Protocol B7981078

A Phase 1, Randomized, Open label, Crossover Study to Estimate the Relative Bioavailability of Pediatric Ritlecitinib Sprinkled in Applesauce, Yoghurt and Strawberry Jam Relative to Intact Blend-In Capsule of Ritlecitinib and the Effect of Food on the Bioavailability of the Capsule Dosage Formulation of Ritlecitinib in Healthy Adult Participants

Statistical Analysis Plan
(SAP)

Version: 1

Date: 27 Mar 2023

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NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 / 27 Mar 2023	Original 02 Feb 2023	N/A	N/A

2. INTRODUCTION

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 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 objective of this study is to estimate the impact of administration methods on the bioavailability of the pediatric ritlecitinib blend-in capsule (BiC) formulation.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7981078.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

Objectives	***Endpoints***
Primary:	***Primary:***
• *To estimate the relative BA of ritlecitinib pediatric capsules (BiC) when sprinkled on food (apple sauce, strawberry jam, and yoghurt) compared to intact blend-in capsules (reference) at a 30 mg dose under fasted conditions in adult healthy participants.* • *To estimate the effect of food on the relative BA of ritlecitinib pediatric capsules at a 30 mg dose.*	• *Plasma AUC_{inf} and C_{max} of ritlecitinib.*

Objectives	*Endpoints*
Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of 30 mg BiCs of ritlecitinib administered to healthy adult participants under fasted and fed conditions.*	• *AE monitoring.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To characterize the PK parameters for ritlecitinib (BiCs) when sprinkled on food (apple sauce, strawberry jam, and yoghurt) compared to intact BiC (reference)*	• *T_{max}, AUC_{inf}, $t_{1/2}$, (if data permit) and other PK parameters such as CL/F, V_z/F.*
• *Validate the PK measurement of ritlecitinib in capillary blood samples collected using micro-sampling device against the PK measurement of ritlecitinib in venous blood samples.*	• *Ritlecitinib microsampling concentration versus plasma concentrations from venous blood samples.*
• *To assess the sensory characteristics and overall palatability of sprinkled BiC by healthy participants.*	• CCI [redacted]

2.3. Study Design

The study will be conducted as a Phase 1, open-label, single dose, randomized 4-crossover periods and 1-fixed period design in a single cohort of approximately 12 healthy male or female participants at a single center. Participants will be randomized into 1 of 4 sequences of treatment as described in Table 2.

Table 2. Study Design and Treatments

Treatment Sequence	***Period 1***	***Period 2***	***Period 3***	***Period 4***	***Period 5 (fixed period)***
1 (n=3)	*A*	*B*	*C*	*D*	*E*
2 (n=3)	*B*	*D*	*A*	*C*	*E*
3 (n=3)	*C*	*A*	*D*	*B*	*E*
4 (n=3)	*D*	*C*	*B*	*A*	*E*

Abbreviations: n = number of participants.
Treatment A: ritlecitinib 1 x 30 mg pediatric capsule in fasted state
Treatment B: contents of ritlecitinib 1 x 30 mg pediatric capsule sprinkled on strawberry jam in fasted state
Treatment C: contents of ritlecitinib 1 x 30 mg pediatric capsule sprinkled on yoghurt in fasted state

Table 2. Study Design and Treatments

Treatment D: contents of ritlecitinib 1 x 30 mg pediatric capsule sprinkled on applesauce in fasted state
Treatment E: ritlecitinib 1 x 30 mg pediatric capsule given with high fat meal

Since ritlecitinib is rapidly eliminated ($t_{½}$ ~2 hours), there will be at least a 48-hour washout between each dose.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints are the plasma AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of ritlecitinib. The test/reference ratios for AUC_{inf} (if data permit), AUC_{last} and C_{max} will be derived with Treatments B, C, and D (pediatric capsules sprinkled in strawberry jam, pediatric capsules sprinkled in yoghurt, and pediatric capsules sprinkled in applesauce, respectively) as the test treatments and Treatment A (pediatric capsules) as the reference treatment. In addition, the test/reference ratios for AUC_{inf} (if data permit), AUC_{last} and C_{max} will be derived with Treatment E (pediatric capsules given with high fat meal) as the test treatment and Treatment A (pediatric capsules) as the reference treatment.

PK parameters following a single dose administration will be derived from the concentration-time profiles using noncompartmental methods as data permit. The various PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 3. *In all cases, actual PK sampling times will be used in the derivation of PK parameters.*

Table 3. Definitions of PK Parameters

Parameter	*Definition*	*Method of Determination*
AUC_{last}	*Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})*	*Linear-log trapezoidal method*
AUC_{inf}	*Area under the plasma concentration-time profile from time zero extrapolated to infinite time*	$AUC_{last} + (C_{last}/k_{el})$ *where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis*
C_{max}	*Maximum plasma concentration*	*Observed directly from the data*
T_{max}	*Time for C_{max}*	*Observed directly from the data as time of first occurrence*
$t_{1/2}$	*Terminal elimination half-life*	$Log_e(2)/k_{el}$ *Only those data points judged to describe the terminal log-linear decline will be used in the regression.*
CL/F	*Apparent clearance after oral dose*	*Dose/AUC_{inf} after oral dose*
V_z/F	*Apparent volume of distribution after oral dose*	*Dose/(AUC_{inf}*k_{el}) after oral dose*

3.2. Secondary Endpoints

The secondary endpoints are the safety and tolerability data, discussed in Section 3.5.

3.3. Baseline Variables

Baseline characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

3.4. Other Endpoints

3.4.1. Other PK parameters for ritlecitinib

Exploratory endpoints include other PK parameters for ritlecitinib such as T_{max}, $t_{1/2}$, CL/F and V_z/F.

3.4.2. Ritlecitinib microsampling concentration

Ritlecitinib microsampling concentration using Tasso device will be collected according to the SoA as specified in the protocol.

3.4.3. Palatability of sprinkled ritlecitinib BiC

CCI [redacted]

CCI [redacted]

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 (AE)
- laboratory data
- vital signs data
- electrocardiogram (ECG) results

3.5.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur during follow-up within the lag time of up to 35 days after the last dose of study intervention will be counted as treatment emergent and attributed to the last treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

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 participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For all periods, the baseline measurement is the predose measurement on Period 1 Day -1.

3.5.3. Vital Signs

Supine blood pressure (BP), pulse rate (PR) and temperature will be measured at times specified in the SoA given in the protocol.

For all periods, the baseline measurement is the predose measurement on Period 1 Day 1.

3.5.4. Electrocardiograms

QT interval, QTcF, PR interval, QRS and heart rate (HR) will be recorded at each assessment time indicated in the SoA given in the protocol. QTcF will be derived using Fridericia's heart rate correction formula:

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

For all periods, the baseline measurement is the latest measurement during the screening period.

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 releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	***Description***
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.*
PK Concentration Set	*The PK concentration population is defined as all participants randomized and treated who have at least one concentration in at least 1 treatment period.*
PK Parameter Set	*The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the CaPS. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Data

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 one 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.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other participants. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

PK Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a participant'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 participant discontinues).

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a dosing error or 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. For instance, if a participant has a vomiting event post dose that is within a duration of time that is 2-times the derived median T_{max} for the population for the administered treatment, then the

pharmacokineticist should consider the exclusion of the PK concentration data collected following the initial vomiting event in that treatment period and the PK parameter data reported for that treatment period from the datasets used to calculate summary statistics or statistical analyses.

5.3.2. Safety Data

Missing values in standard summaries of AEs and laboratory data will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

AUC_{inf} (if data permit), AUC_{last} and C_{max} will be summarized by treatment group and will include the set of summary statistics as specified in Table 4.

For the evaluation of relative bioavailability of pediatric ritlecitinib sprinkled in applesauce, yoghurt and strawberry jam relative to intact blend-in capsule of ritlecitinib, *natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A (pediatric capsules) will be the Reference treatment and Treatments B, C, and D (pediatric capsules sprinkled in strawberry jam, pediatric capsules sprinkled in yoghurt, and pediatric capsules sprinkled in applesauce) will be the Test treatments.*

For the evaluation of food effect on the bioavailability of the capsule dosage formulation of ritlecitinib, *natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A (pediatric capsules) will be the Reference treatment and Treatment E (pediatric capsules given with high fat meal) will be the Test treatment.*

For AUC_{inf}, AUC_{last} and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf}, AUC_{last} and C_{max}, will be plotted by treatment and overlaid with geometric means.

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 CSR. 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.

6.2. Secondary Endpoints

Analyses and summaries of safety data are described in Section 6.6.

6.3. Other Endpoints

6.3.1. Other PK parameters for ritlecitinib

Exploratory endpoints include other PK parameters for ritlecitinib such as T_{max}, $t_{1/2}$, CL/F and V_z/F. The PK parameters will be listed and summarized descriptively by treatment group in accordance with Pfizer data standards on the PK Parameter Analysis Set, as data permit. Missing values will be handled as detailed in Section 5.3.1. Each PK parameter will be summarized by treatment group and will include the set of summary statistics as specified in Table 4.

Table 4. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, CL/F, V_z/F	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
T_{max}	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, SD, %CV, minimum, maximum

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte and group: 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}. This data may be included in the clinical study report.

PK Concentrations:

The plasma concentrations will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration-time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Presentations of concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment 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, SD, %CV, minimum, maximum and the number of concentrations above the LLQ.

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

6.3.2. Ritlecitinib microsampling concentration

The microsamling will be performed in this study, but the results of analyzing this data will not be included in the CSR. Instead, a separate internal bioanalytical report will be issued to document data and conclusions from this analysis.

6.3.3. Palatability of sprinkled ritlecitinib BiC

CCI [redacted]

6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic Summaries

Demographic characteristics will be summarized for enrolled population in accordance with the CaPS.

6.5.2. Study Conduct and Participant Disposition

Participants evaluation groups will show end of study participant disposition. Frequency counts will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the CaPS.

6.5.3. Study Treatment Exposure

Study treatment exposure will be listed by sequence.

6.5.4. Concomitant Medications and Nondrug Treatments

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

6.6. Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

6.6.1. Adverse Events

AEs will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the CaPS.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the CaPS.

6.6.3. Vital Signs

Vital sign data will be databased and available upon request.

6.6.4. Electrocardiograms

ECG data will be databased and available upon request.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is an open-label 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.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

APPENDICES

Appendix 1. SAS Code for Analyses

An example of the PROC MIXED code is provided below:

For the primary objective – relative BA:

```
proc mixed data=tab.pk;
        class seq period trt participant;
        model l&var=seq period trt/ ddfm=KR;
        random participant(seq) /subject=participant(seq);
        lsmeans trt;
        estimate 'B vs A' trt -1 1 0 0 0  /cl alpha=0.1;
        estimate 'C vs A' trt -1 0 1 0 0  /cl alpha=0.1;
        estimate 'D vs A' trt -1 0 0 1 0  /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 the primary objective – food effect:

```
proc mixed data=tab.pk;
        class seq trt participant;
        model l&var=seq trt/ ddfm=KR;
        random participant(seq) /subject=participant(seq);
        lsmeans trt;
        estimate 'E vs A' trt -1 0 0 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;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows
Treatment A: ritlecitinib 1 x 30 mg pediatric capsule in fasted state (reference);
Treatment B: contents of ritlecitinib 1 x 30 mg pediatric capsule sprinkled on strawberry jam
in fasted state (test);
Treatment C: contents of ritlecitinib 1 x 30 mg pediatric capsule sprinkled on yoghurt in
fasted state (test);
Treatment D: contents of ritlecitinib 1 x 30 mg pediatric capsule sprinkled on applesauce in
fasted state (test);
Treatment E: ritlecitinib 1 x 30 mg pediatric capsule given with high fat meal (test)        */
```

Appendix 2. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AA	alopecia areata
AE	adverse event
AUC_{extrap}%	the percent of AUC_{inf} based on extrapolation
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
BA	bioavailability
BiC	blend-in capsule
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CD	Crohn's Disease
CI	confidence interval
C_{last}	last quantifiable concentration
CL/F	apparent clearance after oral dose
C_{max}	maximum plasma concentration
CSR	clinical study report
ECG	electrocardiogram
HR	heart rate
k_{el}	terminal phase rate constant
LLQ	lower limit of quantitation
mg	milligram
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	pulse rate
PR interval	time from the beginning of the P wave to the beginning of the QRS complex
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
r^2	goodness of fit statistic from the log-linear regression
RR	the time between the start of one QRS complex and the start of the next QRS complex
SAP	statistical analysis plan

Abbreviation	Term
SD	single dose; standard deviation
SoA	schedule of activities
$t_{½}$	terminal elimination half-life
TEAE	treatment emergent adverse event
T_{max}	time for C_{max}
UC	ulcerative colitis
V_z/F	apparent volume of distribution after oral dose