Protocol B7981086

A PHASE 1, OPEN-LABEL STUDY IN HEALTHY PARTICIPANTS TO INVESTIGATE THE PHARMACOKINETICS OF RITLECITINIB FOLLOWING SINGLE ORAL ADMINISTRATION OF MODIFIED RELEASE FORMULATIONS UNDER FED AND FASTED CONDITIONS

Statistical Analysis Plan
(SAP)

Version: **2.0**

Date: 25 Mar 2024

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 15 Aug 2023	Original 19 Jun 2023	N/A	N/A
2 25 Mar 2024	Protocol Amendment 1 07 Nov 2023	To remove analysis related to PK collection via Tasso to be consistent with Protocol Amendment 1, and modify safety analysis for ECG and VS.	Section 2.2 removed tertiary objective and endpoints related to Tasso micro-sampling device Section 3.1, 3.2 updated notation for K_{el} Section 3.3 removed analysis of the endpoints related to Tasso micro-sampling device Section 3.4 modified baseline definitions for ECG and VS Section 3.5.3 modified language on post-baseline for calculation of change from baseline in vital signs; removed calculation for maximum decrease/increase Section 3.5.4 modified language on post-baseline for calculation of change from baseline in ECG; removed calculation for maximum decrease/increase Section 4, removed section reference related to PK analysis of Tasso micro-sampling device Section 6.4 removed PK concentration presentation for Tasso micro-sampling device Section 6.5 modified language for demographic summary to be by gender and overall Section 6.6.3 modified language for vital signs summary to be for Periods 1-3 and Period 4

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			Section 6.6.4 modified language for ECG summary to be for Periods 1-3 and Period 4; removed using average for replicate measurements Appendix 1, updated categorization of ECG and VS to be based on change from baseline

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B7981086. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition will also be reflected in a protocol amendment.

(copied from protocol)

Ritlecitinib is a covalent and irreversible inhibitor of JAK3 with high selectivity over the other JAK isoforms (JAK1, JAK2, and TYK2). Ritlecitinib also inhibits irreversibly the tyrosine kinase expressed in TEC family kinases with selectivity over the broader human kinome. Treatment with ritlecitinib is expected to inhibit the inflammatory pathways mediated by IL-7, IL-15 and IL-21, all implicated in UC, CD, AA, RA, and vitiligo. Moreover, due to lack of activity against the other JAK isoforms, ritlecitinib is expected to spare immunoregulatory cytokines such as IL-10, IL-27 and IL-35, which are critical to the maintenance of immunosuppressive functions and immune homeostasis.

The purpose of the study is to evaluate the PK, safety, and tolerability of ritlecitinib following single oral doses as solution and MR formulations in healthy, adult participants under fasted and fed conditions. The objective is to evaluate the relative bioavailability and food effect of 2 new MR capsule formulations, MR1 and MR2. Overall, results from this study will facilitate further development of an MR formulation for future clinical studies.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

As this is an inpatient, healthy volunteer study, estimands are not applicable. The table below is copied directly from the protocol.

Objectives	Endpoints
Primary:	**Primary:**
• To determine the PK profile and relative bioavailability of ritlecitinib as 2 MR capsule formulations, MR1 and MR2, relative to solution formulation under fasted conditions in healthy adult participants.	• PK parameters of ritlecitinib (fasted): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}
Secondary:	**Secondary:**
• To evaluate the effect of food on ritlecitinib exposure following administration as 2 MR capsule formulations, MR1 and MR2 in healthy adult participants.	• PK parameters of ritlecitinib (fed): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}.
• To evaluate safety and tolerability of ritlecitinib following single oral administration as MR1 and MR2 capsule formulations in healthy adult participants.	• Assessment of AEs, clinical laboratory tests, vital signs and 12-lead ECG.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To estimate additional PK parameters of ritlecitinib following single oral administration as MR1 and MR2 capsule formulations in healthy adult participants.	• T_{max}, and if data permit, T_{lag} , CL/F ,V_z/F , and $t_{½}$

2.3. Study Design

This is a single dose, open-label randomized, 4-period, 6-sequence crossover study in a single cohort of approximately 12 healthy male and/or female participants randomized to one of the sequences (containing 1 solution and 2 MR [MR1 and MR2] capsule formulations of ritlecitinib) displayed in Table 2. The first 3 periods are under fasted condition and the fourth period is under fed condition to investigate food effect on the PK of modified release formulations MR1 and MR2.

Table 2. Study Design and Treatments

Sequence	Period 1	Period 2	Period 3	Period 4
1 (n=2)	A	B	C	B, fed
2 (n=2)	B	C	A	B, fed
3 (n=2)	C	A	B	B, fed
4 (n=2)	A	B	C	C, fed
5 (n=2)	B	C	A	C, fed
6 (n=2)	C	A	B	C, fed

A: ritlecitinib 100 mg PO solution
B: ritlecitinib 100 mg (2 x 50 mg) MR1 capsules
C: ritlecitinib 100 mg (2 x 50 mg) MR2 capsules

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The PK profile and relative bioavailability of ritlectinib as 2 MR capsule formulations, MR1 and MR2, relative to solution formulation under fasted conditions will be derived from the concentration-time profiles as shown in the table below, if data permit.

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observe directly from the data
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration versus time curve	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis; k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve

a If data permit.

3.2. Secondary Endpoint(s)

To evaluate the effect of food on ritlecitinib exposure following administration as 2 MR formulations, MR1 and MR2, the following secondary endpoints for the PK of ritlecitinib will be derived from the concentration-time profiles as shown in the table below.

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observe directly from the data
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration versus time curve	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis; k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve

a If data permit.

Another secondary endpoint is evaluating the safety and tolerability of ritlecitinib following single oral administration as MR1 and MR2 capsule formulations through the assessment of AEs, clinical laboratory tests, vital signs, and 12-lead electrocardiogram (ECG).

3.3. Tertiary/Exploratory Endpoint(s)

To estimate additional PK parameters of ritlecitinib following single oral administration as MR1 and MR2 capsule formulations in healthy adult participants, the following tertiary/exploratory endpoints for the PK of ritlecitinib will be derived from the concentration-time profiles as shown in the table below.

Parameter	Definition	Method of Determination
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
CL/F[a]	Apparent Clearance	$Dose/AUC_{inf}$
Vz/F[a]	Apparent volume of distribution after oral dose	$Dose/(AUC_{inf}*k_{el})$ after oral dose
T_{lag}[a]	Lag time	Time prior to the time corresponding to the first quantifiable concentration

a if data permits.

3.4. Baseline Variables

Start and end dates of study treatment: The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of the study drug. The date of last dose of study treatment is the latest date of non-zero dosing of the study drug.

Definition of baseline: For vital signs and ECG, the baseline measurement of Periods 1-3 is the last pre-dose measurement taken on Day 1 of Period 1, and the baseline measurement of Period 4 is the last pre-dose measurement taken on Day 1 of Period 4. For safety labs, the baseline measurement is the pre-dose measurement on Day -1.

3.5. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days, baseline assessment, and list of parameters):

- *adverse events;*
- *laboratory data;*
- *vital signs data;*
- *ECG results.*

3.5.1. Adverse Events

An adverse event (AE) is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the end of the last follow-up date, will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset which was occurred before the first treatment dosing.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

The baseline measurement is the pre-dose measurement on Day -1.

3.5.3. Vital Signs

Supine blood pressure and pulse measurements will be taken at all time points listed in the Schedule of Activities given in the protocol.

For calculation of change from baseline for Periods 1 - 3, the baseline of Period 4 is used as post-baseline; for Period 4, the measurement on Day 3 will be used as the post-baseline measurement.

3.5.4. ECG

Single supine 12-lead ECG will be taken at all time points listed in the Schedule of Activities given in the protocol. For calculation of change from baseline for Periods 1 - 3, the baseline of Period 4 is used as post-baseline; for Period 4, the measurement on Day 3 will be used as the post-baseline measurement.

The QT, QTc, PR, QRS and heart rate will be recorded at each assessment time.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{1/3} \qquad \text{where } RR = 60/HR \text{ (if not provided)}$$

3.5.5. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description	Applicable Analysis (for additional information refer to section 6)
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization.	
Full analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.	
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.	Sections 6.2, 6.5, 6.6
PK concentration	All participants who have at least 1 measurable concentration in at least 1 treatment period.	Section 6.4
PK parameter	All participants who have at least 1 PK parameter of interest (Section 3) quantified in at least 1 treatment period.	Sections 6.1, 6.2, 6.3, 6.4

4.1. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are randomized to, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

4.2. Protocol Deviations

Participants who experience events that may affect their PK profile may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed prior to database closure.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

As this is an exploratory study, no formal hypothesis testing will be performed.

5.2. General Methods

Descriptive analyses will be performed. Some measures will be summarized using graphical representations by treatment, where appropriate.

For continuous variables, the data will be summarized using the number of subjects, mean, median, standard deviation, minimum, and maximum in accordance with current Pfizer's data and reporting standards. For appropriate PK parameters, geometric mean and geometric coefficient of variation (geocv%) will also be summarized. See Section 6.4 for details.

For categorical or ordinal variables, number of subjects, numbers and percentages of subjects meeting the categorical criteria will be supplied in accordance with current Pfizer's data and reporting standards.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

Methods to handle missing PK data are described below.

Concentrations Below the Limit of Quantification:

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ" where LLQ will be replaced with the value for the lower limit of quantification).

Deviations, Missing Concentrations and Anomalous Values:

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

Pharmacokinetic Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues). In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

- *PK parameters of ritlecitinib (fasted): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}*

The outcomes of interest will be assessed for relative bioavailability analyses observations collected under fasted condition (in periods 1-3). These treatments are denoted by letters A, B, and C.

A = ritlecitinib 100 mg PO solution
B = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules
C = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm. The illustrative SAS code is presented in the Appendix 2.

For relative bioavailability analysis, the single dose of ritlecitinib MR1 and MR2 administered in fasted state are the Test treatments. Single dose of ritlecitinib solution under fasted condition is the Reference treatment.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major

deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

A listing of the descriptive and graphical summaries for PK parameters is presented in Section 6.4.

In addition, for the parameters AUC_{inf} (if data permit), AUC_{last} and C_{max}, a listing of the individual subject ratios (Test/Reference) will also be provided. Box and whisker plots for individual subject parameters (AUC_{inf}, AUC_{last}, and C_{max}) will be presented by treatment and overlaid with geometric means.

6.2. Secondary Endpoint(s)

- *PK parameters of ritlecitinib (fed): C_{max}, AUC_{inf} (if data permit), otherwise AUC_{last}*

By the design of the trial, all of the observations made in the fed state are positioned in the single treatment periods and therefore the evaluation of the food effect is potentially confounded by the period effect. We assume that the magnitude of the food effect is much larger than the magnitude of the period effect and will be able to support this assumption by estimating the magnitude of the period effect for periods 1-3 in the relative bioavailability analysis described in Section 6.1.

The analysis will be based on the subset of data observed for the following MR treatments:

B = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules under the fasted state
C = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules under the fasted state

B,fed = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules under the fed state
C,fed = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules under the fed state

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

Note that in this analysis the period is not included as a fixed effect. The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger- degrees of freedom algorithm. The illustrative SAS code is presented in the Appendix 2.

For food effect assessment, ritlecitinib MR1 and MR2 in fasted state are the Reference treatments while ritlecitinib MR1 and MR2 administered in fed state are Test treatments.

Similarly to the analysis in Section 6.1, the residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

A listing of the descriptive and graphical summaries for PK parameters is presented in Section 6.4.

In addition, for the parameters AUC_{inf} (if data permit), AUC_{last} and C_{max}, a listing of the individual subject ratios (Test/Reference) will also be provided. Box and whisker plots for individual subject parameters (AUC_{inf}, AUC_{last} and C_{max}) will be presented by treatment and overlaid with geometric means.

- *Assessment of AEs, clinical laboratory tests, vital signs and 12-lead ECG*

For the secondary endpoint concerning safety, adverse events, laboratory data, vital signs, ECG data, and other safety data will be listed and summarized in accordance with the sponsor reporting standards as described in Section 3.5.

6.3. Tertiary/Exploratory Endpoint(s)

- *T_{max}, and if data permit, T_{lag} , CL/F ,V_z/F , and $t_{½}$*

A listing of the descriptive and graphical summaries for additional PK parameters is presented in Section 6.4.

6.4. Descriptive and Graphical Summaries of PK Parameters

PK parameters will be collected as primary or secondary endpoints per Section 3. Each PK parameter will be summarized by treatment and include the set of summary statistics as specified in the table below, where both mean and median profiles will be presented on both linear and log scales.

Parameter	Summary Statistics
AUC_{inf}[a] AUC_{last} C_{max} CL/F[a] V_z/F[a]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}, T_{lag}[a]	N, median, minimum, maximum.
$t_{1/2}$[a]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

a If data permit

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by treatment: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. These data may be included in the clinical study report.

Presentations for ritlectinib concentrations from venous blood samples will include:

- A listing of all concentrations sorted by subject ID, period and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by treatment and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale).

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each subject (containing all treatments) per scale].

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

6.5. Baseline and Other Summaries and Analyses

Demographic data collected at screening will be reported as part of the standard baseline summary tables. A breakdown of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by gender and all participants in accordance with the sponsor reporting standards.

6.5.1. Study Conduct and Participant Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and

laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.5.2. Study Treatment Exposure

Not applicable.

6.5.3. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

6.6. Safety Summaries and Analyses

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering ritlectinib as PO solution, MR1, or MR2 formulation.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. The baseline measurement is the pre-dose measurement on Day -1.

6.6.3. Vital Signs

For each planned time point, baseline values and change from baseline values in Periods 1-3 and Period 4 will be summarized with descriptive statistics (using sponsor default standards) as appropriate.

These data will be listed in accordance with the sponsor reporting standards. The thresholds used in the categorical summarization of vital signs data are presented in the Appendix 1.

6.6.4. Electrocardiograms

For each planned time point, baseline values and change from baseline values in Periods 1-3 and Period 4 will be summarized with descriptive statistics (using sponsor default standards) as appropriate.

These data will be listed in accordance with the sponsor reporting standards. The thresholds used in the categorical summarization of vital signs data are presented in the Appendix 1.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is a sponsor-open- study, the sponsor may conduct unblinded reviews of the data during the course of the

study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Available safety and PK data may be reviewed.

APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		>30-60	>60

Categories for PR and QRS

PR (ms)	⩾300	
PR (ms) increase from baseline	Baseline >200 and ⩾25% increase	Baseline ⩽200 and ⩾50% increase
QRS (ms)	⩾140	
QRS (ms) increase from baseline	⩾50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	<90	
Systolic BP (mm Hg) change from baseline	decrease ⩾30	increase ⩾30
Diastolic BP (mm Hg)	<50	
Diastolic BP (mm Hg) change from baseline	decrease ⩾20	increase ⩾20
Supine pulse rate (bpm)	<40	>120

Measurements that fulfill these criteria are to be listed in the clinical study report.

Appendix 2. Example SAS Code for Analyses

Examples of the PROC MIXED code is provided below.

We start from the dataset ds with the following letter codes for the treatments

A = ritlecitinib 100 mg PO solution
B = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules
C = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules

B,fed = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules under the fed state
C,fed = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules under the fed state

For analysis of bioavailability, we use a subset of data (ds1) that does not include period 4 (ie, treatments B,fed and C,fed).

A = ritlecitinib 100 mg PO solution
B = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules
C = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules

We calculate contrasts 'A vs B' and 'A vs C'

```
proc mixed data=ds1;

        class seq period trt subject;
        model l&var=seq period trt/ ddfm=KR;
        random subject(seq) ;
        lsmeans trt;
        estimate 'A vs B ' trt -1  1  0   /cl alpha=0.1;
        estimate 'A vs C ' trt  -1  0 1   /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;
```

For analysis of food effect, we use a subset of data (ds2) that includes relevant doses

B = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules
C = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules

B,fed = ritlecitinib 100 mg (2 × 50 mg) MR1 capsules under the fed state
C,fed = ritlecitinib 100 mg (2 × 50 mg) MR2 capsules under the fed state

We calculate contrasts of interest ('B vs B,fed ' and 'C vs C,fed ') without adjustment for period effect.

```
proc mixed data=ds2;
        class seq trt subject;
        model l&var=seq trt/ ddfm=KR;
        random subject(seq) ;
        lsmeans trt;
        estimate 'B vs B,fed ' trt   -1  0  1 0   /cl alpha=0.1;
        estimate 'C vs C,fed ' trt    0  -1 0 1   /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;
```

Appendix 3. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
bpm	beats per minute
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
CL/F	Apparent clearance after oral dose
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee
IST	independent statistical team
ITT	intent-to-treat
k_{el}	first-order elimination rate constant
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection

Abbreviation	Term
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
MNAR	missing not at random
N/A	not applicable
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGS	Statistical Guidance Standards
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal phase half-life
TA	therapeutic area
TEAE	treatment-emergent adverse event
T_{lag}	time before the first concentration above the limit of quantification or above the first concentration in the interval
T_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z	volume of distribution for extravascular dosing
V_z/F	apparent volume of distribution for extravascular dosing
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary