Protocol B7981031

An Interventional PK, PD, Phase 1, Open-Label Study to Investigate PK and PD of Multiple-Dose Ritlecitinib in Children 6 to Less Than 12 Years of Age with Severe Alopecia Areata

Statistical Analysis Plan (SAP)

Version: 1

Date: 15 Nov 2022

[redacted]

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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/ 15 Nov 2022	Original 03 Oct 2022	NA	NA

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B7981031. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

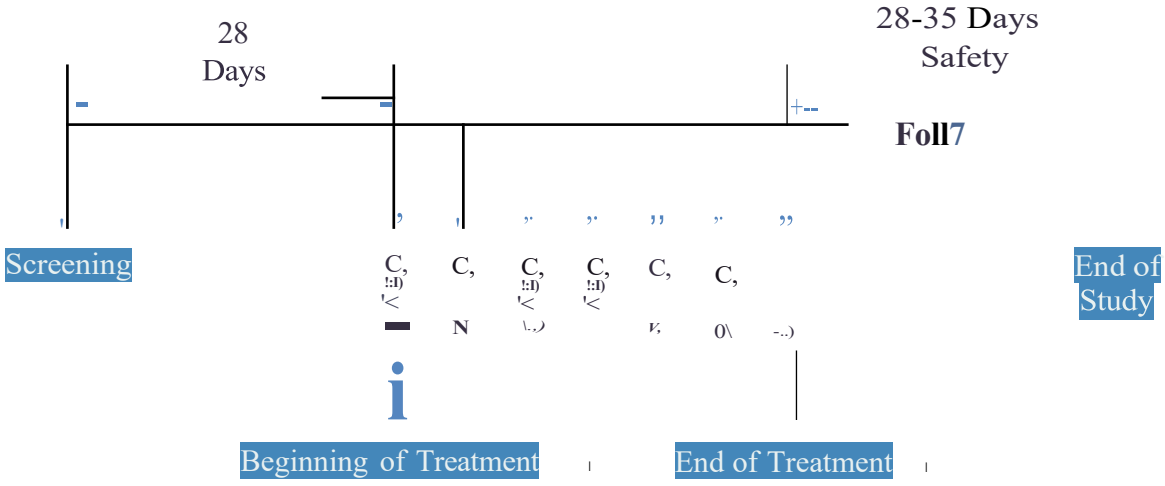
Objectives	***Endpoints***
Primary:	***Primary:***
• *To characterize the PK of ritlecitinib in children with alopecia areata (AA) 6 to <12 years of age.*	• *AUC_{24} on Day 7*
Secondary:	***Secondary:***
• *To further characterize the PK of ritlecitinib in children with AA 6 to <12 years of age.*	• *C_{max}, T_{max}, CL/F, V_Z/F and $t_{½}$ on Day 7*
• *To characterize the PD of ritlecitinib in children with AA 6 to <12 years of age.*	• *Change from baseline in interferon gamma IP-10 and lymphocyte subsets (T cell, B cell, and NK cells) on Day 7*
• *To evaluate the safety and tolerability of ritlecitinib in children with AA 6 to <12 years of age.*	• *TEAE* • *Treatment related AEs.* • *Serious AEs (SAEs) and AEs leading to discontinuation.* • *Clinically significant abnormalities in vital signs.* • *Clinically significant abnormalities in clinical laboratory values.*
• *To assess the overall palatability, acceptability, and tolerability of the proposed commercial age appropriate formulation in children with AA aged 6 to <12 years of age.*	• *Taste assessment*

2.3. Study Design

This is an interventional, PK, PD, Phase 1, open label study in children 6 to less than 12 years of age with 50% scalp hair loss due to AA. The pwpose of the study is to collect data to support dose selection for subsequent studies in the same population.

Participants will be screened and, if all eligibility criteria are met, will receive the first dose of IP within 28 days after the screening visit. Participants will receive 20 mg ritlecitinib in one dose, daily, for 7 consecutive days. On Day 7 (EOT) blood samples for PK will be collected at Ohr (pre-dose), 0.5 hr, 1 hr, 3 hrs, and 8 hrs after dosing. At least 12 evaluable participants with respect to the primary endpoint will be enrolled in the study. Participants that are not able to provide a full set of evaluable PK data or that miss more than one dose may be replaced at the discretion of the sponsor. A follow-up visit will be conducted by phone, 28 to 35 days after the last dose of ritlecitinib (Refer to Figure 1).

Figure 1. B7981031 Study Schema



Visit Types:

- Office visits: Screening, Day 1 (Beginning of treatment), Day 7 (End of Treatment) or Early Tennination
- Telephone visits: Days 2, 4, 6 and End of Study
- Optional home visits or additional office visits are allowed based on discretion of study site persollllel and pai1icipant/legal guardian if considered necessaiy for dosing or safety issues
- PK draws: Day 7 (End of Treatment) or Early Tennination at Ohr (pre-dose), 0.5 hr, 1 hr, 3 hrs, and 8 hrs after dosing.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint is Area under the plasma concentration time profile over the dosing interval 24 hours, at steady-state (AUC_{24}) of ritlecitinib on Day 7.

3.2. Secondary Endpoint(s)

The secondary endpoints are the plasma PK and PD parameters of PF-06651600.

3.2.1. PK Endpoints

The PK parameters will be derived (as data permit) from the concentration-time data using standard noncompartmental methods of analysis as outlined in Table 2. Actual PK sampling times will be used in the derivation of PF-06651600 PK parameters when available. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 2. Plasma PF-06651600 PK Parameters and Definitions

Parameter	***Definition***	***Method of Determination***
AUC_{24}	*Area under the plasma concentration time profile over the dosing interval 24 hrs, at steady-state*	*Linear-log trapezoidal method*
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*
$t_{½}$	*Terminal elimination half-life*	*$Log_e(2)/k_{el,}$ where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression. 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_{24} after oral dose*
V_Z/F	*Apparent volume of distribution after oral dose*	*Dose/(AUC_{24}*k_{el}) after oral dose*

3.2.2. PD Endpoints

The main PD parameters are the change from baseline in interferon gamma IP-10 and lymphocyte subsets (T cell, B cell, and NK cells) on Day 7.

3.2.3. Safety Endpoints

Safety data are also considered as secondary endpoints and are discussed in Section 3.5.

3.2.4. Taste Acceptability

Taste acceptability data will be used to assess the overall palatability, acceptability, and tolerability of the proposed age appropriate formulation in children with AA aged 6 to <12 years of age.

3.3. Other Endpoint(s)

None.

3.4. Baseline Variables

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

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)
    - Treatment-emergent AEs
    - Treatment related AEs
    - SAEs and AEs leading to discontinuation
- Clinically significant abnormalities in vital signs
- Clinically significant abnormalities in clinical laboratory values.

3.5.1. Adverse Events

Any events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur in a non-treatment period (ie follow-up period) within the lag time of 28 days will be counted as treatment emergent and attributed to the previous treatment taken. Similarly, the time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Vital Signs

Blood Pressure (BP) and Pulse Rate (PR) will be measured at times specified in the SoA given in the protocol. The baseline measurement is the latest measurement during the Screening period.

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

For each laboratory parameter, 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.*

For purposes of analysis, the following analysis sets are defined:

Population	***Description***
PK Concentration	*The PK concentration population is defined as all participants treated who have at least 1 concentration.*
PK Parameter	*The PK parameter analysis population is defined as all participants treated who have at least 1 of the PK parameters of primary interest.*
PD Parameter	*The PD parameter analysis population is defined as all participants treated who have at least 1 of the PD parameters of primary interest.*
Safety	*All participants 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.*

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 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, standard deviation (SD), Interquartile Range (IQR), 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 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.

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 dosing error), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Pharmacodynamic Data

Missing data for PD endpoints will be treated as such and no imputed values will be derived when presenting descriptive statistics at scheduled assessments.

5.3.3. Safety Data

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The primary endpoint is the AUC_{24} on Day 7. The parameter will be summarized descriptively, as applicable, in accordance with Pfizer data standards.

The analysis population will be used for the primary endpoint analysis are the PK Concentration set and PK parameter sets.

6.2. Secondary Endpoint(s)

6.2.1. PK endpoints

The plasma PK parameters will be summarized descriptively, as applicable, in accordance with Pfizer data standards. Individual participant and median profiles of the plasma concentration-time data will be plotted using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales. Plasma concentrations will be listed and summarized descriptively by nominal PK sampling time.

Each PK parameter will be summarized and will include the set of summary statistics as specified in Table 3.

Table 3. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
AUC_{24}, 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

6.2.2. PD Endpoints

All of the PD endpoints will be summarized by time point and change from baseline for these endpoints will also be summarized at specific time points as reported in the SoA.

6.2.3. Taste Assessment Analyses

Taste acceptability data will be listed and summarized descriptively (frequencies and percentages) at day 7 among all participants assigned to study intervention and who take at least 1 dose of study intervention.

6.2.4. Safety data

See Section 6.5.

6.3. Subset Analyses

There are no planned subset analyses.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

Demographic characteristics (age, gender, ethnicity, race, weight, height and body mass index) will be summarized for enrolled population in accordance with the CaPS. The safety analysis set will be considered for the analysis.

6.4.2. 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.

6.4.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.4.4. Concomitant Medications and Nondrug Treatments

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

6.5. 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.

6.5.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

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

6.5.2. Laboratory Data

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

6.5.3. Vital Signs

Vital sign 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 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. List of Abbreviations

Abbreviation	Term
AA	alopecia areata
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AUC	Area under the concentration-time curve
AUC_{24}	Area under the plasma concentration time profile over the dosing interval 24 hrs, at steady-state
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	CDISC and Pfizer Standards
CDISC	Clinical Data Interchange Standards Consortium
C-SSRS	Columbia – Suicide Severity Rating Scale
CL	apparent clearance
CL/F	apparent clearance after oral dose
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
eSAE	electronic serious adverse event
HR	heart rate
IQR	Interquartile Range
NK	natural killer
OIRC	Opportunistic Infection Review Committee
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SoA	schedule of activities
TEAE	Treatment emergent adverse event
T_{max}	time to reach C_{max}
t½	terminal elimination half-life
V_Z/F	Apparent volume of distribution after oral dose
WOCBP	woman/women of childbearing potential