# STATISTICAL ANALYSIS PLAN

NCT Number: NCT03724916

Study Title: A Phase 1b Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TAK-079 in Combination With Standard Background Therapy in Patients With Moderate to Severe Systemic Lupus Erythematosus

Study Number: TAK-079-2001

SAP Amendment and Date:

Version 2.0 : 19 November 2021

# STATISTICAL ANALYSIS PLAN

Study Number: TAK-079-2001

Study Title: A Phase 1b Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TAK-079 in Combination With Standard Background Therapy in Patients With Moderate to Severe Systemic Lupus Erythematosus

Phase: 1b

Version: Final, v2.0

Date: 19-NOV-2021

Prepared by: [redacted]

Based on:

Protocol Version: Amendment 01

Protocol Date: 19 February 2019

[redacted]

## REVISION HISTORY

| Version | Approval Date | Primary Rationale for Revision |
|---|---|---|
| Original version | 21-DEC-2020 | Not applicable |
| 2.0 | 19-NOV-2021 | To make SAP consistent with Amendment 01 of the protocol and to clarify statistical analysis methods, as outlined in Section 9.1. |



[redacted]

## TABLE OF CONTENTS

## ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ADA | antidrug antibody(ies) |
| AE | adverse event |
| AUC | area under the concentration-time curve |
| CI | confidence interval |
| [redacted] | [redacted] |
| Cmax | maximum observed concentration |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Ctrough | trough concentration |
| %CV | percent coefficient of variation |
| [redacted] | [redacted] |
| ECG | electrocardiogram |
| eCRF | electronic case report form (refers to any media used to collect study data [ie, paper or electronic]) |
| [redacted] | [redacted] |
| ICF | informed consent form |
| Ig | Immunoglobulin |
| IgA | Immunoglobulin A |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NK | natural killer |
| PB | plasmablast |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PT | preferred term |
| PTE | pretreatment event |
| QTc | corrected QT interval |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SD | standard deviation |

[redacted]

| Abbreviation | Term |
|---|---|
| SLE | systemic lupus erythematosus |
| [redacted] | [redacted] |
| SOC | system organ class |
| SOE | schedule of events |
| TEAE | treatment-emergent adverse event |
| [redacted] | [redacted] |
| WHO | World Health Organization |

# 1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

## 1.1 Objectives

### 1.1.1 Primary Objective

*The primary objective of this study is to evaluate the safety and tolerability of TAK-079 in comparison with matching placebo, administered once every 3 weeks over a 12-week dosing period in patients with active systemic lupus erythematosus (SLE) who are receiving stable background therapy for SLE.*

### 1.1.2 Secondary Objective(s)

*The secondary objective of the study is to assess the PK, PD, and immunogenicity of TAK-079 administration over a 12-week dosing period.*

### 1.1.3 Exploratory Objective(s)

[redacted]

## 1.2 Endpoints

### 1.2.1 Primary Endpoint(s)

*The primary endpoints of this study will evaluate the safety and tolerability of TAK-079 to include the incidence, type, and grade of adverse events (AEs), as well as the percentage of patients with ≥1 AE leading to study treatment discontinuation.*

### 1.2.2 Secondary Endpoint(s)

*The secondary endpoints will include:*

*1. Pharmacokinetic evaluations of TAK-079.*

*2. Pharmacodynamics evaluations of TAK-079.*

*3. Immunogenicity assessments of TAK-079.*

### 1.2.3 Exploratory Endpoint(s)

[redacted]

[redacted]

## 2.0 STUDY DESIGN

*This phase 1b double-blind, placebo-controlled, multicenter study will evaluate the safety, PK, and PD of TAK-079 in a study population receiving standard principal investigator-directed background therapy for moderate to severe SLE.*

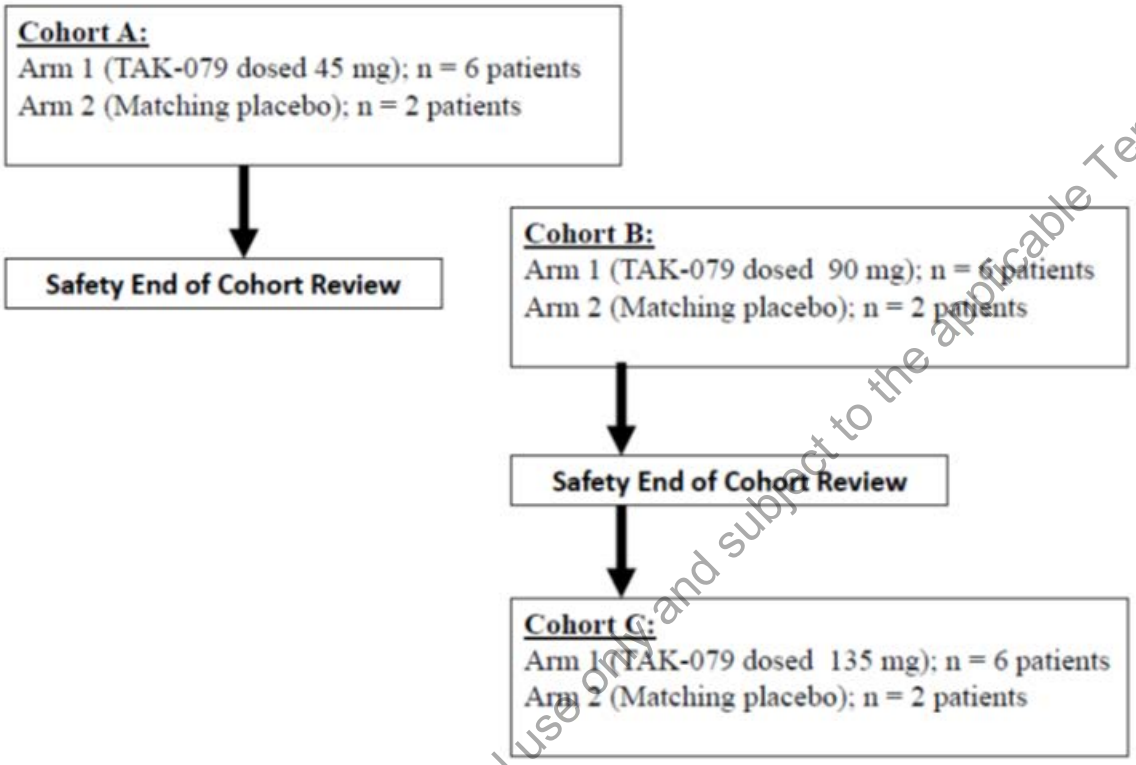
*The study will compare active TAK-079 with matching placebo in combination with a background SLE standard treatment, across 3 sequentially enrolling cohorts in a double-blinded study design. A 3:1 randomization, within each cohort, will assign each patient to: (1) TAK-079 administered as a single SC injection every 3 weeks for 12 weeks (total of 4 doses); or, (2) matching placebo given in same route and schedule (see Protocol Figure 2.a). Each cohort will enroll 8 patients; 6 patients will be randomized to TAK-079 dosing and 2 patients to TAK-079 matching placebo. After each dosing day, patients will return for postdose assessments as outlined in Protocol Table 3.a and Protocol Table 3.b.*

*Following completion of the 12-week dosing period, patients will return for an additional 12 week safety follow-up period, completing safety visits every 4 weeks and ending this postdosing study period with a safety visit on Week 24. Based on clinical assessments at this visit, patients may complete the study or may advance to the long-term safety follow-up period, for an additional on-study 12-week safety monitoring period (based on end-of-study criteria outlined in Protocol Table 9.c), during which time the end of study parameters not met and deemed by the principal investigator as study related, will continue to be assessed and followed as outlined in Protocol Section 9.4.*



[redacted]

**Protocol Figure 2.a TAK-079-2001 Study Cohort Reviews**






## 3.0 STATISTICAL HYPOTHESES AND DECISION RULES

### 3.1 Statistical Hypotheses

No formal tests of statistical hypotheses are planned.

### 3.2 Multiplicity Adjustment

No multiplicity adjustments are planned.

## 4.0 SAMPLE-SIZE DETERMINATION

*This study is not statistically powered for any hypothesis testing. The sample size of 6 active and 2 placebo patients for each of the 45 mg, 90 mg, and 135 mg dose groups (Cohorts A, B, and C, respectively) are considered to be sufficient to fulfill the study objectives of the evaluation of safety, tolerability, and PK of each cohort.*

# 5.0 ANALYSIS SETS

## 5.1 Safety Analysis Set

*The safety analysis set will consist of all patients who are enrolled and received at least 1 dose of study drug. Patients in this analysis set will be used for demographic, baseline characteristics and safety summaries.*

## 5.2 PK Analysis Set

*The PK analysis set will consist of all patients who receive study drug and have at least 1 measurable serum concentration.*

## 5.3 PD Analysis Set

*The PD analysis set will consist of all patients who receive study drug and have at least 1 postdose PD measurement.*

## 5.4 Immunogenicity Analysis Set

The immunogenicity analysis set will consist of all subjects from the safety population who have the baseline immunogenicity sample and at least 1 postdose immunogenicity sample assessment.

# 6.0 STATISTICAL ANALYSIS

## 6.1 General Considerations

Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the coefficient of variation (%CV) and geometric mean may also be included in the summary of continuous data. Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate.

For PK related tables, mean, SD, median, minimum, and maximum will be rounded to 3 significant digits and CV% will presented to 1 decimal place.

Categorical data will be summarized using the number and percent of subjects for each category, where appropriate. Percentages will be reported to 1 decimal place.

Unless otherwise stated, baseline value is defined as the last observed value before the first dose of study medication.

There will be no visit windows.

For values with several non-missing measurements, for example triplicate ECGs, the average of triplicate assessments will be used.

Subjects who receive placebo in each cohort will be pooled across the cohorts. All summaries will be presented by the pooled placebo group, TAK-079 doses, TAK-079 overall subjects in the study separately.

### 6.1.1 Handling of Treatment Misallocations

For analyses based on the safety, PK, PD, or immunogenicity analysis sets, subjects will be analyzed as treated, i.e., actual treatment. For analyses based on all randomized subjects, subjects will be analyzed as randomized, i.e., planned treatment.

## 6.2 Disposition of Subjects

The summary and listing of disposition of subjects will be based on all randomized subjects. The number of subjects in the safety set will be presented. Disposition will be tabulated in terms of subjects who prematurely discontinued from study treatment, subjects who completed study treatment, subjects who prematurely discontinued from the study, and subjects who completed the study. Primary reasons for premature discontinuation from study or study treatment, as entered on the electronic case report form (eCRF), will also be tabulated. Percentages will be based on the number of subjects in the safety set.

In addition, the number of subjects randomized will be summarized for each country and site.

Major protocol deviations will be summarized and listed based on all randomized subjects. Protocol deviations related to COVID-19 will be summarized and listed.

The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

## 6.3 Demographic and Other Baseline Characteristics

### 6.3.1 Demographics

Summary statistics will be presented for continuous variables (for example, age and weight). The number and percentage subjects within each category will be presented for categorical variables (for example, race and sex). Individual subject demographic and baseline characteristic data will be listed. Placebo data will be pooled across the cohorts.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized for subjects who are screened, but not enrolled in the study.

Individual demographic characteristics, date of informed consent form (ICF), and reason for screen failure will be listed.

The analysis and listing of demographics and baseline characteristics will be based on the safety analysis set.



[redacted]

### 6.3.2 Medical History

Medical history refers to any significant conditions or diseases that stopped at or prior to informed consent or are ongoing at informed consent.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1 or higher) and will be summarized by treatment using System Organ Class (SOC) and MedDRA preferred term (PT). The table will include number and percentages of subjects, and will be sorted in alphabetical order by SOC. Within an SOC, PTs are sorted in decreasing frequency based on the total number of subjects. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms. Summaries will be based on safety analysis set.

All medical history data will be presented in listings based on the safety analysis set.

## 6.4 Prior and Concomitant Medications

Concomitant medications, blood products, and procedures will be recorded from the first dose of TAK-079 or matching placebo, through the end of the safety follow-up period (i.e., end of safety follow-up visit in Week 24 or, when applicable, end of long-term safety follow-up visit in Week 36). Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication are to be recorded. Medications will be coded using the World Health Organization Drug Dictionary (WHODD, B3 Global version SEP2018 or later). The number and percentage of patients taking prior medications and concomitant medications will be tabulated by WHO drug generic term based on safety analysis set.

All prior medications and concomitant medications data will be presented in listing. This listing will be based on safety analysis set. There will be no imputation for missing concomitant medication dates.

## 6.5 Efficacy Analysis

Efficacy endpoints will be summarized by descriptive statistics. Additionally, where applicable, analyses of treatment effects will be presented in terms of point estimates and 2-sided 95% confidence intervals (CIs). The safety analysis set will be used for all efficacy analyses.

### 6.5.1 Primary Endpoints Analysis

There are no primary efficacy endpoints for the study.

### 6.5.2 Secondary Endpoints Analysis

There are no secondary efficacy endpoints for the study.

### 6.5.3 Exploratory Endpoints Analysis

[redacted]

[redacted]



[redacted]

[redacted]

## 6.6 Safety Analysis

Safety measures include AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters. The safety analysis set will be used for all summaries of safety parameters.

For all safety summary tables stated under this section, the tables will be summarized by placebo, each TAK-079 dose level, and TAK-079 overall. Placebo data will be pooled across the dose levels.

### 6.6.1 Adverse Events

A Pre-Treatment Event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study, but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. PTE and AE verbatim terms will be coded by SOC and PT using MedDRA (version 23.1 or higher).

Treatment-Emergent Adverse Events (TEAE)s will be defined as AEs that occur after the first dose of study drug received in the treatment period and until the end of safety follow up.

TEAEs will be presented by intensity. Serious TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose modification (e.g. described as dose delay, dose skipped) and TEAEs leading to death will also be summarized using SOC and PT.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a patient reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary.

AEs with missing intensity will be listed as such in the AE listings, but will be summarized as severe in summary tables. Similarly, if the relationship of an event is missing, the event will be considered as related but in listings it will be presented as missing.



[redacted]

In general, AEs will be tabulated at the following levels: overall summary (subjects with at least 1 AE in any dose or treatment), the MedDRA SOC, and the MedDRA PT. The tables will include the number and percentage (N [%]) of subjects. The following summary tables will be generated for all cohorts:

- Overview of Treatment-Emergent Adverse Events.
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Most Frequent (N>2) Non-Serious Adverse Events by Preferred Term. AE events of TAK-079 overall will be used to decide whether the event of AEs>2.
- Most Frequent (N>2) Non-Serious Adverse Events by System Organ Class and Preferred Term. AE events of TAK-079 overall will be used to decide whether the event of AEs >2.
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- TEAE Overall, by Toxicity, Seriousness, Relatedness, and Discontinuation by SOC, HLT and PT.

Data listings will be provided for PTEs, TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose modification of study drug with modification including dose delay and dose skipped, SAEs and AEs that resulted in death.

There will be no imputation for missing adverse events dates.

### 6.6.2 Clinical Laboratory Evaluations

Unless otherwise stated in the protocol, all laboratory samples are to be sent to the study central laboratory for analysis, under the conditions for handling and shipping as outlined in the study laboratory manual. If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Clinical laboratory evaluations are obtained, handled, stored, and shipped to the designated central laboratory, in accordance to the laboratory manual. Clinical chemistry and hematologic assays are outlined Protocol Table 9.a and urinalysis assays are outlined in Protocol Table 9.b. Timings of these assessments should be in accordance to the study SOE (see Protocol Table 3.a and Protocol Table 3.b).

All laboratory test parameters will be displayed in individual subject data listings in both SI units and conventional (CV) units. For test results not in SI units, the conversion to SI units will be done using the known conversion factors. If necessary, SI units from the central laboratory may

be converted to Takeda's preferred SI units. All summaries and analyses will be based on the values using these preferred SI units.

Study baseline will be used for change from baseline.

The actual values, change from baseline, and percent change from baseline in clinical laboratory parameters will be summarized. Figures of mean actual values and changes from baseline by visit will also be generated. Individual subject profiles over time for selected parameters may be plotted as needed.

CTCAE grading (version 4.03) for lab values are summarized by creating a shift table for the toxicity grades for baseline to worst toxicity grade post-baseline. All clinical laboratory data will be presented in both SI and conventional units in data listings.

### 6.6.3 Vital Signs

Individual results of vital signs that meet abnormal criteria and are clinically significant per the PI will be captured as an AE by the investigator.

A summary table of vital sign parameters by visit will be generated. All vital signs will be listed in a data listing.

### 6.6.4 12-Lead ECGs

A single 12-lead ECG is to be collected at the screening visit (for assessment of eligibility) and at the end of safety follow-up visit, and will be read locally.

Pre-dose triplicate 12-lead ECGs, obtained before each study dose, are to be collected just before PK sampling, during timeframes outlined in Protocol Table 3.a and Table 3.b.

Overall ECG interpretation category (normal, abnormal not clinically significant, abnormal clinically significant, not evaluable) is collected by eCRF at baseline and at each scheduled postbaseline visit. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations, not evaluable, with missing, if applicable, and total categories overall.

Rate-corrected QT interval (millisec) of electrocardiograph (QTc) will be calculated using Bazett's correction and Fridericia's correction, if necessary. The formulas are:

QTc (Bazett) = QT / (RR^0.5)

QTc (Fridericia) = QT / (RR^0.33)

where RR = 60 / heart rate (bpm)

All ECG parameters will be listed in a data listing.



[redacted]

### 6.6.5 Extent of Exposure and Compliance

The total number of doses taken and the total amount of dose taken will be summarized descriptively in the pooled placebo group and TAK-079 arms.

Treatment compliance will be summarized in terms of the percent of scheduled doses received in the pooled placebo group and TAK-079 arms. The percent of scheduled doses received for each subject is defined as: [(Actual total number of doses taken) ÷ (Planed number of doses)] *100.

The date and time of each dose for each subject will be reported in a data listing.

## 6.7 Pharmacokinetic, Pharmacodynamic, [redacted] Analyses

### 6.7.1 Pharmacokinetic Analysis

Due to sparse PK sampling, no noncompartmental analysis will be conducted. TAK-079 concentration-time profile will be summarized using descriptive statistics. Individual TAK-079 concentration-time data, individual $C_{trough}$ parameter (the last concentration reached before the next dose administration) and individual $C_{max}$ parameter (the maximum observed concentration) will be presented in listings and tabulated using summary statistics by treatment group. Individual and mean concentration-time profiles will be plotted by treatment group. The PK analysis set will be used for summaries and analyses of PK parameters.

A population PK model may be developed. If developed, the population PK model may be reported separately. The analysis plan for the population PK analysis may be separately defined, and the results of these analyses may be reported separately.

### 6.7.2 Pharmacodynamic [redacted] Analysis

Individual values, change from baseline, and mean change from baseline and/or percent change from baseline at different timepoints for placebo and each TAK-079 dose level will be calculated for the pharmacodynamic measures listed in Appendix 9.3 [redacted] listed below.

- Serum immunoglobulin levels.
- [redacted]
- Autoantibodies. Only subjects who are positive for a specific SLE antibody at baseline will be summarized for that autoantibody.
- [redacted]

Descriptive summaries may include geometric mean and CV% where needed.

For PD [redacted] parameters, figures of mean values and mean percent change from baseline will be generated. Mean percent change from baseline will not be plotted for measures related to receptor occupancy, instead mean change from baseline will be generated. Individual subject profiles over time for selected parameters may be plotted as needed.

The PD analysis set will be used for summaries, listings and analyses of PD [redacted] parameters.

[redacted]

[redacted]

## 6.8 Immunogenicity Analysis

Immunogenicity analysis (ADA transient, persistent, negative, and titer) will be summarized using descriptive statistics as applicable. The immunogenicity analysis set will be used for all summaries of immunogenicity parameters. [redacted]

(A) Transiently positive ADA response is defined as patients who have confirmed positive ADA status in 1 or 2 post baseline assessment(s).

(B) Persistently positive ADA response is defined as patients who have confirmed positive ADA status in more than 2 post baseline assessments.

A positive ADA assessment at each post baseline visit is defined as having either (1) a negative assessment at baseline and a positive assessment value, or (2) a positive value at baseline and the assessment value meets the criterion for treatment boosted ADA response (at least 4 times the baseline value.)

## 6.9 Interim Analyses

The Sponsor may perform unblinded reviews or analyses of data from one or more dose cohorts after all patients enrolled in those cohorts have completed the Safety Follow-up Period or prematurely discontinued from the study. The Sponsor would receive treatment assignments only for individual subjects within the pertinent cohorts while remaining blinded to treatment assignments of the other subjects. Details on the unblinding process and steps to minimize bias are described in the Data Access Management Plan.

# 7.0 REFERENCES

Not applicable.

# 8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Plans to potentially perform unblinded reviews of completed cohorts were not documented in the protocol but have been added to this analysis plan. The purpose of such analyses would be for internal planning by the Sponsor.

Due to sparse PK sampling, only a limited set of PK summaries will be provided. AUCs, and dose proportionality may not be evaluated.

[redacted]

# 9.0 APPENDIX

## 9.1 Changes From the Previous Version of the SAP

Changes made from the previous version of the SAP that have a material impact to the planned statistical analysis methods are described below. In addition, there were textual changes purely to improve the flow, organization, and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

| SAP Section | Change | Rationale for Change |
|---|---|---|
| 6.1 General Considerations | Added clarification for presenting summaries of PK data. | To define the rule for presenting the summaries to be consistent with the data collected. |
| 6.2 Disposition of Subjects | Updated analysis set for presenting disposition of subjects and the calculation of percentages. | For additional clarity of presenting the disposition. |
| 6.2 Disposition of Subjects | Added statement for reporting protocol deviations related to COVID-19. | To add new summaries reporting COVID-19 related protocol deviations. |
| 6.6.5 Extend of Exposure and Compliance | Updated the reporting of exposure and compliance to include the pooled placebo group. Added clarification on the calculation of compliance. | For comparison of the placebo group with the active groups. |
| 6.7.2 Pharmacodynamic [redacted] Analysis | Clarified the parameters to be reported for pharmacodynamics [redacted] by updating the text and adding a table in the appendix. | For add clarification on the parameters to be reported. |
| 6.8 Immunogenicity Analysis | Added definition of ADA transient and ADA persistent. | To add more concise definition. |

## 9.2 Analysis Software

All data analyses and figures will be generated using SAS System® Version 9.4 or higher.

## 9.3 Pharmacodynamic Parameters

Table 1: Pharmacodynamic Parameters

| Parameter as Collected | Parameter Name to Present in TLFs |
|---|---|
| B Cells % of Lymphocytes Absolute Count Tube 2 | B Cells/uL |
| B cells %Lymphocytes Tube 2 | B Cells %Lymphocytes |
| CD27++HLADR++ PB %PB Tube 2 | CD27++HLADR++ PB %PB |
| CD27++HLADRdim/- PB %PB Tube 2 | CD27++HLADRdim/- PB %PB |
| Granulocytes % of WBC Absolute Count Tube 2 | Granulocytes/uL |
| Granulocytes % WBC singlets Tube 2 | Granulocytes %WBC singlets |
| Lymphocytes % of WBC Absolute Count Tube 2 | Lymphocytes/uL |
| Lymphocytes % WBC singlets Tube 2 | Lymphocytes %WBC singlets |
| Monocytes % of WBC Absolute Count Tube 2 | Monocytes/uL |

[redacted]

| Parameter as Collected | Parameter Name to Present in TLFs |
|---|---|
| Monocytes % WBC singlets Tube 2 | Monocytes %WBC singlets |
| NK Cells % of Lymphocytes Absolute Count Tube 2 | NK Cells/uL |
| NK cells %Lymphocytes Tube 2 | NK Cells %Lymphocytes |
| Plasma blasts %B cells Tube 2 | Plasmablasts %B Cells |
| Plasma Cells % of B cells Absolute Count Tube 2 | Plasma Cells/uL |
| Plasma cells %B cells Tube 2 | Plasma Cells %B Cells |
| Plasmablasts % of B cells Absolute Count Tube 2 | Plasmablasts/uL |
| Receptor Occupancy % Plasma cells | Receptor Occupancy %Calculation Plasma Cells (%) |
| Receptor Occupancy % Plasmablasts | Receptor Occupancy %Calculation Plasmablasts (%) |
| Receptor Occupancy % TAK/TSF+ B Cells | Receptor Occupancy %Calculation CD38+ B Cells (%) |
| Receptor Occupancy % TAK/TSF+ Granulocytes | Receptor Occupancy %Calculation CD38+ Granulocytes (%) |
| Receptor Occupancy % TAK/TSF+ Lymphocytes | Receptor Occupancy %Calculation CD38+ Lymphocytes (%) |
| Receptor Occupancy % TAK/TSF+ Monocytes | Receptor Occupancy %Calculation CD38+ Monocytes (%) |
| Receptor Occupancy % TAK/TSF+ NK Cells | Receptor Occupancy %Calculation CD38+ NK Cells (%) |
| Receptor Occupancy % TAK/TSF+ T Cells | Receptor Occupancy %Calculation CD38+ T Cells (%) |
| T Cells % of Lymphocytes Absolute Count Tube 2 | T Cells/uL |
| T cells %Lymphocytes Tube 2 | T cells % Lymphocytes |
| TAK/TSF+ B Cells % Parent Absolute Count Tube 2 | CD38+ B Cells/uL |
| TAK/TSF+ B cells % Tube 2 | CD38+ B Cells %B Cells |
| TAK/TSF+ Granulocytes % Parent Absolute Count Tube 2 | CD38+ Granulocytes/uL |
| TAK/TSF+ Granulocytes % Tube 2 | CD38+ Granulocytes %Granulocytes |
| TAK/TSF+ Lymphocytes % Parent Absolute Count Tube 2 | CD38+ Lymphocytes/uL |
| TAK/TSF+ Lymphocytes % Tube 2 | CD38+ Lymphocytes %Lymphocytes |
| TAK/TSF+ Monocytes % Parent Absolute Count Tube 2 | CD38+ Monocytes/uL |
| TAK/TSF+ Monocytes % Tube 2 | CD38+ Monocytes %Monocytes |
| TAK/TSF+ NK Cells % Parent Absolute Count Tube 2 | CD38+ NK Cells/uL |
| TAK/TSF+ NK cells % Tube 2 | CD38+ NK Cells %NK Cells |
| TAK/TSF+ T Cells % Parent Absolute Count Tube 2 | CD38+ T Cells/uL |
| TAK/TSF+ T cells % Tube 2 | CD38+ T Cells %T Cells |
| Lymphocytes AF647 Mean MFI Tube 2 | Lymphocytes CD38 Mean MFI |
| Monocytes AF647 Mean MFI Tube 2 | Monocytes CD38 Mean MFI |
| Granulocytes AF647 Mean MFI Tube 2 | Granulocytes CD38 Mean MFI |
| T cells AF647 Mean MFI Tube 2 | T Cells CD38 Mean MFI |

| Parameter as Collected | Parameter Name to Present in TLFs |
|---|---|
| NK cells AF647 Mean MFI Tube 2 | NK Cells CD38 Mean MFI |
| B cells AF647 Mean MFI Tube 2 | B Cells CD38 Mean MFI |
| Plasma blasts AF647 Mean MFI Tube 2 | Plasmablasts CD38 Mean MFI |
| CD27++HLADR++ PB AF647 Mean MFI Tube 2 | CD27++HLADR++ PB CD38 Mean MFI |
| CD27++HLADRdim/- PB AF647 Mean MFI Tube 2 | CD27++HLADRdim/- PB CD38 Mean MFI |
| Plasma cells AF647 Mean MFI Tube 2 | Plasma Cells CD38 Mean MFI |
| WBC count (x10^6) (from Sysmex) | WBC count (x10^6) |

# STATISTICAL ANALYSIS PLAN APPROVAL FORM

| | |
|---|---|
| Drug: TAK-079 | Protocol Number: TAK-079-2001 |
| Protocol Name: | A Phase 1b Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TAK-079 in Combination With Standard Background Therapy in Patients With Moderate to Severe Systemic Lupus Erythematosus |
| Statistical Analysis Plan (SAP) Version Number: 2.0 | Date: 19 NOV 2021 |

I confirm the final SAP for above noted study and approve the content for submission to the SAP approval team.

| | |
|---|---|
| **Biostatistics Author** | [redacted] Ph.D.<br>Study Statistician<br>Rare Disease TAU Statistics |
| | Print Name and Title |
| | DocuSigned by:<br>[redacted]<br>Signer Name: [redacted]<br>Signing Reason: I am the author of this document<br>Signing Time: 19-Nov-2021 \| 23:06:48 JST<br>43EB1764F14349988EA20AB23CF25486 |
| | Signature and Date (DD/MM/YYYY) |

Statistical Analysis Plan Approval by SAP Approval Team Members
I approve the final SAP for the above study as it pertains to my area of expertise.
Note: An approver may delegate the review and approval of this document to an appropriately qualified and clearly identified (by name and title) designee.

| | |
|---|---|
| **SAP Signatory** | [redacted] Ph.D.<br>[redacted] Statistician<br>[redacted] Statistics<br>Rare Disease TAU Statistics |
| | Print Name and Title |
| | DocuSigned by:<br>[redacted]<br>Signer Name: [redacted]<br>Signing Reason: I approve this document<br>Signing Time: 19-Nov-2021 \| 23:11:06 JST<br>02A32628C89F40C88A2476724AEC1F31 |
| | Signature and Date (DD/MM/YYYY) |