) dose of baricitinib TF administered in the fasted state

Table 2. Treatment Sequences in Part B of Study I4V-MC-JAGU

Sequence	Period 1	Period 2
1	TF_{fasted}	TF_{fed}
2	TF_{fed}	TF_{fasted}

Abbreviations: TF_{fasted} = 4 mg dose of baricitinib suspension test formulation administered in the fasted state; TF_{fed} = 4 mg dose of baricitinib suspension test formulation administered after a high-fat, high-calorie meal.

Figure 1 illustrates the study design.

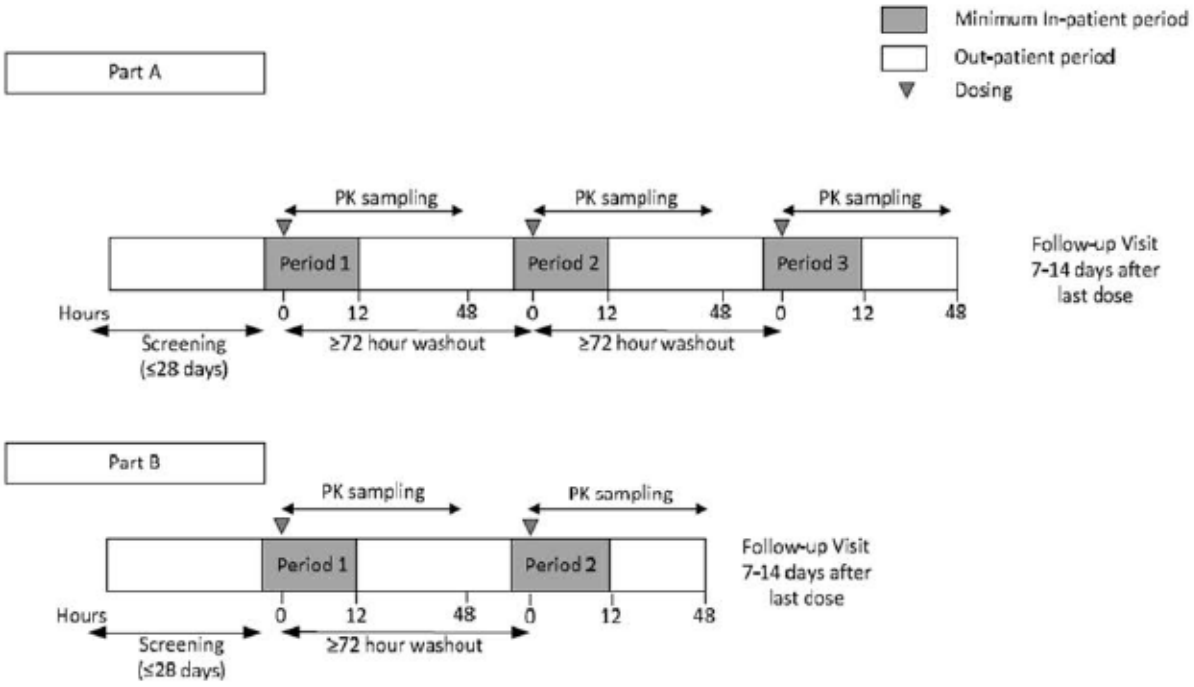

Figure 1. Illustration of Study Design for Protocol I4V-MC-JAGU

6. TREATMENTS

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

Part	Study Treatment Name	Abbreviation	Treatment order in TFL
A	4 mg baricitinib tablet with 240 mL water (fasted)	R	1
	4 mg baricitinib suspension without water (fasted)	T1	2
	4 mg baricitinib suspension with 240 mL water (fasted)	T2	3

B	4 mg baricitinib suspension (fasted)	TF_{fasted}	4
	4 mg baricitinib suspension (high-fat meal)	TF_{fed}	5

7. SAMPLE SIZE JUSTIFICATION

In Part A, 26 subjects may be enrolled to ensure that 20 complete the study.

For maximum observed drug concentration (C_{max}), assuming an intra-subject coefficient of variation of 16%, 20 subjects provide 90% power to show bioequivalence for a 95% confidence interval (CI) using 0.8 and 1.25 as the lower and upper bioequivalence limits, respectively. A 95% CI was used to calculate the power for this study to assure both comparisons of the suspension formulation (with and without water) versus the commercial tablet had adequate power using the Holm's step-down procedure. This procedure adjusts for multiplicity maintaining the family-wise type 1 error rate.

For area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) and area under the concentration versus time curve from time zero to time t_{last}, where t_{last} is the last time point with a measurable concentration (AUC[0-t_{last}]), assuming an intra-subject coefficient of variation (CV) of 7.8% and 7.6%, respectively, 20 subjects provide greater than 99% power to show bioequivalence for a 95% CI using 0.8 and 1.25 as the lower and upper bioequivalence limits, respectively.

In Part B, it is planned that up to 18 subjects will be enrolled in order that 14 complete the study; however, this number may be revised based on interim analysis of the intra-subject variation in PK parameters of baricitinib suspension formulation in Part A of the study.

Subjects who are randomized and discontinue the study prior to completion of all study periods in their assigned study part may be replaced to ensure that a minimum of 20 subjects complete Part A of the study and 14 complete Part B. Replacement subjects will complete all 3 periods (Part A) or 2 periods (Part B), following the sequence of the withdrawn subject.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of study drug, and have at least one postdose safety assessment.

The "Full analysis set" will include all data from all subjects receiving at least one dose of baricitinib in that study part, with evaluable PK data, according to the treatment the subjects actually received. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

The "Completer analysis set" will include data from subjects who receive all doses of baricitinib for that study part and have evaluable PK data, according to the treatment the subjects actually

received. Subjects may be excluded from the PK summary statistics and statistical analysis if a 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 for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that are databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, min, max and N; for log-normal data (e.g. 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. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Since subjects in Part A and Part B of this study will be different (no subject overlap between the two parts), the treatment sequences used in each part have different treatment groups and different duration (i.e. in Part A subjects are assigned to sequences with 3 periods and in Part B, with 2 periods), TFLs will be done separately for Part A and Part B.

Data analysis will be performed using SAS® Version 9.3 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed for each study part. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed for each study part.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4.1 or later).

Plasma concentrations of baricitinib will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t_{last}, where t_{last} is the last time point with a measurable concentration
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) derived by extrapolation
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	apparent terminal half-life
CL/F	L/h	apparent clearance
V_Z/F	L	apparent volume of distribution during the terminal phase
V_{SS}/F	L	apparent volume of distribution at steady state

An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for predose sampling times which will be set to zero.
- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.
- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.
- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination

phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on observed last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when both of the following conditions are met:

    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other concentrations BQL that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted using actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using nominal sampling times.

- The average concentration profiles will be graphed using arithmetic mean concentrations.

- The predose average concentration will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding ± 10% of the nominal sampling time will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements and were collected within ± 10% of the nominal sampling time.

Treatment of Outliers during Pharmacokinetic Analysis

This procedure provides justification for excluding data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a predose sample is quantifiable.

- For any questionable datum that does not satisfy the above criterion, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values
Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

PK parameters will be evaluated to delineate the effects of baricitinib formulation. For the primary analysis, log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) estimates will be evaluated in a linear mixed effects model with fixed effects for formulation, period, sequence, and a random effect for subject (sequence). The treatment differences between each test compared to the reference formulation will be back-transformed to present the ratios of geometric least squares (LS) means and the corresponding CIs. The Holm step-down procedure for an overall 0.1 alpha level will be used. This analysis applies only to Part A.

Bioequivalence between the suspension formulation administered either with or without water and the commercial tablet will be concluded if the 95% CI for C_{max}, AUC(0-t_{last}), and AUC(0-∞) are all completely contained within the interval (0.80, 1.25). If at least one of the administrations has all three 95% CIs contained within the interval (0.8, 1.25), then the second administration will be declared bioequivalent if the 90% CIs for C_{max}, AUC(0-t_{last}), and AUC(0-∞) are all completely contained within the interval (0.80, 1.25). The following comparisons shall be made:

- 4 mg baricitinib suspension with 240 mL water (fasted) vs 4 mg baricitinib tablet with 240 mL water (fasted)
- 4 mg baricitinib suspension without water (fasted) vs 4 mg baricitinib tablet with 240 mL water (fasted)Example SAS code is provided below.

```
proc mixed data=dataset;
class subject group period sequence;
model l&var=group period sequence / cl solution outpred=resids;
random intercept / subject=subject(sequence);
lsmeans group / pdiff cl;
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;
quit;
```

The same model will be used to compare the relative bioavailability of the suspension formulation administered with (test) and without (reference) water, with a significance level of 0.1. This analysis applies to Part A.

To determine the effect of a high-fat, high-calorie meal on the PK of baricitinib when administered as a single 4 mg dose of the suspension formulation, the ratio of geometric LS means between the fasted and fed states for C_{max}, AUC(0-t_{last}), and AUC(0-∞) will be evaluated. A linear mixed effects model with fixed effects for fasted/fed status, period, sequence, and a random effect for subject (sequence) will be used. The treatment differences between each fasted and fed state will be back-transformed to present the ratios of geometric LS means and the corresponding 90% CIs. This analysis applies to Part B.

The t_{max} will be analyzed using a Wilcoxon signed rank test for the comparisons listed above and for fasted vs fed for each study part. Estimates of the median difference based on the observed medians, 95/90% CIs, and p-values from the Wilcoxon test will be calculated.

9.4 Safety and Tolerability Assessments

The following analyses will be done separately for Part A and Part B.

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated.Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2016). Concomitant medication will be listed.

9.4.2 Clinical laboratory parameters

All clinical chemistry, hematology and urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

9.4.3 Vital signs

Vital signs data will be listed for individual subjects.

9.4.4 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented.

9.4.5 Other assessments

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

9.4.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

A formal interim analysis of PK data will be performed after all PK data are available for Part A. Statistical analysis will be conducted to test the baricitinib suspension formulation, administered with and without water, for bioequivalence with the commercial tablet formulation. The dosing method for the suspension formulation that is bioequivalent to the commercial tablet formulation will be used in Part B. If both administration methods are bioequivalent to the commercial tablet formulation, suspension will be administered without water in Part B, for ease of administration. If the suspension formulation is not bioequivalent to the commercial tablet formulation using either administration method, all available data will be used to assess the most appropriate way to administer the drug in Part B.

Intra-subject variability estimates of PK parameters will be used to determine the number of subjects required to complete Part B of the study.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

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

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

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported

as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 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 centre of the table, such as, "No serious adverse events occurred for this study."

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