Study title: A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis

Document: Statistical Analysis Plan (SAP)

Version number: Final v2.0

Date: 10 Oct 2019

[redacted]

Statistical Analysis Plan (SAP)

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis
Protocol Number:	CLR_16_23
Protocol Version, Date	[redacted]
[redacted]	[redacted]
Document Version, Date:	[redacted]

Prepared by:

[redacted]

On behalf of:

Sun Pharma Global FZE

[redacted]

[redacted]

Statistical Analysis Plan (SAP)

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SIGNATURE PAGE

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[redacted]

REVISION HISTORY

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

Abbreviation or special term	Explanation
ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BSA	Body Surface Area
CASPAR	Classification of Psoriatic Arthritis
CI	Confidence Interval
cm	Centimetre
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
DAS	Disease Activity Score
DBL	Database Lock
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HAQ-DI	Health Assessment Questionnaire Disability Index
hsCRP	high sensitivity C-reactive protein
IA	Interim Analysis
IMP	Investigational Medicinal Product

[redacted]

IVRS	Interactive Voice Response System
kg	Kilogram
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Activities
MDA	Minimal Disease Activity
MMRM	Mixed Model for Repeated Measurements
n	Number of non-missing observations
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PK	Pharmacokinetics
PPAS	Per Protocol Analysis Set
PsA	Psoriatic Arthritis
PsAID	PsA Impact of Disease
PT	Preferred Term
PtGA	Patient Global Assessment
Q1	Lower Quartile
Q3	Upper Quartile
q4wk	Every 4 weeks
q12wk	Every 12 weeks
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36	36-item Short Form
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
$T_{1/2}$	Half-life
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings and Figures

[redacted]

T_{max}	Time of maximal concentration
TNF	Tumor-necrosis factor
ULN	Upper Limit of Normal
VAS	Visual Analog Scale

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed description of the statistical methods, data derivations and data presentations to be employed for study protocol CLR_16_23 "A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Phase 2b Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects with Active Psoriatic Arthritis" which was originally [redacted]

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

This SAP supersedes the statistical considerations identified in Protocol CLR_16_23 and where considerations are substantially different, they will be identified as such in this document.

This SAP has been developed and approved prior to database lock and unblinding of the clinical database for Protocol CLR_16_23.

[redacted]

2 STUDY OBJECTIVES

2.1 Primary objectives

[redacted]

- [redacted]

[redacted]

- [redacted]

2.2 Secondary objectives

[redacted]

- [redacted]
- [redacted]

2.3 Exploratory objectives

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

3 STUDY DESIGN

3.1 General study design

This is a randomized, multinational, double-blind, placebo-controlled, multiple-dose, Phase 2b study. The study will consist of a Screening Period [redacted] a double-blind, placebo-controlled period [redacted] a double-blind follow-up period [redacted] and [redacted] During the wash-out period, subjects will [redacted] receive tildrakizumab and will be treated according to the Investigators' discretion.

Adult patients with active PsA who satisfy the inclusion criteria and do not meet the exclusion criteria will be enrolled in this study. Approximately [redacted] will be randomized into the Double-Blind treatment period.

The Study Flow Chart is presented in Figure 1.

[redacted]t

[redacted]

[redacted]

Subjects who fail to show minimal response to treatment [redacted] may have their background medications adjusted according to the maximum permitted daily dose as described in the protocol and continue in the study.

Subjects who show clinical response to treatment [redacted]

Subjects receiving placebo or [redacted] tildrakizumab during [redacted] Subjects in [redacted] are not deriving sufficient clinical benefit in the opinion of the Investigator at any time [redacted], should be discontinued from study drug and [redacted] so that they may receive additional treatment as determined by the Investigator.

Subjects discontinued from IMP at any time (apart from withdrawal of informed consent) will be required to complete the [redacted] assessment a minimum of [redacted] enter the [redacted]. Subjects who withdraw from the study during [redacted] will undergo the [redacted] assessments [redacted].

On completion of [redacted] subjects may enter the [redacted] providing they meet the inclusion/exclusion criteria for the [redacted] and the Investigator deems they would benefit from continued treatment with tildrakizumab. In circumstances where the [redacted] study site activation has not occurred at the time the subject reaches the end of [redacted] they may enter from washout period if the required eligibility conditions are met.

3.2 Randomization and blinding

3.2.1 Randomization

A randomization schedule will be computer-generated before the start of the study. After all Screening procedures are performed and results of screening tests are available [redacted], eligible subjects will be activated in the interactive voice recognition system (IVRS), and [redacted] to the following treatment groups:

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

[redacted]

3.2.2 Blinding

This is a double-blind study. Investigational sites, subjects, and study team members directly involved in study activities will remain blinded to study treatment assignments until the last subject completes their double-blind follow-up period and wash-out period. A separate document will provide further details related to unblinding of personnel involved in reporting activities for the Interim Analysis (IA).

PK and anti-drug antibodies (ADA) data will be kept confidential only after database lock and unblinding at study completion.

3.2.3 Unblinding

In an emergency, in which the Investigator must know a subject's treatment allocation to ensure the subject's safety, the Investigator will contact IVRS. When the Investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The Investigator will then receive details of the IMP for the specified subject. The system will automatically inform the [redacted], the medical monitor, and the [redacted] that the code has been broken, but no treatment assignment will be communicated.

3.3 Study treatments and assessments

The maximum study duration from screening to end of the wash-out period is [redacted]

All subjects eligible for study participation will enter the double blind treatment period and receive one of the 5 treatments assigned per the schedule outlined in the study flow chart. [redacted]

- [redacted]

[redacted]

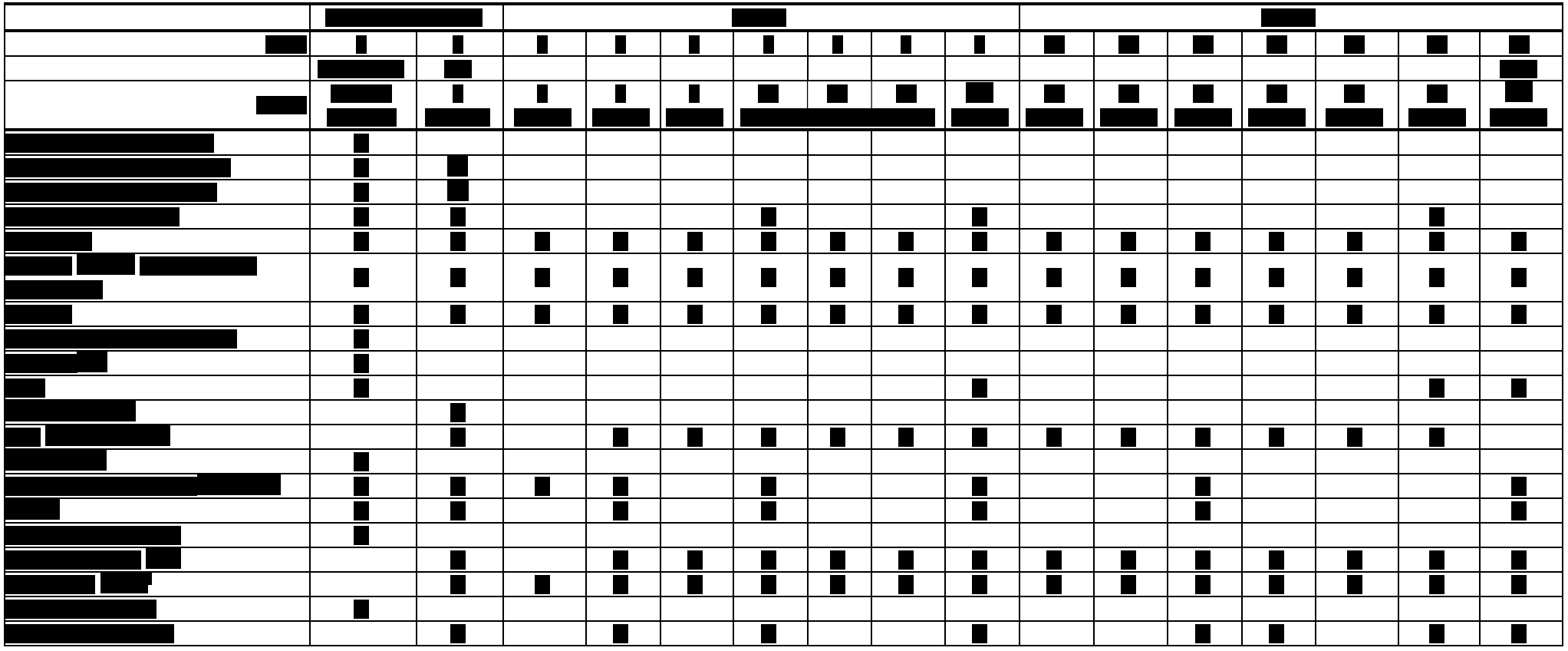
- [redacted]
- [redacted]
- [redacted]
- [redacted]

If a subject misses a visit and/or a scheduled dose of IMP, the site must reschedule a visit to ensure the dose of IMP is taken as soon as possible within the visit window. If after 2 attempts to reschedule, the subject still is not able to take the dose, the Sponsor should be contacted to determine if the subject should be discontinued from the study.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Schedule of Assessments in [redacted].

[redacted]

[redacted]



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Statistical Analysis Plan (SAP)

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Statistical Analysis Plan (SAP)

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Statistical Analysis Plan (SAP)

[redacted]

4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint

The primary efficacy endpoint is the proportion of subjects who achieve ACR20 at Week 24.

The ACR20 is defined as at least a [redacted] and [redacted]: 1) the Physician Global Assessment (PGA) of disease activity (as measured using a VAS), 2) the Patient Global Assessment (PtGA) of disease activity (as measured using a VAS), 3) patient pain assessment (as measured using a VAS), 4) patient self-assessed disability (as measured using the HAQ-DI), and 5) acute-phase CRP[1].

The components of the ACR assessments that will be used in this study are:

- Tender joint counts [redacted]
- Swollen joint counts [redacted]
- PGA of disease activity [redacted]
- PtGA of disease activity [redacted]
- Patient's pain assessment [redacted]
- Patient's self-assessed disability (HAQ-DI)
- Acute-phase hsCRP

If the value in any of the components at a time point is missing, the component variables that are not missing will be used to determine the response status. As a general principle, if there are sufficient non-missing components to determine whether the ACR endpoint is a response or non-response, then ACR endpoint is not missing, else if the available non-missing components are not sufficient to determine the response status of ACR endpoint then it is considered missing.

If the baseline value of any component is [redacted], the following algorithm will be used in evaluating the percent change from baseline:

- If change from baseline is also [redacted] then percent change from baseline is set to be [redacted]
- If change from baseline is [redacted], then percent change from baseline is set to be [redacted]

These percentages will be used to derive the ACR endpoints.

In addition, any CRP value below the LLOQ will be reported as [redacted] in database and will be [redacted] and used in analyses.

Another version of ACR20 will be derived with ESR replacing hsCRP.

[redacted]

4.2 Secondary efficacy endpoints [redacted]

The secondary efficacy endpoints of this study are:

Parts 1 and 2

- The proportion of subjects who achieve ACR20 [redacted]
- The proportion of subjects who achieve ACR50 [redacted]

  ACR50 will be derived similarly as for ACR20 [redacted]
- The proportion of subjects who achieve ACR70 [redacted]

  ACR70 will be derived similarly as for ACR20 [redacted]
- Change from Baseline in the individual components of ACR response at [redacted]
  - Tender joint counts [redacted]
  - Swollen joint counts [redacted]
  - PGA of disease activity (VAS)
  - PtGA of disease activity (VAS)
  - Patient's pain assessment (VAS)
  - Patient's self-assessed disability (HAQ-DI) [redacted]
  - Acute-phase hsCRP
  - ESR
- The proportion of subjects who require adjustment of background therapy [redacted]
- The proportion of subjects who achieve a DAS28-CRP [redacted]

  The DAS28-CRP is a composite score derived from examination of the [redacted] for swelling and tenderness, CRP level, and patient global health assessment.

  DAS28-CRP takes into account the following items:
  - TJC28: [redacted]
  - SJC28: [redacted]
  - CRP: [redacted]
  - GH: [redacted]

[redacted]

[redacted]

If any of the components is missing, DAS28-CRP will be missing.

- The proportion of subjects who achieve MDA criteria at [redacted].

  A psoriatic arthritis patient is defined as having a Minimal Disease Activity (MDA) response [redacted] when the patient meets [redacted] of the [redacted] following criteria: 1) tender joint count [redacted]; 2) swollen joint count [redacted] 3) PASI score [redacted] or BSA [redacted] 4) patient Arthritis Pain (VAS) [redacted]; 5) patient's global arthritis assessment [redacted]; 6) HAQ-DI score [redacted]; 7) tender entheseal points [redacted]

  If there are sufficient non-missing components to determine whether the MDA is a response or non-response, then MDA is not missing. If the available non-missing components are not sufficient to determine the response status of MDA then it is considered missing.

- Change from Baseline in LDI and LEI at [redacted]

  The Leeds dactylometer is a validated tool for assessing dactylitis. The dactylometer is used to measure the circumference of the base of the affected digit and is compared to the contralateral digit. [redacted] The final score for each digit is calculated and recorded on the CRF page. [redacted]

  The LEI examines tenderness at 6 sites: [redacted]. For each entheseal site, assessment is made of the adjacent joint in terms of tenderness and soft-tissue swelling, [redacted]. LEI is the number of sites in which enthesitis is present. The LEI score range is [redacted] A missing assessment (ie, no box checked) or not assessed (ie, NOT DONE box checked) for any site will result in the LEI score being coded as missing.

4.3 Exploratory endpoints

The exploratory endpoints of this study are:

<u>Parts 1 and 2:</u>

- [redacted]

  A subject's PASI is a measure of overall PsO severity and coverage. PASI consists of 2 major steps: 1) calculating the BSA covered with lesions and 2) assessment of the severity of lesions.

  - Body surface area involvement (%BSA): [redacted]

[redacted]

[redacted]

- Lesion severity: The basic characteristics of psoriatic lesions – erythema, induration and scaling – provide a means for assessing the severity of lesions. [redacted]

In each area, the sum of the intensity rating scores for erythema, induration and scaling is multiplied by the score representing the percentage of this area involved by psoriasis, multiplied by a weighting factor [redacted] The sum of the numbers obtained for each of the four body areas is the PASI.

[redacted]

The PASI combines the assessment of the intensity of lesions and the area affected into a single score in the [redacted] The PASI evaluation will only be conducted for subjects with moderate disease [redacted]

PASI75/90/100 is defined as at least 75%, 90%, and 100% reduction from baseline in PASI total score, respectively.

- SF-36 at measured time points ([redacted])
- PsAID questionnaire at measured time points

The PsAID questionnaire is a self-reported tool that assesses the impact of PsA on people's lives. The questionnaire assesses 9 items: pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, and anxiety, fear and uncertainty ([redacted]). The PsAID is calculated based on the 9 item ratings.

[redacted]

[redacted]

[redacted]

If one of the items has missing value for rating, it will be imputed with the mean values of the ratings for the rest 8 items. The PsAID will be calculated with above formula. [redacted]

- ACR20, ACR50, ACR70, the components of ACR, DAS28-CRP, MDA, LDI, and LEI at other measured time points

Part 3:

ACR20, ACR50, ACR70, the components of ACR, LDI, LEI, PASI, and HAQ-DI at measured time points

4.4 Safety endpoints

The safety endpoints of this study are:

- Adverse events (AEs)
- Laboratory assessments
- Suicidal ideation and behavior (C-SSRS)
- Vital signs
- ECG
- Physical examination
- ADA to tildrakizumab, including titer and neutralizing antibodies

[redacted]

5 SAMPLE SIZE AND POWER

[redacted]

[redacted]

6 ANALYSIS POPULATIONS

6.1 Full Analysis Set (FAS)

The FAS will include all randomized subjects who have received at [redacted] of IMP (tildrakizumab or placebo). Analyses will be based on randomized treatment.

6.2 Per Protocol Analysis Set (PPAS)

The PPAS will include all subjects in the FAS without any major protocol deviations that could have influenced the validity of the data for the primary efficacy endpoint. The deviations can include but are not limited to:

- Key inclusion/exclusion criteria not satisfied
- Presence of relevant protocol deviations with respect to factors likely to affect the efficacy of treatment where the nature of protocol deviations will be defined before breaking the blind
- Rescue medication use
- Inadequate study medication compliance which will be determined before breaking the blind

Major protocol deviations to be excluded from the PPAS will be finalized and documented in a memo prior to the lock and unblinding of the database.

6.3 Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who [redacted] of IMP. Analyses will be based on the actual treatment received.

6.4 PK Analysis Set

The PK Analysis Set will include all subjects in the Safety Analysis Set who have sufficient tildrakizumab concentration data to obtain reliable estimates of at least one PK parameters.

6.5 ADA Evaluable Set

The ADA Evaluable Set will include all subjects in the Safety Analysis Set who have at [redacted] Assay results from the placebo portion of the trial will not included in the immunogenicity assessment, although subjects who are randomized to [redacted] will be included in the assessment if they are treated with tildrakizumab in Part 2.

6.6 Protocol deviations/violations and exclusions from analysis sets

All violations and exclusions of subjects from analysis sets will be identified at the Classification

[redacted]

Meeting just prior to study unblinding, through clinical review input provided by Sponsor, using the following sources of information:

- Supportive subject listings, provided by the [redacted] ahead of the Classification Meeting, based on data recorded on the eCRF.
- Protocol Deviation Logs, provided by [redacted].

Further, deviations from protocol will be classified as major/minor or key/non-key depending on what is available in [redacted]

The protocol deviations that will lead to subject exclusion from the PPAS are listed as below. It is possible that unexpected deviations will arise as the study moves forward. Therefore, more deviation categories may be added to the list later. Prior to database lock, a classification meeting will be conducted to identify subjects to be excluded from PPAS, and the decision will be documented in a separate file.

- Subject without a diagnosis of PsA by the Classification of Psoriatic Arthritis (CASPAR) criteria with symptoms present for at least 6 months
- [redacted]
- Non-compliance with study treatment [redacted]
- Disallowed concomitant medications
- [redacted]

[redacted]

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived variables

Details for deriving efficacy variables are discussed in [redacted] The below set of variables are the basic demographic variables and some general variables.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7.2 Handling of missing data and outliers

7.2.1 Missing data analysis methods

In the primary analysis, ACR20 response rate at [redacted], missing values will be handled by setting the ACR20 value to nonresponsive. This approach will be used for all [redacted] endpoints (ACR20, ACR50, ACR70, DAS28-CRP, PASI75/90/100, and MDA) at all time points.

For a composite [redacted] endpoint (such as ACR20), if the values for any of the components at a time point are missing, the non-missing component variables will be used to determine the response status. If the response status cannot be determined due to missing components, then the composite response-type endpoint status is considered [redacted] for that time point.

For the HAQ-DI, LDI, LEI, SF-36 and PsAID instruments, rules suggested by the developers of these will be followed in calculating scores when individual question/items may be missing.

Details on handling missing data are outlined in [redacted].

In general, missing values for any of the endpoints will not be imputed when summarizing these endpoints using descriptive statistics.

In addition, missing values for safety endpoints will not be imputed.

[redacted]

7.2.2 Handling of missing or incomplete dates

Imputation rules for missing or partial AE start date are defined below:

If the start date has month and year but day is missing, the first day of the month will be imputed

- [redacted]
- [redacted]

If the start date has year, but day and month are missing, the 1st of January will be imputed

- [redacted]
- [redacted]

If the start date of an event is completely missing, then it is imputed with the first dose date.

Imputation rules for missing or partial AE stop date are defined below:

- [redacted]
- [redacted]

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

Imputation rules for missing or partial medication start/stop dates are defined below:

Missing or partial medication start date:

- [redacted]
- [redacted]

Missing or partial medication stop date:

- [redacted]
- [redacted]
- [redacted]

8 STATISTICAL METHODS

8.1 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum and maximum. One additional decimal point for mean and median and [redacted] for SD will be used.

For categorical variables, summaries will include counts of subjects and percentages. [redacted]

[redacted]

For summary purposes, baseline will be defined as the last available value prior to the date of first IMP administration; all summaries will be presented by treatment group, unless otherwise specified.

For reporting purpose, summary tables for efficacy variables and safety variables will be displayed by nominal visit as appropriate. Unscheduled assessments will not be included in the summary tables, but will be in data listings.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by treatment group, subject number, date/time and visit. The treatment group as well as patient's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all randomized subjects.

The treatment groups will be displayed in the format below in tables including [redacted]:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The treatment groups will be displayed in the format below for tables including [redacted] and all listings:

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

8.2 Protocol deviations

Population membership details will be listed, including reason for exclusion from each population.

All major protocol deviations identified will be summarized by treatment group and overall.

A listing will include the inclusion/exclusion criteria violated at Screening and at Baseline Visits as well as other protocol deviations identified based on data recorded on the eCRF and/or protocol deviation Logs [redacted]

8.3 Subject disposition

The number of subjects in the following categories will be summarized overall and by treatment group:

- Randomized
- Full Analysis Set (FAS)
- Per Protocol Analysis Set (PPAS)
- Safety Analysis Set
- PK Analysis Set
- ADA Evaluable Set

The number and percentage [redacted]) of subjects in each of the following disposition categories will be summarized overall and by treatment group:

- Completed treatment at [redacted]
- Prematurely discontinued the treatment and the reasons for discontinuation
- Completed study (i.e., completed the wash-out period)
- Prematurely discontinued the study and the reason for discontinuation

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation.

8.4 Demographics and baseline characteristics

The demographics and baseline characteristics, medical history, prior and concomitant medications

[redacted]

will be summarized by treatment group and overall for the FAS. Individual subject listings will be provided to support the summary tables.

8.4.1 Demographics

Age (years), height (cm), weight (kg) and other continuous demographic variables at Screening will be summarized descriptively. Gender, primary race, ethnicity and other categorical variables will be summarized using FAS.

Year of birth, age, gender, primary race, ethnicity, height and weight will be listed as part of demographic listing.

8.4.2 Baseline characteristics

Rheumatoid factor, body surface area (BSA) affected by psoriasis, tender joint counts, swollen joint counts, PGA of disease activity, PtGA of disease activity, patient's pain assessment, HAQ-DI, hsCRP, ESR, DAS28-CRP, LDI, LEI, PASI, SF-36, and PsAID at baseline will be summarized. [redacted] affected by psoriasis at baseline will be summarized as well.

8.4.3 Medical history

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using the most recently available version of the Medical Dictionary for Regulatory Affairs® (MedDRA). A listing of medical history will be provided as well.

Quantiferon testing and chest X-ray results at screening will be summarized using frequency counts for FAS.

8.4.4 Prior and concomitant medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary and categorized as follows:

Prior medications and concomitant medications will be summarized descriptively using frequency tables by ATC class and preferred term by treatment group on the Safety Analysis Set. Prior medications are those with a stop date before the first dose of study drug, and concomitant medications are those with a stop date on or after the first dose of study drug or ongoing.

Details for imputing missing or partial start and/or stop dates of medication are described in [redacted]

Prior biologic and prior anti-TNF medications will be summarized in a separate table.

[redacted]

8.5 Extent of exposure

8.5.1 Treatment Duration

Duration of study drug exposure [redacted] will be calculated as: [redacted] regardless of study drug interruption.

Study drug exposure will be summarised by treatment group on the Safety Analysis Set using descriptive statistics.

Exposure to randomized study drug will also be categorised in intervals [redacted].

8.5.2 Treatment Compliance

Study drug compliance will be calculated as: [redacted]. If only one syringe among the two is administered at a visit, the number of dose will be counted [redacted] If both syringes are administered at a visit, the number of dose will be counted [redacted] total number of doses planned will count [redacted] If a subject discontinues treatment, the total number of doses will be counted from [redacted].

Study drug compliance will be summarized by treatment group by the number of subjects (n), mean, SD, median, min, and max. They will also be summarized in categories [redacted].

Study drug compliance summaries will be based on the Safety Analysis Set.

8.6 Efficacy analyses

8.6.1 Analysis methods

Analysis of proportions

The Cochran-Mantel-Haenszel (CMH) test, incorporating prior anti-TNF use [redacted] and Baseline weight [redacted], will be used to compare response rates of response–type variables between each of the respective active dose arms and placebo. In addition, the [redacted] Should assumptions per the [redacted] not be satisfied, pairwise comparisons will be based on [redacted] after collapsing across levels of the stratification factors. In this case, the response rate difference and CI will be based on normal approximation without considering stratification.

[redacted] repeated measures analysis of continuous endpoints

[redacted]

A [redacted] analysis will be performed. The SAS procedure PROC MIXED will be used. The preferred model will include the fixed categorical effects of treatment, visit, treatment-by-visit interaction, prior TNF use[redacted] Baseline weight [redacted] as well as the continuous fixed covariates of baseline value. An unstructured matrix for the within-subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the [redacted]

In case of non-convergence with the unstructured matrix, other within-subject error variance-covariance matrices, such as [redacted] will be considered.

The model will provide [redacted]

8.6.1.1 Multiplicity

In order to control for[redacted] the [redacted] will be used in the determination of dose level success against placebo. There are [redacted] for the primary endpoint ACR20: [redacted]. The [redacted] from [redacted] the four comparisons above are ordered from lowest to highest value. The first p-value [redacted] the sequence will be compared with [redacted] the second lowest will be compared with [redacted] the third lowest will be compared with [redacted] and the highest will be compared with [redacted] If any p-value is less than the specified value, the corresponding test is declared significant. This test procedure will protect [redacted] at the [redacted] level.

8.6.2 Analysis of primary efficacy endpoint(s)

The primary efficacy variable is ACR20 at [redacted] ACR20 will be analysed with [redacted] as described in [redacted] Early withdrawals and any other subjects with ACR20 undeterminable [redacted] will be classified as [redacted]. Subjects who fail to show minimal response to treatment [redacted] may have their background medications adjusted according to the maximum permitted daily dose described in the protocol and continue in the study. Any subject requiring these adjustments will be counted as a non-responder for the primary analysis.

The primary efficacy analysis will be carried out using the subjects from the FAS. To control for [redacted], the [redacted] will be used. The pair-wise comparisons for the primary endpoints [redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Subgroup analysis will be performed for each of the following subgroup variables:

- Prior anti-TNF use [redacted]
- Baseline weight [redacted]

[redacted]

[redacted]

[redacted]

Estimates of the difference between the treatment groups, along with the [redacted] CI ([redacted]), will be presented for each defined category of each subgroup variable.

If sample size for a category of a subgroup factor is too small, the analysis for that subgroup may not be performed.

The primary purpose of the subgroup analyses is to check for consistency of results across stratification factors.

A sensitivity analysis of ACR20 with ESR replacing CRP will be performed.

8.6.3 Analysis of secondary endpoints

All secondary analyses will be performed using the FAS, unless otherwise stated. The response-type endpoints [redacted] will be analyzed based on the methods described for ACR20 in primary analysis. Continuous endpoints ([redacted]

[redacted]

will be analyzed based on an MMRM analysis that includes the fixed effects of treatment, visit, treatment by visit interaction, prior anti-TNF use [redacted] Baseline weight [redacted] and Baseline value. Due to [redacted] Tildrakizumab and placebo group switching [redacted] Tildrakizumab [redacted], the comparisons between active drug and placebo will not be

[redacted]

performed for the secondary endpoints collected after [redacted]. Response-type and continuous endpoints after [redacted] will be summarized descriptively. In addition, proportion of subjects who require adjustment of background therapy at [redacted] be presented with descriptive statistics.

[redacted]

[redacted].

8.6.4 Analysis of exploratory endpoints

The response-type endpoints (PASI 75/90/100) up to [redacted] will be analyzed based on the CMH methods described for ACR20. Continuous endpoints ([redacted]) up [redacted] will be analyzed based on an MMRM analysis as described for secondary endpoints. Response-type and continuous endpoints after [redacted] will be summarized descriptively.

In addition, there will be sub-groups of patients in Part 3 who either did or did not receive any new therapy for PsA and these will be analyzed separately for ACR20, ACR50, and ACR70.

All the exploratory analyses will be based on the FAS except PASI, which will be based on the subjects in [redacted] who have baseline [redacted]

8.7 Safety analyses

Safety analyses will be conducted on the Safety Analyses Set (treated subjects) and will be performed for all safety variables specified below.

All safety data will be summarized by treatment group.

The safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters, vital signs, and ECG) will only include subjects from the Safety Analysis Set who have data available for both the baseline and the time point under consideration unless otherwise specified.

No statistical test will be performed.

8.7.1 Adverse events

All AEs will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the most recently available version of the MedDRA dictionary.

In summaries by SOC and PT, adverse events will be sorted within each SOC and PT in alphabetical order. In summaries by PT, AEs will be sorted within each PT in alphabetical order.

Details for imputing missing or partial start dates of adverse events are described in [redacted].

TEAEs are defined as any AE occurring or worsening on or after the first dose of IMP. AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- Related TEAEs (AE will be defined as related if causality is possibly, probably, or certain)
- TEAEs by maximum severity
- TEAEs leading to discontinuation
- Serious TEAEs
- TEAEs leading to death.

An overall summary for the categories above will be prepared by study part, treatment group and overall. A TEAE in [redacted] is defined with the event start date on/after the [redacted] but before [redacted] date of IMP or on/before the last dose date of IMP if the subject discontinues treatment before [redacted] A TEAE in [redacted] defined with the event start date on/after [redacted] dosing date but on/before the [redacted] A TEAE in [redacted] is defined with the event start date after the last dose date of IMP.

In addition, all TEAEs will be summarized by study part [redacted] SOC, PT and treatment group using frequency counts and percentages (i.e., number and percentage of subjects with an event).

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in a specific study part, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in a specific study part, the subject will only be counted once at the system organ class level in adverse event frequency tables.

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary table will also be provided based on the most intense event - independent of relationship to study treatment.

[redacted]

[redacted]

[redacted]

In addition, a listing containing individual subject adverse event data for TEAEs leading to discontinuation from study, Serious TEAEs, TEAEs leading to death, [redacted] will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in an individual subject data listing.

8.7.2 Clinical laboratory evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units. If a lab value is reported using a nonnumeric qualifier [redacted], the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

Clinical laboratory parameters observed values and changes from Baseline will be summarized at each scheduled visit. Shift tables from baseline to post-baseline in lab parameters for each treatment group during [redacted] will be displayed by visit.

[redacted]

Values outside the [redacted]

8.7.3 Vital signs

Vital sign [redacted] will be summarized at each scheduled visit.

A listing of vital signs by subject will be produced.

8.7.4 Physical examinations

Physical examination results will be summarized with incidence of [redacted]" by body system at each scheduled visit. All physical examination data and abnormalities will be listed.

8.7.5 Electrocardiograms

The overall ECG interpretation will be summarized by presenting the [redacted] with [redacted]. In addition, shift tables from baseline to post-baseline in overall ECG interpretation during [redacted] will be displayed by visit and treatment group.

ECG parameter [redacted] will be summarized at each scheduled visit.

An accompanying listing of subjects will be produced and it will display all ECG findings during the study in subjects with abnormal ECGs, as determined by the investigator.

8.7.6 Assessment of Suicidal Ideation and Behavior

Subjects will be assessed for suicidal ideation and behavior at the Screening Visit using the Baseline (Lifetime) C-SSRS, and each subsequent visit using the C-SSRS Since Last Visit version.

The C-SSRS consists of 2 major aspects: Suicidal Ideation and Suicidal Behavior. Based on outcomes and data analyses suggested by the C-SSRS website, the following endpoints will be used to analyze C-SSRS data:

- Presence of Suicidal Ideation: [redacted]
- Presence of Suicidal Behavior: [redacted].
- Suicidal ideation score: [redacted]

The number of subjects with presence of suicidal ideation/behavior will be summarized at each assessment time. The C-SSRS data will be summarized using worst-case shift tables. Worst-[redacted]

[redacted]

8.8 Other analysis

8.8.1 Analysis of Pharmacokinetic Endpoints

Plasma tildrakizumab concentration data will be listed by individual subject and summarized by time and tildrakizumab dose group.

PK parameters of AUC, C_{max}, C_{min}, and $T_{1/2}$ will be summarized with descriptive statistics (n, mean, SD, geometric mean, coefficient of variation [%CV], minimum, first, second (i.e., median) and third quartiles, and maximum).

The PK Analysis Set will be used for the analysis.

Exploratory PK analyses will be performed by another vendor and described in a separate SAP.

8.8.2 ADA to Tildrakizumab

For each subject, tildrakizumab serum concentrations and ADA sample results are matched to actual sampling times and treatment. Subjects are grouped based on the actual treatment received, rather than the treatment group at randomization. Subjects have baseline samples taken prior to dosing to assess for any preexisting immune response that may be detected by the ADA assays. Subjects are considered positive if at least one pre-treatment or post-dose sample is positive at any time. Positive subjects are subsequently categorized into treatment-emergent positive if the positive sample occurs following treatment with tildrakizumab or non-treatment emergent positive if the subject has an immune response present at baseline and the response is not boosted following treatment.

The presence of tildrakizumab can interfere with the [redacted] at concentrations [redacted] the drug tolerance level (DTL) of [redacted] Therefore, samples with a negative test result in the [redacted] can only be described as [redacted] in the case of a tildrakizumab concentration below [redacted]. The immunogenicity status of a subject is considered to be negative if all pre-treatment and post-dose samples tested negative in the ADA assay and if the concentration of tildrakizumab in the last post-dose sample is below the DTL. Therefore, an integrated evaluation of ADA results and drug serum concentrations is required for interpretation of immunogenicity results.

To summarize, subjects are categorized in one of four immunogenicity categories as described in Table 3. [redacted]. The proportion of non-treatment emergent positive subjects is similarly reported. [redacted]

Table 3 Immunogenicity Subject Status Definitions

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

The anti-tildrakizumab immunogenicity status of evaluable subjects, along with titer and neutralizing antibody, will be summarized by dose level in [redacted] Only data from [redacted] is used and placebo samples in [redacted] are excluded. The anti-tildrakizumab immunogenicity status of evaluable subjects will be further summarized by treatment group and by dose level for [redacted]. ADA data will be presented in a listing.

8.8.3 Correlation of ADA with Pharmacokinetics

Mean plots of tildrakizumab concentration (µg/mL) versus time for ADA positive and ADA negative or inconclusive during [redacted] will be displayed for subjects in groups of [redacted].

8.8.4 ADA to Efficacy Endpoints

The impact of ADA on the responder type of efficacy endpoints [redacted] will be summarized by dose level for [redacted] Only data from [redacted] is used and placebo samples in [redacted] are excluded.

8.9 [redacted]

[redacted]

[redacted]

9 REPORTING CONVENTION

This section details the format and layout of all TFLs and statistical output that will be produced in conjunction with the Clinical Study Report. The table of contents and templates for the TFLs will be produced in a separate document.

All data analyses and generation of TLFs will be performed using SAS 9.4® or higher.

The following reporting conventions will be adopted for the presentation of study data:

- The tables and listings will be provided in a Word document in landscape format, Courier New 8 with the following margins: top: 1.50 in, bottom: 1.00 in, left: 1.00 in, right: 1.00 in, header: 1.50 in, footer: 0.50 in. The output alignment will be centered on the page and the titles and footnotes will be center aligned.
- The ICH[3,4] numbering convention will be used for all TLFs.
- The analysis population represented on the tables will be clearly identified in the title of the table.
- Dates will appear as DDMMMYY format; times as HH:MM format[redacted]
- For the presentation of summary data, results will be aligned on the decimal point and be centered within the column. Unless otherwise stated, tables will summarize the results per treatment group (Active treatment, Placebo) and overall.
- All listings will be ordered by investigational site, patient number, date/time and visit. The treatment group (Active treatment, Placebo) as well as patient's sex and age will be stated on each listing. Line break spacing will be added (for example between different patients, visits) to facilitate review of the listings.
- All TLFs will have the SAS program path and name, output filename and date/time of production in the footnote, and will include the following hierarchy of titles and footnotes (as an example):

[redacted]

[redacted]

[redacted]

10 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

[redacted].

11 REFERENCES

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

12 APPENDICES

12.1 Endpoint definition and derivation details

12.1.1 Health Assessment Questionnaire – Disability Index (HAQ-DI)

There are 8 categories assessed by the HAQ-DI[5]: 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. For each of these categories, patients report the amount of difficulty they have in performing 2 or 3 specific activities. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

[redacted]

For each question in the questionnaire, the level of difficulty is [redacted]

[redacted]

In order to compute score patient must complete 6 of the 8 categories

1. [redacted]

[redacted] of categories answered [redacted] This yields a single disability score.

[redacted].

12.1.2 36-item Short Form

The SF-36 v2[6] is a multi-purpose survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these 8 domains and 2 summary measures of physical and mental health. All domains and summary components are scored such that a higher score indicates a higher functioning or health level.

These 8 domains are as follows:

a. Physical Functioning (PF). [redacted]

b. Role-Physical (RP). [redacted]

[redacted]

c. Bodily Pain (BP). [redacted]

d. General Health (GH). [redacted]

e. Vitality (VT). [redacted]

f. Social Functioning (SF). [redacted]

g. Role-Emotional (RE). [redacted]

h. Mental Health (MH). [redacted]

The summary component scores are:

a. Physical Component Summary (PCS).

b. Mental Component Summary (MCS).

[redacted]

Data Derivation Details to Obtain Scale Scores for SF-36

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

Statistical Analysis Plan (SAP)

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]