Official title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Assess the Efficacy and Safety of Tildrakizumab in the Treatment of Moderate to Severe Nail Psoriasis.

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Statistical Analysis Plan

Protocol Title: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL STUDY TO ASSESS THE EFFICACY AND SAFETY OF TILDRAKIZUMAB IN THE TREATMENT OF MODERATE TO SEVERE NAIL PSORIASIS

Protocol Number: TILD-18-19

Investigational Product: Tildrakizumab

Type of Study: 3b

[redacted]

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[redacted]

[redacted]

[redacted]

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List of Abbreviations

Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CGIC	Clinician Global Impression of Change
CGIS	Clinician Global Impression of Severity
CI	Confidence intervals
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBF	Database Freeze
DBL	Database Lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECI	Event of Clinical Interest
eCRF	Electronic Case Report/ Record Form
EoS	End of Study
EoT	End of Treatment
FCS	Fully Conditional Specification
FDA	Food & Drug Administration
IA	Interim Analysis
IBMCP	Interim Blinding Maintenance and Communication Plan
ICH	International Conference on Harmonisation
ICSR	Interim Clinical Study Report
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular events
MAR	Missed at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
M-N	Miettinen-Nurminen
mNAPSI	modified Nail Psoriasis Severity Index
MNAR	Missing Not at Random
NAPPA-QoL	Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life
NAPSI	Nail Psoriasis Severity Index
NRI	Non-responder Imputation
NRS	Numeric Rating Scale
OC	Observed Cases
PASI	Psoriasis Area and Severity Index
PD	Protocol Deviations
PGA	Physician Global Assessment
PGIC	Patient Global impression of Change
PGIC-P	Patient Global impression of Change for Pain

PGIS	Patient Global Impression of Severity
PGIS-P	Patient Global Impression of Severity for Pain
PN	Preferred Name
PPS	Per Protocol Set
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SoA	Schedule of Activities
SOC	System Organ Class
SPIL	Sun Pharmaceutical Industries Limited
s-PGA	Static Physician's Global Assessment
SSRE	Sample size re-estimation
TEAE	Treatment-emergent Adverse Event
ViSENPsO	Visual Medical Scale to Evaluate Nail Psoriasis Severity
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) has been developed following the review of Sun Pharmaceutical Industries Limited (SPIL) Protocol TILD-18-19 (Amendment 3 dated 23 Dec 2022), and the corresponding case report form (CRF) (version 5, dated 22MAY2021). This SAP describes the analysis sets and specific details for the statistical methods to be used for the analysis and reporting of all efficacy and safety data collected during the conduct of Protocol TILD-18-19. When needed, this SAP supersedes the statistical considerations identified in Protocol TILD-18-19 and its amendments (as applicable). Where considerations are substantially different, they will be identified as such in this document. This SAP has been developed and finalized prior to database lock of the clinical database for Protocol TILD-18-19. If additional analyses are required to supplement the planned analyses or there are changes to the planned analysis described in this SAP, they may be performed and will be identified in the Clinical Study Report (CSR).

This SAP is being written with consideration of the recommendations outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the most recent ICH E3 Guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."

2 PROTOCOL SUMMARY

2.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tildrakizumab in the treatment of moderate to severe psoriasis of the nails. Approximately 96 eligible subjects (approximately 48 per arm) with moderate to severe plaque psoriasis and concomitant moderate to severe nail psoriasis will be randomized into the study. Eligible subjects will be randomized to one of the 2 arms in a 1:1 ratio: Arm A: Tildrakizumab 100 mg, SC (n = 48) and Arm B: Placebo, SC (n = 48). The study is planned with a primary analysis, which will be performed when the last subject has completed the Week 28 visit and a final analysis to be performed when the last subject has completed the study.

The study will comprise 3 parts:

PART 1: Double-blind Placebo-controlled (Day 1 to Week 28)

After a Screening Period of up to 28 days and on Day 1, all eligible subjects will be randomized 1:1 to receive either tildrakizumab 100 mg or placebo administered by SC injection on Week 0 (Day 1), Week 4, and Week 16. Subjects should receive the first dose of study treatment within 24 hours of randomization. The treatment period for the double-blind placebo-controlled part of the study is 28 weeks.

Early Escape: At Week 16, subjects who experience significant worsening of plaque psoriasis (defined as an increase in Static Physician's Global Assessment [s-PGA] by, at least, 2 from the baseline measurement) will be eligible for early escape. Subjects selected for early escape by the Principal Investigator at Week 16 will have study medication discontinued, and will

complete the End of Treatment visit assessment, followed by the observational safety follow-up period. Subjects entering early escape will not be replaced for purpose of statistical analysis and will be included in the appropriate analysis populations as defined in Section 3.5.

Following the last subject's Week 28 visit (or early termination prior to Week 28), Week 28 analysis may be conducted on available data to evaluate safety and efficacy, and a Week-28 clinical study report (CSR) may be developed after database lock (DBL). In this case, when all the randomized patients have either completed the Week 28 evaluations or have stopped study participation prior to the Week 28 visit, the first database freeze (DBF) will occur (referred to as Week 28 DBF hereafter). When all patients randomized in this trial have either completed the Week 72 evaluations or have ceased study participation prior to the Week 72 visit, the second DBL will take place [referred to as the Final (Week 72) DBL henceforth], and subsequent CSR will be generated. The sponsor might opt to have a single DBL and CSR at the last subject's Week 72 visit (or early termination prior to Week 72) without a DBL at Week 28.

All assessments in PART 1 are scheduled to happen before or on the date of injection at Week 28. The analysis of efficacy and safety endpoints for PART 1 will follow the analysis visit window and definitions as specified in the sections below.

PART 2: Double-blind Active Treatment Extension (Week 28 to Week 52)

At Week 28, subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg at Weeks 28, 32, and 44. Subjects initially randomized to tildrakizumab 100 mg will continue to receive tildrakizumab at Weeks 28, 40, and 52. In order to maintain the blind, subjects in both treatment arms will receive matching placebo injections at specified time points as described in the Schedule of Activities (SoA) in the Clinical Protocol.

Subjects who experience significant worsening of plaque psoriasis at Week 28 (defined as an increase in s-PGA by, at least, 2 from the baseline measurement) will be discontinued from treatment. Subjects who do not fulfill this criterion at Week 28 will continue to receive tildrakizumab in Part 2 as described above.

All assessments in PART 2 are scheduled to happen after the date of injection at Week 28 and before or on the date of injection at Week 52. The analysis of efficacy and safety endpoints for PART 2 will follow the analysis visit window and definitions as specified in the sections below.

PART 3: Observational Safety Follow-up (Week 52 to Week 72)

After Week 52 (or early termination of study treatment prior to Week 52), the study treatment should be stopped and all subjects, including those who terminated early from Part 1 and 2 will enter the 20-week Observational Safety Follow-up period to monitor safety and tolerability for 20 weeks following the last dose of study treatment. During the follow-up period, subjects should continue on study-approved concomitant medications only, however, may be placed on appropriate therapies for safety concerns or significant worsening of

psoriasis based on the judgment of the Investigator. The subjects will not receive study treatment during the follow-up period.

Subjects who withdraw from the study will undergo the assessment that corresponds to the last assessment of the study part from which they are leaving. Subjects discontinued from study treatment at any time (apart from withdrawal of informed consent) will complete the EoT (Week 52) assessment approximately 4 weeks after the last dose of study treatment and enter the 20-week Observational Safety Follow-up. Subjects who withdraw from the study during Part 3 will undergo the Week 72 (End of Study [EoS]) assessments approximately 4 weeks after their last visit.

All assessments of safety in PART 3 are scheduled to happen after the date of injection at Week 52. The analysis of efficacy and safety endpoints for PART 3 will follow the analysis visit window and definitions as specified in the sections below.

2.2 Study Objectives

The objective of this study is as follows:

2.2.1 Primary Objective

The primary efficacy objective of this study is:

- To assess the efficacy of tildrakizumab in subjects with moderate to severe nail psoriasis, as measured by the proportion of subjects who achieve at least a 75% improvement from baseline in total-modified Nail Psoriasis Severity Index (mNAPSI) at Week 28.

2.2.2 Secondary Objectives

The key secondary objective of this study is:

- To assess the efficacy of tildrakizumab in the treatment of moderate to severe nail psoriasis compared with placebo as measured by Visual Medical Scale to Evaluate Nail Psoriasis Severity (ViSENPsO) at Week 28.

The additional secondary objectives of this study are:

- To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain numeric rating scale (NRS) score at Week 28.

- To assess the efficacy of tildrakizumab in the treatment of moderate to severe nail psoriasis compared with placebo as measured by mNAPSI, NAPSI, and ViSENPsO at Week 28.

- To assess the efficacy of tildrakizumab in the treatment of plaque psoriasis compared with placebo, as measured by Psoriasis Area and Severity Index (PASI), Physician's Global Assessment-Skin (PGA-S) score and body surface area (BSA) involvement at Week 28
- To assess the effect of tildrakizumab on nail pain compared with placebo as measured by nail pain NRS score improvement from baseline at Week 28.

2.2.3 Other/Exploratory Objectives

The exploratory objectives of this study are:

- To assess the effect of tildrakizumab over time at measured time points through Week 52 as measured by mNAPSI, NAPSI, Nail Pain NRS, BSA, PGA-S, static Physician's Global Assessment (s-PGA), PASI,[redacted]

- To assess the effect of tildrakizumab on Quality of Life (QoL) as measured by:
  - Dermatology Life Quality Index (DLQI) and
  - Nail Assessment in Psoriasis and Psoriatic Arthritis QoL (NAPPA- QoL).

- To assess the effect of tildrakizumab measured by using anchor scales:
  - Clinician Global Impression of Change (CGIC)
  - Clinician Global Impression of Severity (CGIS)
  - Patient Global impression of Change (PGIC).
  - Patient Global Impression of Severity (PGIS).
  - Patient Global Impression of Severity for pain (PGIS-P).
  - Patient Global Impression of Change for pain (PGIC-P).

2.2.4 Safety Objective

The safety objective of this study is:

- To assess the safety and tolerability of tildrakizumab in subjects with moderate to severe nail psoriasis over 52 weeks.

2.3 Study Endpoints

The study endpoint of this study is as follows:

2.3.1 Primary Endpoint

The primary endpoint of this study is:

- The proportion of subjects who achieve at least a 75% improvement from baseline in total-mNAPSI (mNAPSI75) at Week 28.

2.3.2 Secondary Endpoints

The key secondary endpoint of this study is:

- The proportion of subjects with, at least, a score of "0 - normal" or "1 – minimal nail psoriasis" and a 2-point decrease from baseline at Week 28 as measured by the ViSENPsO.

The other secondary endpoints of this study are:

- The proportion of subjects with at least 3 point decrease from baseline, in Nail Pain NRS score at Week 28 in subjects with baseline nail pain NRS score of ≥ 3 (where NRS of ≥ 3 will be based on average score from 7-daily records at Baseline.)
- Change in patient-reported nail pain NRS score from Baseline at Week 28.
- The proportion of subjects achieving total-fingernail mNAPSI 90, mNAPSI 100, NAPSI 75, NAPSI 90, and NAPSI 100 at Week 28.
- Change in total-fingernail mNAPSI score from baseline at Week 28.
- Change in total-fingernail NAPSI score from baseline at Week 28.
- [redacted]
- The proportion of subjects achieving PASI 75, PASI 90, and PASI 100 at Week 28.
- The proportion of subjects achieving a PGA-S score of "clear" or "almost clear" with at least a 2-point reduction from baseline to Week 28.
- Percentage change in total BSA involvement from baseline to Week 28.

- The proportion of subjects with, at least, 30% decrease in Nail Pain NRS score from Baseline at Week 28 in subjects with a baseline nail pain NRS score of ≥ 3 (where NRS of ≥ 3 will be based on average score from 7-daily records at Baseline.)

2.3.3 Other/Exploratory Endpoints

The exploratory endpoints of this study are:

- Change from Baseline in mNAPSI, NAPSI, Nail Pain NRS, BSA, PASI, and the proportions of PGA-S, s-PGA, [redacted] results at measured time points through Week 52.
- The proportion of subjects achieving a PGA-S, s-PGA score of "clear" or "almost clear" with at least a 2-point reduction from baseline through Week 52.
- [redacted]
- Change from Baseline in DLQI score (total and 6 domain scores) and NAPPA-QoL score at measured time points through Week 52.
- The proportions of CGIC, PGIC, PGIC-P category results at measured time points through Week 52.
- Change from Baseline in CGIS, PGIS, and PGIS-P at measured time points through Week 52.

[redacted]

- Subjects achieving mNAPSI75, mNAPSI90 and mNAPSI100 at Week 52
- Subjects achieving NAPSI75, NAPSI90 and NAPSI100 at Week 52

2.3.4 Safety Endpoints

The safety endpoints of this study are:

- The percentage of subjects with incidence, seriousness, and severity of all adverse events.
- The percentage of subjects with severe infections, defined as any infection meeting the regulatory definition of a serious adverse event (SAE), or any infection requiring intravenous (IV) antibiotics whether or not reported as a serious event as per the regulatory definition.

- The percentage of subjects with malignancies (excluding carcinoma in situ of the cervix).
- The percentage of subjects with non-melanoma skin cancer.
- The percentage of subjects with melanoma skin cancer.
- The percentage of subjects with major adverse cardiovascular events (MACE)
- The percentage of subjects with study treatment-related hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, etc.).
- The percentage of subjects with injection site reactions (e.g. pain, erythema, edema etc.).
- The percentage of subjects with adverse event of clinical interest
- The percentage of subjects with abnormal physical examination findings
- Change in electrocardiogram results from baseline at Week 52
- Change from Baseline in vital signs parameters at measured time points through Week 52
- Change from Baseline in laboratory test results (Hematology, Biochemistry, and Urinalysis) at measured time points through Week 52
- Change from Baseline in C-SSRS results at measured time points through Week 52

2.5 Blinding

This is a double-blind study with limited access to the randomization code. Tildrakizumab and placebo will be identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study center staff, subject, Sponsor, or study vendors. The treatment codes will be held by the Clinical Supplies Department of the Sponsor or their designated Contract Research Organization (CRO).

All subjects will be dosed at the same time points to maintain the study blind throughout the study. Returned study treatment should not be re-dispensed to the subjects.

[redacted]

[redacted]

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of Summaries

Descriptive statistics (number [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]) for continuous variables and frequency and percentages for discrete variables will be utilized. All summaries and analyses conducted will be by assigned therapy and/or combined total subjects, where appropriate. Data obtained on the eCRF and entered into the database will be provided in data listings showing individual subject values. Unless otherwise noted, the data listings will be sorted first by treatment assignment, subject number and then by date within each subject number.

[redacted]

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (i.e., SD) will be displayed to two decimal places greater than the original value.

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.4 or higher.

3.2 Definition of Baseline Values

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the first intake of study treatment (this includes unscheduled visits).

For Nail Pain NRS, the complete observation will be performed on the average score for each visit that will be based on the seven daily scores. The complete score at a given visit will be based on an average of no less than four of the seven prompted valid daily recall observations. No imputation of missing daily recalls will be used, and the change in averaged scores at Baseline and Week 28 will provide the basis for analysis. Hence, baseline NRS will be defined as the average score of the 7 consecutive daily scores leading up to the Baseline Visit (Visit 2); the baseline score will be computed if there are four or more valid scores out of the seven prompted assessments. If a subject missed 4 or more entries during the 7 days before Baseline visit, the Baseline NRS value will be considered as undefined (missing) for the subject.

For numerical variables, change from Baseline will be calculated as the difference between the post-Baseline value and the corresponding Baseline value and calculated as: post-Baseline value – Baseline value. The percent change from Baseline will be calculated as change from Baseline divided by the Baseline value, expressed as a percentage.

3.3 Analysis Time points

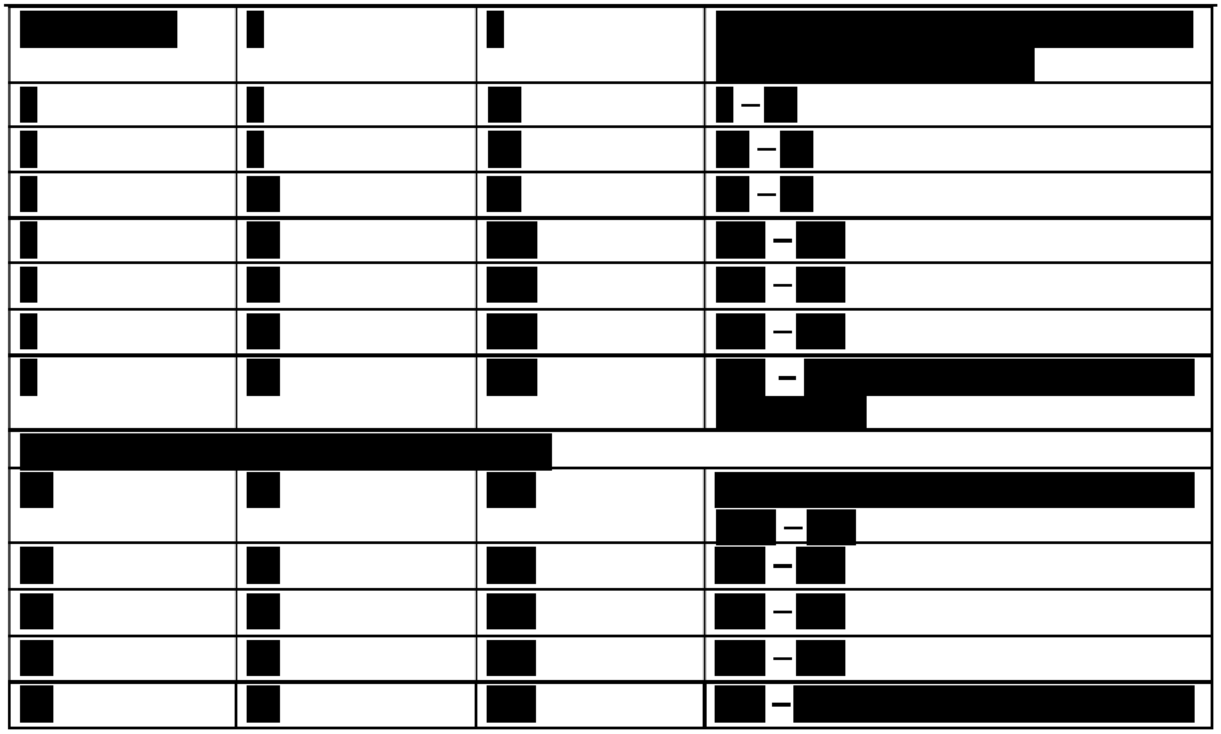
Unless specified otherwise, efficacy and safety endpoints will be analyzed according to their scheduled study visits; unscheduled and early termination visits will be mapped to windowed analysis visits defined by actual study day as in table 1.1 below. If there is no evaluation available from the scheduled study visit, and more than one non-missing evaluation is assigned to an analysis window, the evaluation closest to the target day will be used for the analysis. If the two visits are equidistant from the target day, the earlier visit will be used. For early terminated patients, Part 3 is to start the day of last assessment after the last injection plus 28 days.

The following analysis visit windows will apply:

Table 1.1 Analysis Visit Windows

For: ViSENPsO, NAPSI, mNAPSI, PGA-S, BSA, PASI, and C-SSRS

Derived Visit	Week	Target Day	Analysis Window
Part 1: Double-blind Placebo-controlled			



In particular, NRS pain score will be recorded daily in patient diary for the 7 days leading up to each scheduled visit. The analysis visit for NRS will be assigned the same as for the subsequent visit according to Table 1.1, ie, as 7 consecutive days prior to that visit. In the event of a missed visit, the available NRS scores will be mapped to an analysis visit according to Table 1.1, using the last diary entry date as anchor. Any NRS entries outside of the 7-day window will be excluded from the calculation of average NRS. At least 4 out of the 7 daily records are required to calculation of average.

All other assessments (ECG, laboratory data) will be analyzed according to the assigned (nominal) visit unless otherwise specified.

For any events/assessments on or after the first administration of study drug, study day is calculated as: event/assessment date – date of first administration of study drug + 1. As such, Day 1 is defined as the date of first administration of study drug.

For any events/assessments before the first administration date, study day is calculated as event/assessment date – date of first administration of study drug.

3.4 Protocol Deviations

All protocol deviations (PD) will be tracked throughout the study and classified by deviation type, either minor or major. Protocol deviations represent a failure to adhere to the clinical study protocol. The two types of deviations are defined as:

- Minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.
- Major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB or which has a major impact on the subject's rights, safety or well-being, or the

[redacted]

Prior to primary analysis database freeze and final database lock, each deviation will be reviewed to determine if it excludes the patient from any of the analysis sets or any particular

planned analysis. These determinations will then be described in the relevant clinical study report. Deviations that result in exclusion of subjects from the Per Protocol Set (PPS) will be presented in a listing. Minor protocol deviations will be presented as well. All deviations will be retained within the deviations tracker (considered the source document).

Protocol deviations attributable to the COVID-19 pandemic regardless of whether deemed major or minor will be provided in a separate listing by study parts (i.e., Parts 1, 2, 3) if deemed necessary.

3.5 Analysis Populations

The following analysis sets will be used in the study:

Intent-to-Treat (ITT) Set: All randomized subjects regardless of the treatment actually received.

Safety Analysis Set (SAF): All randomized subjects who have received at least 1 dose of study treatment.

Per Protocol Set (PPS): All subjects in the ITT population who have completed the 28-week placebo-controlled treatment without any major protocol deviation that could impact data interpretability for the primary and key secondary efficacy endpoints. [redacted]

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

The composition of the PPS will be determined in blind review of the database conducted prior to the primary analysis at Week 28. Prior to breaking the blind at Week 28, alternate criteria for exclusion from the PPS may be applied to accommodate unforeseen events that occurred during the conduct of the study.

The primary efficacy and key secondary endpoints will be analyzed using the ITT Set as well as the PPS for supportive analyses.

Safety endpoints will be analyzed descriptively based on the SAF, and subjects will be summarized based on the actual treatment they received.

3.6 Treatment Assignment

The study treatment in this study is tildrakizumab and placebo. All subjects will be dosed at the same time points to maintain the blind throughout the study. The study arms will receive study treatment during the course of the study as follows:

Arm A:

- Tildrakizumab 100 mg SC injections at Weeks 0, 4, 16, 28, 40 and 52.
- Placebo injections at Weeks 32, and 44.

Arm B:

- Placebo injections at Weeks 0, 4, 16, 40, and 52.
- Tildrakizumab 100 mg SC injections at Weeks 28, 32 and 44.

3.7 Center Pooling Strategy

Not Applicable.

3.8 Coding Dictionaries

Adverse events, medical history, and concurrent procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or a more recent version. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) March 1, 2019 B3 Global.

4 STATISTICAL / ANALYTICAL ISSUES

4.1 Handling of Dropouts or Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses as applicable.

For all primary and supportive/sensitivity analyses (including analyses based on Observed Cases [OC]) described below, subjects with missing primary or key secondary efficacy endpoint baseline data will have baseline values imputed as the median of other subjects' non-missing baseline values, considering the analysis set used for the primary analysis (i.e., ITT).

Missing post-baseline data will be handled as per specifications detailed below.

For dichotomized primary and secondary endpoints, subjects with missing data will be imputed using non-responder imputation (NRI) unless noted below and in Table 5 from Section 9.

In addition, sensitivity analyses using last-observation-carried forward (LOCF) (for primary and key secondary efficacy endpoints), and multiple imputation (MI) including a tipping point analysis (for primary and key secondary efficacy endpoints) will be conducted using the ITT set as appropriate. The details are as follows:

- Last observation carried forward (LOCF): The last observed value will be carried forward for any subsequent missing values for endpoints through Week 28. Baseline values will not be carried forward to post-Baseline visits.
- Multiple Imputation (MI): Multiple imputations is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution

of missing data given the observed data and covariates, creating multiple completed data sets. These completed datasets can then be analyzed using standard analysis methods. Details of the imputation model as well as the tipping point analysis are provided in Section 9.3 .

Continuous efficacy endpoints up to Week 28 will be analyzed with ANCOVA and MMRM under a Missing at Random (MAR) assumption with no imputation.

A summary of the imputation methods for all efficacy endpoints are shown in Table 5 in Section 9.

All safety endpoints will be analyzed as observed cases (OC) in SAF. No other imputation will be used unless otherwise specified.

4.2 Adjustments for Covariates

The primary and secondary efficacy analyses will adjust for baseline body weight class (≤ 90 kg or >90 kg) and prior exposure to TNF-alpha inhibitors (Yes/No).

[redacted]

4.4 Multicenter Studies

Descriptive summaries of the primary and key secondary efficacy endpoints will be presented for each individual study center to evaluate potential heterogeneity across sites.

4.5 Multiple Comparison / Multiplicity

For the primary and secondary endpoints, overall study Type 1 error will be controlled for multiplicity using a step-down sequential testing approach. To begin, the primary endpoint

[redacted]

Hypothesis testing for additional secondary endpoints will be performed at two-sided 0.05 level of significance only if both the primary endpoint and key secondary endpoint test significant. Statistical comparisons for other secondary endpoints will be performed for descriptive purpose.

[redacted]

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

4.6 Examination of Subgroup

Subgroup analyses will be considered exploratory and will describe results based on the dichotomization of subjects using the relevant subgroup criteria for subject inclusion/exclusion. The table below describes the planned subgroup analyses.

Table 4 Subgroup Analyses of Efficacy Endpoints

Subgroup definition	Efficacy/Safety Endpoint Class	Part 1 Timepoint *
Prior Anti-TNF use for psoriasis (yes, no)	Primary and Key Secondary Efficacy	Week 28
Baseline weight class (≤ 90 kg or > 90 kg)	Primary and Key Secondary Efficacy	Week 28
Gender (male, female)	Primary and Key Secondary Efficacy, Overall AE summary	Week 28

Subgroup definition	Efficacy/Safety Endpoint Class	Part 1 Timepoint *
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other (As collected in EDC))	Primary and Key Secondary Efficacy, Overall AE summary	Week 28
Age (< 65, ≥ 65)	Primary and Key Secondary Efficacy, Overall AE summary	Week 28
Ethnicity (Hispanic or Latino, Not Hispanic or Latino	Primary and Key Secondary Efficacy, Overall AE summary	Week 28
* Time point describes the visit associated with a primary analysis of an efficacy endpoint for subgroup analysis.		

Subgroup analyses will be conducted using the ITT population with NRI where applicable. Subgroup analyses for efficacy and safety by gender (Male vs. Female), age (< 65 vs. ≥ 65), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other (As collected in EDC)) and ethnicity (Hispanic or Latino vs. Not Hispanic or Latino) will also be performed.
Additional subgroup analyses may be performed if required.

[redacted]

6 STUDY POPULATION CHARACTERISTICS

6.1 Study Eligibility

A listing of patients violating inclusion/exclusion criteria will be provided for all enrolled subjects.

6.2 Disposition of Subjects

The number and frequency of subjects who were screened, screen failures (overall and by reason of screen failure), randomized, completed (overall and by each part of the study), and discontinued (overall and by each part of the study) will be presented. A summary of reasons for discontinuation will be provided. The number of subjects in the all randomized, ITT, PPS, and SAF will be summarized. Subjects that were excluded from the PPS and reason for exclusion will be listed and separately summarized in the disposition table.

Due to the outbreak of COVID-19 pandemic, COVID-19 related subject disposition events will be further summarized per FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (thereinafter referred to as FDA COVID-19 Guidance)[a], for the following:

- Number of subjects discontinued from the study for reasons related to COVID-19
- Number of subjects with visits altered (e.g., deviated visits) or missed due to COVID-19
- Number of subjects with any efficacy assessments not done at each visit due to COVID-19 associated criteria.

See also Section 11 for COVID-19 pandemic impacted subject assessment considerations.

7 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Demographic and Disease Characteristics

Demographic and baseline characteristics generally will be summarized descriptively overall and by treatment in the ITT, SAF, and PPS analysis sets. The following demographic and Baseline variables will be included:

- Age (years)
- Gender
- Race
- Ethnicity
- Prior use of TNF-alpha inhibitors (Yes/No)
- Weight (kg)
- Weight category (≤90 kg or >90 kg)
- Height (cm)
- BMI (kg/m^2)
- The Presence of Psoriatic Arthritis in Medical History
- Baseline ViSENPsO
- Baseline mNAPSI
- Baseline NAPSI

[a] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency, accessed 08-June-2021

- Baseline Nail Pain NRS Score
- Baseline PASI
- Baseline PGA-S score (Whole Body)
- Baseline total BSA
- Baseline s-PGA
- Baseline DLQI
- Baseline NAPPA-QOL

All demographic data and baseline disease characteristics data will be listed by subject.

7.2 Medical History and Concomitant Nondrug Treatment/Procedure

Medical history and concurrent procedures will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) Version 24.0 or a more recent version and will be presented in a by-subject listing.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary March 2019 B3 Global. Prior medications include medications used to treat the disease conditions and any other medications taken within 6 months prior to enrollment and stopped prior to start of treatment. Concomitant medications during the study are defined as any medications that are ongoing or with stop dates on or after date of first study medication administration.

For the determination of prior vs. concomitant medications, the following rules regarding the stop date will be applied:

- If the stop date is missing completely, the medication is assumed to be a concomitant medication.
- If only year was recorded, and it is before Baseline, it is a prior medication; if year is same or after Baseline, it is assumed to be a concomitant medication.
- If day is missing, but month and year are before Baseline, it is a prior medication; if month and year are the same as Baseline, it is assumed to be a concomitant medication; if month and year are after Baseline, it is a concomitant medication.
- If start date is after Baseline, it is a concomitant medication regardless.

Concomitant medications will be further categorized by Study Part (1, 2, 3) as following:

- Part 1 (Day 1 to Week 28): includes all concomitant medications that are ongoing or with stop dates on or after date of first study medication, but do not start after Week 28 dosing

- Part 2 and 3 (Week 28 and beyond): includes all concomitant medications that start after Week 28 dosing

The number and percentage of subjects taking prior medications or concomitant medications (overall and by study parts) will be summarized by anatomical therapeutic chemical (ATC) level 3 and preferred name (PN) for the SAF. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to two or more PNs in the same classification. All prior and concomitant medications will be listed by subject.

[redacted]

9 EFFICACY ANALYSIS

Efficacy endpoints will be summarized descriptively by randomized treatment and by visit for subjects within ITT and PPS as per the specifications below. The ITT will be considered as the primary population for primary efficacy analysis and the PPS as supportive; the ITT will be considered as the primary population for key secondary and all other efficacy endpoint analysis. Subgroup analyses may also be performed if sufficient subjects are identified to contribute to such analyses. See Section 4.6 for additional details.

A summary of the analysis populations, associated imputation methods used, and statistical models employed for all efficacy endpoints analyses is shown in Table 5 below. The first analysis set mentioned in each section of Table 5 is to support the primary analysis for the relevant efficacy endpoint.

[redacted]

[redacted]

9.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the proportion of subjects achieving at least a 75% improvement from baseline in the total mNAPSI score at Week 28.

The modified Nail Psoriasis Severity Index (mNAPSI) is a numeric tool for the evaluation of nail psoriasis, which ranges from 0 – 130. Three features or groups of features (pitting, onycholysis and oil-drop dyschromia, and crumbling) of each fingernail will be graded on a scale from 0 to 3. Four features (leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula) will be graded as either 1 (present) or 0 (absent) for each fingernail. See Appendix 8 of the protocol for additional details.

Subjects are required to have a mNAPSI of ≥20 at Screening and Baseline.

An mNAPSI 75 (mNAPSI 90, mNAPSI 100) response is accomplished when the mNAPSI score is reduced by at least 75% (90%, 100%) at a visit compared to the baseline mNPASI score.

9.1.3 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint of mNAPSI75 response at Week 28 will be analyzed using the ITT Set. A Cochran-Mantel-Haenszel (CMH) test will be performed stratified by body weight class (≤90 kg or >90 kg) and prior exposure to TNF-alpha inhibitors (Yes/No) for psoriasis. Common proportion difference between the treatments and the associated 95% confidence interval will be calculated using Miettinen-Nurminen (M-N) stratified body weight class (≤90 kg or >90 kg) and prior exposure to TNF-alpha inhibitors (Yes/No). The p-value from the CMH test comparing tildrakizumab 100 mg with placebo will be reported for inference. If the assumption of Mantel-Fleiss criterion has not been satisfied (less than 5), statistical comparison will be based on GLMM model with treatment group, stratification factors, i.e., body weight class (≤90 kg or >90 kg) and prior exposure to TNF-alpha inhibitors (Yes/No) for psoriasis, visit, treatment group by visit interaction and subjects as the random effect. An unstructured covariance matrix will be used to fit such model. In case, if the model fails to converge, a covariance structure such as compound symmetry or autoregressive model may be used. (PROC GLIMMIX with logit link for logistic regression model).

Observed data after the occurrence of an intercurrent event (ICE) through Week 28 will be handled as a non-responder. Missing values will be imputed using non-responder imputation (NRI). This method corresponds to a composite strategy.

The same analysis will also be conducted for ITT and PP as additional supportive analysis using Observed Cases (OC) where all observed data regardless of the occurrence of any ICE will be included in the analysis as is.

Sensitivity analyses of the primary efficacy endpoint are described in Section 9.3 below.

9.2 Secondary Efficacy Analysis

9.2.1 Estimand and Intercurrent Events for Key Secondary Endpoint

Estimand and intercurrent events for key secondary efficacy analysis (ViSENPsO response) is defined in similar fashion as primary efficacy analysis, as detailed below.

[redacted]

[redacted]

9.2.2 Secondary Efficacy Endpoints

The key and additional secondary endpoints are described in Section 2.3.2. The key secondary endpoint will be included in multiplicity adjustments as described in Section 4.5 .

Key definitions for secondary endpoints are described as following:

[redacted]

Nail Pain NRS (Numeric Rating Scale)

The NRS is a simple assessment tool that subjects will use to report the intensity of their pain during the study in patient diary. Subjects will complete pain assessments by responding, on a scale of 0 to 10, with 0 being 'no pain' and 10 being the 'worst nail pain imaginable', how would he/she rate the worst nail pain experienced during previous 24 hours, on each of the seven (7) consecutive days leading up to the visit. At Screening, pain NRS will be assessed once.

A treatment response in the NRS will be defined two ways:

- achieving at least 3-point decrease from the baseline 7-day average score, defined among subjects with a baseline NRS score of ≥ 3.
- achieving at least 30% reduction from the baseline 7-day average score, defined among subjects with a baseline NRS score of ≥ 3.

Analysis will be performed based on the average of the 7 daily scores leading up to each scheduled visit according to the analysis windows defined in Section 3.3. No less than 4 of the 7 daily observations within the analysis window are required in order to calculate the average score. If subject has less than 4 valid entries, the NRS value will be considered as missing for that analysis visit.

NAPSI (Nail Psoriasis Severity Index)

The NAPSI scale assesses the following items: nail pitting, nail onycholysis and oil-drop dyschromia, nail crumbling, and nail leukonychia, splinter hemorrhages, hyperkeratosis, red spots in the lunula.

A score is 0 if the items are not present, 1 if they are present in 1 quadrant of the nail, 2 if present in 2 quadrants of a nail, 3 if present in 3 quadrants of a nail, and 4 if present in 4 quadrants of a nail. Each nail has a matrix score (0-4) and a nail bed score (0-4), and the total nail score is the sum of those 2 individual scores (0-8) sum of the total score of all involved fingernails is the total NAPSI score for that patient at that time point. The sum of the scores from all fingernails is 0-80.

A NAPSI 75 (NAPSI 90, NAPSI 100) response is accomplished when the NAPSI score is reduced by at least 75% (90%, 100%) at a visit compared to the baseline NAPSI score.

PASI (Psoriasis Area and Severity Index)

PASI is a measure of overall psoriasis severity and coverage. PASI consists of 2 major steps: 1) calculating the BSA covered with lesions and 2) assessment of the severity of lesions. The second step in turn consists of assessing the lesions' erythema (redness), induration (thickness) and scaling. The PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no psoriasis on the body) to 72 (the most severe case of psoriasis). Detailed scoring algorithms for PASI are provided in Appendix 1 PASI Scoring.

Subjects are required to have a PASI score of ≥12 at Screening and Baseline.

A PASI 75 (PASI 90, PASI 100) response is accomplished when the PASI score is reduced by at least 75% (90%, 100%) at a visit compared to the baseline PASI score.

PGA-S (Physician Global Assessment-Skin)

The PGA is used to determine the overall severity of a subject's psoriasis lesions at a given time point. Overall lesions will be graded for thickness, erythema, and. The sum of the 3 scales will be divided by 3 to obtain the final PGA score from 0 to 5.

A PGA-S response is defined as achieving a PGA-S score of "clear" or "almost clear" with at least a 2-point reduction at a visit compared to the baseline.

s-PGA (static Physician's Global Assessment)

A 6-point scale (0=clear to 5=severe) is used for s-PGA. Subjects are required to have a s-PGA score of ≥3 at Screening and Baseline.

9.2.3 Analysis of Secondary Efficacy Endpoints

Binary endpoints

The following binary endpoints will be analyzed in a similar manner as the primary efficacy endpoint based on the analysis population specified in Table 5 in Section 9. A CMH test (rather than M-N methodology) will be used, stratified by prior use of TNF-alpha inhibitors (yes or no) and baseline body weight class (≤90 kg or >90 kg).

- ViSENPsO response at Week 28 (key secondary endpoint)
- ≥ 3-point decrease in Nail Pain NRS score from Baseline at Week 28 in subjects with baseline nail pain NRS score of ≥ 3
- mNAPSI90 at Week 28
- mNAPSI100 at Week 28
- NAPSI75 at Week 28
- NAPSI90 at Week 28
- NAPSI100 at Week 28
- PASI 75 at Week 28
- PASI 90 at Week 28
- PASI 100 at Week 28
- PGA-S response at Week 28

- 30% decrease in Nail Pain NRS score from Baseline at Week 28 in subjects with baseline nail pain NRS score of ≥3

Continuous endpoints

Change from baseline to week 28 in total-fingernail mNAPSI and total-fingernail NAPSI scores (endpoints included in the hierarchical order of Section 4.5) during the double-blinded period will be analyzed based on the ITT population using MI to handle missing data.

MI procedures for continuous efficacy endpoint (total-fingernail mNAPSI and total-fingernail NAPSI scores):

Missing post-baseline total-fingernail mNAPSI or NAPSI scores through Week 28 will be imputed for the ITT separately for each treatment group using the Markov Chain Monte Carlo (MCMC) method. 50 copies of the dataset with monotonic missing pattern will be generated. For each of the 50 datasets, missing values at scheduled visits (Weeks 4, 8, 12, 16, 20, 24, and 28) will be imputed using a monotone regression model including treatment, presence of TNF-alpha inhibitors at baseline (yes or no), baseline body weight class (≤90 kg or >90 kg), baseline mNAPSI or NAPSI score, and mNAPSI or NAPSI scores at the previous scheduled visits. Change from baseline in mNAPSI or NAPSI score will be derived based on the imputed datasets.

Once imputations are made, the week 28 data of each of the 50 complete datasets will be

analyzed using the ANCOVA model with treatment, randomization stratification factors (prior use of TNF-alpha inhibitors (yes or no), Baseline body weight class (≤90 kg or >90 kg)), and baseline value of the relevant endpoint included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula.

NAPSI scores will be imputed using the same method as mNAPSI as stated above with replacement of mNAPSI with NAPSI in the imputation model.

Example SAS code is provided in Section 15.

Change from baseline to week 28 in other continuous endpoints (nail pain NRS and total BSA) during the double-blinded period will be analyzed based on the ITT population using OC.

All continuous endpoints will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization stratification factors (prior use of TNF-alpha inhibitors (yes or no), Baseline body weight class (≤90 kg or >90 kg)), and baseline value of the relevant endpoint included in the model.

Additionally as supportive analysis, they will also be analyzed based on the ITT population for OC using a mixed model for repeated measures (MMRM) procedure that includes fixed effects for treatment, visit, treatment by visit interaction, prior use of TNF-alpha inhibitors

(yes or no), Baseline body weight class (≤90 kg or >90 kg), and baseline value of the relevant endpoint as a covariate, comparing the change from Baseline between tildrakizumab arm and placebo arm (refer to Section 15 15 for MMRM procedures).

- Mean change in nail pain NRS score from Baseline at Week 28
- Mean change in total-fingernail mNAPSI score from Baseline at Week 28
- Mean change in total-fingernail NAPSI score from Baseline at Week 28
- Mean percentage change in total BSA involvement from Baseline to Week 28

Treatment difference between tildrakizumab arm and placebo arm will be reported, along with the associated 95% CI and p-value.

[redacted]

Supportive and sensitivity analyses of the key secondary efficacy endpoint will be conducted in a similar manner as the primary efficacy endpoint and as specified in Table 5. No supportive or sensitivity analyses will be conducted for all other secondary endpoints. Continuous endpoints will be analyzed using MMRM without imputation.

[redacted]

Example SAS code is provided in Section 15.

[redacted]

9.4 Other/Exploratory Efficacy Analysis

9.4.1 Other/Exploratory Efficacy Endpoints

Other efficacy endpoints are described in Section 2.3.3.

Key definitions for other efficacy endpoints are described as following:

DLQI (Dermatology Life Quality Index)

The DLQI is a 10-question questionnaire to assess treatment response on the subject's quality of life, covering 6 domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment. Each question is scored from 0 to 3, giving a possible score range from 0 (no impact) to 30 (maximum impact).

Detailed scoring algorithms for DLQI are provided in Appendix 2 DLQI Scoring.

NAPPA-QoL (Nail Assessment in Psoriasis and Psoriatic Arthritis Quality of Life)

NAPPA-QoL is a 20-item questionnaire describing the QoL with nail psoriasis on the hands and/or feet over the past week. Answers are given in Likert scales from 0 to 4. Factor analysis revealed three scales named 'Signs' (nail status), 'Stigma' (nail impact: stigma and emotional status), and 'Everyday life' (nail impact: everyday life).

Detailed scoring algorithms for NAPPA-QoL are provided in Appendix 3 NAPPA-QoL Scoring.

CGIC (Clinician Global Impression of Change)

The CIGC is a simple questionnaire that reflects a clinician's belief about the efficacy of treatment. The CGIC describes the overall change in patient's nail psoriasis since he/she started taking the study medication: much better, a little better, no change, a little worse, much worse.

CGIS (Clinician Global Impression of Severity)

CIGS is a global index that is used by clinicians to rate the severity of a specific condition in patients (a single-state scale): none, mild, moderate, severe, very severe.

PGIC (Patient Global Impression of Change)

PGIC is a simple questionnaire that reflects a patient's belief about the efficacy of treatment: much better, a little better, no change, a little worse, much worse.

PGIC-P (Patient Global Impression of Change for pain)

PGIC-P is a simple questionnaire that describes the overall change in nail pain: much better, a little better, no change, a little worse, much worse.

PGIS (Patient Global Impression of Severity)

The Patient Global Impression of Severity is a global index used to rate the severity of a specific condition (a single-state scale): none, mild, moderate, severe, very severe.

PCIS-P (Patient Global Impression of Severity for pain)

PGIS-P to evaluate the intensity of nail pain at the post-baseline visits wherein PGIS will also be recorded: none, mild, moderate, severe, very severe.

Inter-rater reliability of the ViSENPsO Scale

For a subset at selected sites, the ViSENPsO will be administered to the same patient by two internal assessors at the Baseline and EoT visits. For this, a psychometric analysis plan will be created, which will detail all the exploratory and correlation analyses between the newly developed ViSENPsO Scale and clinical variables and will be presented separately.

9.4.2 Analysis of Other/Exploratory Efficacy Endpoints

All exploratory endpoints will be summarized using the ITT population using descriptive statistics for all scheduled visits through Week 52.

In addition, subject achieving mNAPSI75 and subjects achieving ViSENPsO response by visit will also be analyzed using the same method as primary/key secondary efficacy endpoints in an exploratory manner.

10 SAFETY ENDPOINTS

The safety and tolerability of the study drugs are determined by reported adverse events (AEs), physical examinations, electrocardiogram results (ECGs), vital signs, and laboratory test results (Hematology, Biochemistry, and Urinalysis), and Columbia-Suicide Severity Rating Scale (C-SSRS).

All safety summaries will be based on the entire SAF.

Following reporting of Week 28 results, a group comprising formerly placebo-treated subjects who migrate to tildrakizumab 100 mg for the remainder of the study will be identified for reporting at the end of the study.

10.1 Adverse Events

The incidence of treatment-emergent AEs (TEAE) will be summarized and tabulated by treatment group, MedDRA (Version 24.0 or higher) System Organ Class (SOC) and Preferred Term (PT). A TEAE is defined as an AE that first occurred or worsened in severity after the first administration of study treatment.

AEs that cannot be definitely determined as occurring prior to first study drug administration will be counted as TEAEs unless either the partial start date or a partial or complete end date indicates the AE as occurring prior to treatment. Partial dates entered in the AE form will be imputed for the purposes of determining whether the record is a treatment emergent adverse event based on the following:

- AE onset dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the month and year of first dosing of study drug, in which case the date will be imputed using the date of first dosing of study drug.
- AE onset dates with missing day and month will be assumed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the year of first dosing of the study drug, in which case the date will be imputed using the date of the first dosing of study drug.
- Partial or missing AE resolution dates will not be imputed.

Several occurrences of the same AE in one subject will be counted once at the worst severity grade. If severity is missing, the event will be classified as of unknown severity for analysis and summarization.

The relationship of each AE to the study drug will be grouped as related (definitely, probably, possibly related) or unrelated (unlikely to be related, unrelated). Several occurrences of the same AE in one subject will be counted once and the one with the closest relationship to study medication will be counted. If an AE is missing the relationship to study medication, the event will be assumed to be related to study drug for analysis and summarization.

AEs will be further categorized by Study Part (1, 2, 3) as follows:

- Part 1 (Day 1 to Week 28): includes all AEs that first occurred or worsened in severity after the first study medication administration, but do not start after the Week 28 study medication administration.
- Part 2 and 3 (Week 28 and beyond): includes all AEs that first occurred or worsened in severity after the Week 28 injection. These will be performed for the final analyses.

Non-TEAEs will be listed only and will not be included for analysis and summarization.

All AEs will be presented in a by-treatment and by-subject listing for Part 1, detailing the verbatim term, SOC, PT, injection site reaction or not, related to study indication or not, start date, stop date, time since most recent dose of IP, severity, outcome, relationship to study drug, action taken regarding study drug, other action taken, seriousness and criteria for seriousness. Serious AEs (SAEs) and TEAEs leading to study medication discontinuation, AEs of Special Interest (AESI), and events of clinical interest (ECI) will also be presented in separate listings.

An AE profile for the SAF will be provided for Part 1, Parts 2 and 3, and overall, which summarizes the subject incidence, by treatment received for the following information:

- Any TEAEs;
- Drug-related TEAEs;
- Any TEAEs with an outcome of death;
- Treatment-emergent SAEs;
- Drug-related treatment-emergent SAEs;
- TEAEs leading to discontinuation of study medication;
- Drug-related TEAEs leading to discontinuation of study medication;
- Any AEs of special interest, including:
    - Injection site reactions
    - Severe infections
    - Malignancies (excluding carcinoma in situ of the cervix).
    - Non-melanoma skin cancer
    - Melanoma skin cancer
    - Major Adverse Cardiovascular Events (MACE)
    - Study treatment-related hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, etc.).

[redacted]

Study treatment-related hypersensitivity reactions will be identified based on Sponsor review of treatment-blinded listings of AE preferred terms prior to declaration of the IA DB freeze.

The number and percentage of subjects with TEAEs will be summarized for each treatment arm and/or in total by SOC and PT. Drug-related TEAEs, TEAEs leading to discontinuation of study drug, drug-related TEAEs leading to discontinuation of study drug, treatment-emergent SAEs, and drug-related treatment-emergent SAEs, AESI and ECI will be summarized in the same manner. For these summaries, subjects with multiple AEs will be counted only once per SOC and PT.

TEAEs by maximum severity and TEAEs by relationship to study treatment, and commonly occurring TEAEs, i.e., those that occur in 1% or more of the subjects in either treatment arm, will be summarized by SOC and PT by treatment received in Part 1, Parts 2 and 3, and overall.

Injection site reactions will be described in a by-subject listing and may be summarized separately if deemed necessary.

COVID-19 related adverse events may also be summarized separately if deemed necessary.

10.2 Clinical Laboratory Evaluation

Absolute values and changes from Baseline of clinical laboratory data (hematology, chemistry, continuous urinalysis parameter, and lipids) will be summarized with descriptive statistics at Baseline, and Week 28 (i.e., Part 1 , and through Week 52 and Week 72 for the final analysis. For the laboratory values which have the normal range (e.g., below/within/above the normal range) or categorical result (e.g., −/±/+), a shift table will display the cross tabulation of the Baseline result category versus the result of the post-treatment period at each visit according to the study part being reported.

All clinical laboratory data relevant to the reporting period (i.e., Part 1 or overall) will be listed by subject. Values outside the normal ranges will be flagged. Flags will describe direction relative to normal range in relevant parameters.

10.3 Vital Signs

Vital signs measurements including temperature, pulse rate, systolic blood pressure, diastolic blood pressure, and respiratory rate at each scheduled visit and changes from baseline during the treatment period will be summarized by treatment arm. Vital signs will also be presented in a shift table displaying the cross tabulation of the Baseline result category versus the result of the post-treatment period at each scheduled visit. The categories of each vital sign parameters are as below:

[redacted]

All vital signs measurements will be listed by subject.

10.4 12-Lead Electrocardiogram (ECG)

The ECG measurements at each scheduled visit (Baseline and Week 52 Visit) and change from baseline during the treatment period will be summarized by treatment arm.

All ECG measurements and the overall interpretation will be listed by subject. Abnormal QTcF values will be flagged in the listing. QT results for subjects having no reported QTcF values will be transformed to QTcF values and flagged in the listing.

10.5 Physical Examinations

The frequency of subjects with abnormal evaluations of body system findings for physical examinations will be summarized by visit and treatment group; abnormal physical examination findings will also be presented in a by-subject listing.

10.6 Other Safety Parameters

The subjects will be assessed for suicidal ideation and behavior using Columbia-Suicide Severity Rating Scale (C-SSRS) at screening, baseline, and each subsequent visit. C-SSRS contains two categories: (1) Suicidal Ideation (questions 1-5), most severe ideation will also be collected; (2) Suicidal behavior (questions 6-10).

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories listed below have been re-ordered from the actual scale in an increasing order of severity from 1 to 10 to facilitate the definitions of the comparative endpoints.

Table 6 C-SSRS Outcomes

Categories
Suicidal Ideation (1-5)
1 – Wish to be dead
2 – Non-specific active suicidal thoughts
3 – Active suicidal ideation with any methods (not plan) without intent to act
4 – Active suicidal ideation with some intent to act, without specific plan
5 – Active suicidal ideation with specific plan and intent
Suicidal behavior (6-10)

Categories
6 – Preparatory acts or behavior
7 – Aborted attempt
8 – Interrupted attempt
Suicidal acts (9-10)
9 – Non-fatal suicide attempt
10 – Completed suicide

The following are numerical scores derived from the above C-SSRS categories.

- Suicidal Ideation Score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.
- Suicidal Behavior Score: The maximum suicidal behavior category (6-10 on the C-SSRS) present at the assessment. Assign a score of 0 if no behavior is present.
- Suicidal Ideation or Behavior Score: The maximum suicidal ideation or behavior category (1-10 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation or behavior is present.

Subjects are also classified into two risk levels:

- Intermediate risk level is indicated by a response of "yes" to Questions 1 to 3 and the absence of a "yes" response to Questions 4 and 5 in suicidal ideation section.
- High risk level is indicated by a response of "yes" to Questions 4 or 5 in the suicidal ideation section, or any positive response in the behavioral section of the C-SSRS.

Change in binary response to the questions from no to yes in any questions will be summarized in a shift table describing baseline vs post-baseline per visit, and worst post-baseline overall. Categorical scores will be analyzed similarly. C-SSRS risk levels are also summarized by visit. Results from the C-SSRS will be listed by subject. Results to Week 28 will be described in the Part 1 analysis, and overall results to Week 52 will be described in the final analysis.

11 COVID-19 PANDEMIC IMPACTED SUBJECTS ASSESSMENT

COVID-19 impacted subjects will be identified from study tracking documentation and event-level impacts will be integrated to the EDC. If a total of 5% or more subjects in analysis population have one or more COVID-19 related event(s) (e.g., missing visits) that impact the primary analysis (defined as any protocol deviations with causality of 'COVID-19' with deviation date on or before Week 28 visit date), then the sensitivity analysis will be performed after excluding these subjects. Events that counted towards 'events exceeding a 5% subject-level incidence' of the relevant analysis set will be presented using descriptive statistics for the incidence of subject-level impacts .

See also Section 6.2 for presentation of COVID-19 pandemic related subject disposition.

13 REFERENCES

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14 DATA-HANDLING RULES

This section describes rules for calculations that would be common to all applicable tables. Some rules specific to a table can be found in the relevant mock-ups.

14.1 Demographics and Baseline Characteristics

1) Age = (Date of informed consent - Date of birth + 1) / 365.25 and truncated to complete years.
2) Conversion factors and calculations for height, weight, and BMI:
   - Height (in cm) = height (in inches) * 2.54
   - Weight (in kg) = weight (in lbs) * 0.4536
   - BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

14.2 Safety

1) For purposes of flagging individual subject data, laboratory test result abnormalities are defined as values above or below the normal range.
2) Conversion factor for temperature:

   Temperature (in °C) = 5/9 (Temperature [in °F]-32).
3) Conversion factors for ECG QT to QTcF if any subjects do not have reported QTcF values but have reported QT and RR values:

   Fridericia formula: $QTcF = QT / (RR^{1/3})$

Appendix 1 PASI Scoring

PASI is evaluated within each of the four body regions: a) head, b) upper limbs, c) trunk, and d) lower limbs;

- Each body area is assigned a multiplier based on BSA (0.1, 0.2, 0.3, and 0.4, respectively).
- Within each body region, a severity score for each of the clinical signs of plaque (erythema [E], induration/thickness [I], and scaling [S]) and an area score will be assigned.
- Lesion(s) within each body region will be scored for individual clinical signs as 0 = Clear, 1 = Mild, 2 = Moderate, 3 = Marked, 4 = Very marked
- The sum of each of the 3 scores for each body region will give 4 separate sums (A).
- Area score (B) will be assigned as
    - 0 = 0%,
    - 1 = >0% - <10%,
    - 2 = 10% - <30%,
    - 3 = 30% - <50%,
    - 4 = 50% - <70%,
    - 5 = 70% - <90%, and
    - 6 = 90% - 100%.
- Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).
- Multiply each of the Subtotals (C) by the body surface area represented by that region (D).
- The total score is the sum of the scores of the individual body regions; it ranges from 0 (no psoriasis on the body) to 72 (the most severe case of psoriasis).

Appendix 2 DLQI Scoring

The Dermatology Life Quality Index (DLQI) questionnaire is an assessment of treatment response on the subject's quality of life to measure how much the scalp psoriasis has affected the subject's life during the previous week. The DLQI questionnaire has 10 questions and 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment), ranging from 0 to 30.

The scoring of DLQI will follow the developer's manual. Specifically:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
- If two or more questions are left unanswered the questionnaire is not scored.
- If question 7 is answered 'yes' this is scored 3. If question 7 is answered 'no' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If "Not relevant" is ticked, the score for Question 7 is 0. If it is answered 'no', but the second half is left incomplete, the score will remain 0.
- If two or more response options are ticked, the response option with the highest score should be recorded.
- If there is a response between two tick boxes, the lower of the two score options should be recorded.
- The DLQI can be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored.

Appendix 3 NAPPA-QoL Scoring

NAPPA-QOL is a 20-item nail specific quality of life questionnaire which assesses specific quality of life conditions in the past week. Answers are given in Likert scales from 0 to 4. For use in clinical trials, a global score including all items without weighting is used and mean values are determined.

The data of NAPPA-QOL are coded with numbers:

- 0 = Not at all
- 1 = Somewhat
- 2 = Moderately
- 3 = Quite a bit
- 4 = Very
- 5 = "does/did not apply to me"
- -9 = missing value

The response "currently not in a relationship" in item 13 is scored as missing. If an item is answered with two or more "x" or by ticking between two checkboxes, it is treated as missing.

The NAPPA-QOL global score is computed by averaging all items. In case more than 25% of the items are missing (5 or more items missing), the score is not computed for the respective patient. The NAPPA-QOL subscales ('signs', 'stigma', 'everyday life') are computed by averaging the respective items. In case more than 25% of the respective items are missing, the score is not computed for the respective patient.

The three subscales are comprised of the following items:

'Signs' (nail status):
3) Reduced strength of nails (e.g. brittle, thin, atrophied or coming off)
4) Symptoms such as hardened, thickened or raised nails
5) Changed appearance of your nails
7) How different do your nails now look?
8) My nail psoriasis makes care of my nails difficult
9) I often catch my nails on things

'Stigma' (nail impact: stigma and emotional status):
14) I avoid touching other people because of the nail psoriasis.
15) I try to hide my nails.
16) I am embarrassed by the way my nails look.
17) My nails look ugly.
18) I have the feeling that other people react negatively to me because of my nail psoriasis.
19) I have the feeling that other people stare at my nails.
20) I feel depressed or less self-confident due to the nail psoriasis.

'Everyday life' (nail impact: everyday life):
1) Itchy fingers/toes
2) Pain or other abnormal sensations in the finger/toes
6) Difficulty in gripping things
10) My nail psoriasis makes working with my hands difficult
11) I cannot lead a normal working life because of my nail psoriasis.
12) My leisure and sports activities are restricted by my nail psoriasis.
13) Nail psoriasis is a burden on my relationship. Or: O currently not in a relationship