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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF SCD-044 IN THE TREATMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACLS	Advanced Cardiac Life Support
ACR	American College of Rheumatology
AE	Adverse Event
ALC	Absolute Lymphocyte Counts
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease-2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-Reactive Protein
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GGT	Gamma Glutamyltransferase
HAQ-DI	Health Assessment Questionnaire of Disability
HBsAg	Surface Antigen of The Hepatitis B Virus (HBV)
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL	High-Density Lipoproteins
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IGA	Investigator's Global Assessment
INR	International Normalized Ratio
ITT	Intent to Treat
LDL	Low-Density Lipoprotein
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
mNAPSI	Modified Nail Psoriasis Severity Index

NRS	Numeric Rating Scale
OCT	Optical Coherence Tomography
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PP	Per Protocol
PPPGA	Palmoplantar Physician Global Assessment
PRES	Posterior Reversible Encephalopathy Syndrome
PsA	Psoriatic Arthritis
PSSD	Psoriasis Symptoms And Signs Diary
PT	Prothrombin Time
PtAP	Patient Assessment of Pain
PtGA	Patient Global Assessment of Disease Activity
QTcF	QT Corrected by Fridericia's Formula
RF	Rheumatoid Factor
S1P	Sphingosine-1-Phosphate
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
VZV	Varicella Zoster Virus
WBC	White Blood Cells

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol "A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of SCD-044 in the Treatment of Moderate to Severe Plaque Psoriasis", version 4.1, dated July 28, 2023.

Sun Pharmaceutical Industries Ltd. is developing a Sphingosine 1-phosphate (S1P) receptor agonist, SCD-044 to treat moderate to severe plaque psoriasis. The current study is a Phase IIb dose ranging study to assess the efficacy and safety of SCD-044 in the treatment of moderate to severe plaque psoriasis.

2. OBJECTIVES AND ESTIMANDS

2.1 Primary Objective

The primary objective of this study is to determine the effect of SCD-044 treatment on moderate to severe plaque psoriasis, as measured by proportion of subjects showing at least 75% improvement in Psoriasis Area and Severity Index (PASI) at Week 16.

2.2 Primary Estimand

The primary estimand is defined as follows:

Population of interest	Subjects with moderate to severe plaque psoriasis
Outcome Measure/Endpoint	Achieving at least 75% improvement in PASI at Week 16
Treatment	SCD-044 [redacted] and placebo once daily
Intercurrent Event	• Use of prohibited medications (as determined during blinded data review) • Early treatment discontinuation due to lack of efficacy, protocol deviation or AEs Composite strategy will be applied to these intercurrent events and the subjects with intercurrent events will be treated as non-responders.
Population-level Summary Measure	Difference in proportions between each the active treatment arms and placebo arm

2.3 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of SCD-044 as measured by proportion of subjects achieving predefined improvement in Investigator's Global Assessment (IGA) of disease severity

- To evaluate the efficacy of SCD-044 as measured by proportion of subjects achieving predefined improvement in Psoriasis Area and Severity Index (PASI) and change in PASI scores over the treatment period
- To assess the effect of SCD-044 on the subject reported outcome measure of Psoriasis Symptoms and Signs Diary (PSSD)
- To assess the effect of SCD-044 on quality of life, as measured by Dermatology Life Quality Index (DLQI)
- To evaluate the efficacy of SCD-044 as measured by change in body surface area (BSA) involvement over the treatment period
- To assess the effect of SCD-044 on Patient Global Impression of Severity (PGIS)
- To assess the effect of SCD-044 on Patient Global Impression of Change (PGIC)
- To evaluate the PASI75 response in non-responders at low dose and intermediate dose when switched to high dose of SCD-044
- To assess the safety and tolerability of SCD-044 in subjects with moderate to severe plaque psoriasis
- [redacted]

2.4 Key Secondary Estimand

The key secondary estimand is defined similar to the primary estimand as follows:

Population of interest	Subjects with moderate to severe plaque psoriasis
Outcome Measure/Endpoint	Achieving an IGA of '0' or '1' with at least 2-grade reduction from baseline at Week 16
Treatment	SCD-044 [redacted] and placebo once daily
Intercurrent Event	• Use of prohibited medications (as determined during blinded data review) • Early treatment discontinuation due to lack of efficacy, protocol deviation or AEs. Composite strategy will be applied to these intercurrent events and the subjects with intercurrent events will be treated as non-responders.
Population-level Summary Measure	Difference in proportions between each the active treatment arms and placebo arm

2.5 Tertiary Objectives

The tertiary objectives of this study are:

- To evaluate the efficacy of SCD-044 in the treatment of Scalp psoriasis as measured by Scalp IGA
- To evaluate the efficacy of SCD-044 in the treatment of nail psoriasis as measured by modified Nail Psoriasis Severity Index (mNAPSI) scores

- To evaluate the efficacy of SCD-044 in the treatment of psoriatic arthritis as measured by American College of Rheumatology (ACR) response
- To evaluate the efficacy of SCD-044 in the treatment of Palmoplantar Psoriasis as measured by Palmoplantar Physician Global Assessment (PPPGA) score

2.6 Exploratory Objectives

The exploratory objectives of this study are:

- [redacted]
- [redacted]
- [redacted]
- To evaluate the effect of SCD-044 on subject reported outcome of itching associated with Psoriasis
- To evaluate the effect of SCD-044 on Psoriatic Arthritis (PsA)-related Pain (Patient Assessment of Pain (PtAP)
- [redacted].

3. STUDY OVERVIEW

3.1 Study Design

Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be assigned to treatment with the investigational products or placebo control according to a randomization scheme and [redacted] schedule.

- **Part I**: 16 weeks; Subjects will be randomized to placebo, Low dose ([redacted] Intermediate dose ([redacted] or High dose ([redacted] of SCD-044 in [redacted] to assess primary and secondary endpoints at Week 16
- [redacted]

[redacted]

- [redacted] esponse of [redacted] at Week 28 will
- [redacted]

[redacted]

Clinical Evaluations will be performed at:

[redacted]

- [redacted]
- [redacted]

[redacted]

Phone or in person contacts may be scheduled [redacted] to collect information on concomitant medication, compliance with the study drug use, health changes (AEs & AESI), queries for PML and PRES and to provide instructions.

[redacted]

Subjects will be admitted into the study after informed consent has been obtained. An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Early Discontinuation will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures scheduled for that Unscheduled Visit will be performed. Subjects who are discontinued early from the study must attend the Follow-up visit 4 weeks after the date of Early Discontinuation.

If necessary due to the coronavirus disease-2019 (COVID-19) pandemic, Visits 17, and 18 may have assessments done at home or remote visit. Remote visits must be discussed and

consulted with the Contract Research Organization's (CRO) and the Sponsor's Medical Monitor (MM) before planning. Scheduled blood collection (for these visits only) may be waived if the individual subjects have not had a clinically significant changes or undesired trend in lab or chemistry values prior to Visit 15. Subjects that have remote assessments or delayed Visits 17, or 18 will be recorded in the electronic case report form (eCRF) and noted as a minor protocol deviation.

COVID-19 related protocol deviations will be analyzed to assess whether a protocol amendment or other modifications are needed. The Sponsor together with investigators plan to assess the COVID-19 situation to evaluate the benefit: risk of the study on an ongoing basis.

Changes in study visit schedules, missed visits, or subject discontinuations may lead to missing information (e.g., for protocol-specified procedures). It is important to capture specific information in the subject records that explains the basis of the missing data, including the relationship to COVID-19, for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19).

A subset of eligible subjects will participate in photographic evaluation.

Randomization and re-randomization will be stratified by [redacted]. Approximately, the same number of male and female subjects will be enrolled between treatment groups. [redacted]. Approximately, the same number of subjects who have prior exposure to biologics therapy for psoriasis will be enrolled between treatment groups.

The assigned Investigational Product will be administered orally once a day. Subjects will be required to use diaries to document the date of study treatments, any missed treatments and the occurrence of all adverse events.

The duration of each subject's participation in the study will be approximately 56 weeks (393 days).

If the Principal Investigator determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure and the subject may be treated using the standard care.

Subjects with conditions or treatments that may affect cardiovascular safety (e.g., heart rate less than [redacted] history of uveitis or history of pulmonary conditions such as active severe respiratory disease (e.g., COPD, tuberculosis or pulmonary fibrosis, severe asthma or asthma requiring regular treatment with oral steroids) will be excluded due to the known mechanism-based AEs within this class which may expose such subjects to unwarranted excess risk for a condition with available alternatives.

[redacted]

[redacted]

[redacted]

3.3 Randomization and Unblinding Procedures

In order to maintain the study blind, the randomization schedule will be generated by a third party. Randomization will be performed according to a computer-generated randomization scheme. [redacted]

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

[redacted]

  - [redacted]

4. STUDY ENDPOINTS/OUTCOMES

4.1.1 Primary endpoint

The primary endpoint is the proportion of subjects with at least 75% improvement in PASI (PASI75) at Week 16.

4.2 Key secondary endpoint

Key secondary endpoint of this study is the proportion of subjects achieving IGA of "clear" (0) or "almost clear" (1) with at least two-grade reduction from baseline to Week 16.

4.3 Other secondary endpoints

The other (non-key) secondary endpoints of this study are:

- [redacted]
- [redacted]
- [redacted]
- Change from Baseline in PSSD score at Weeks 16, [redacted] and 52
- Change from Baseline in DLQI score at Weeks 16, [redacted] and 52
- Proportion of subjects with DLQI score of 0 or 1 at Weeks [redacted] 52.
- Proportion of subjects with IGA score of "clear" or "almost clear" with at least two-grade [redacted]
- [redacted]
- Change from baseline in BSA involvement at Weeks [redacted] and 52
- Change from baseline in PGIS at Weeks [redacted] and 52
- Proportion of subjects with improvement in PGIC at Weeks [redacted] 52
- [redacted]
- Proportion of non-responders (<PASI75) at Week 16 in the low and intermediate dose groups who achieve a PASI75 response at Week [redacted] Week 52 after switch over to high dose
- [redacted]
- Frequency, type, and severity of adverse events (AEs)

4.4 Tertiary endpoints

Tertiary endpoints of this study are:

- Proportion of subjects with Scalp IGA "clear" or "almost clear" with at least two-grade reduction from baseline at Weeks [redacted] and 52 among subjects with a baseline Scalp IGA score of ≥3
- Proportion of subjects with nail psoriasis (baseline mNAPSI score of ≥20) who achieve at least a 75% improvement from baseline in total fingernail mNAPSI at Weeks [redacted] and 52
- Proportion of psoriatic arthritis subjects who achieve ACR20 response at Weeks [redacted] and 52
- Proportion of subjects with PPPGA score of 0 or 1 at Weeks [redacted] and 52 among subjects with a baseline PPPGA score of ≥3

4.5 Exploratory endpoints

Exploratory endpoints include:

- [redacted]
- [redacted]
- [redacted]
- Proportion of subjects achieving ≥ 4-point improvement in Itch Numeric Rating Scale (NRS) from baseline at Weeks [redacted], and 52 among subjects with a baseline Itch NRS of ≥4
- Proportion of subjects achieving ≥ 4-point improvement in Scalp Itch NRS from baseline at Weeks [redacted] and 52 among subjects with a baseline Scalp Itch NRS of ≥4
- Change from baseline in subject global assessment of PtA-P at Weeks [redacted] and 52 among subjects with PsA at baseline
- [redacted]

5. ANALYSIS POPULATIONS

5.1 Safety Population

The Safety Population will consist of all subjects who were randomized into the study and dispensed study drug. This population will be the primary population for the safety analysis. Subjects will be analyzed according to the actual treatment received.

5.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will consist of all randomized subjects regardless of whether they received the investigational product. This population will be the main population for the efficacy analyses. Subjects will be analyzed according to the treatment they were randomized to receive.

5.3 Per-Protocol (PP) Population

The Per-Protocol (PP) Population will consist of all ITT subjects who meet all inclusion/exclusion criteria, complete Part I of the study and have no protocol violations that affect proper administration of the treatment or accurate evaluation of its effectiveness. For more information on protocol violations see section 6.6. This population will be the supportive population for the efficacy analyses. Subjects will be analyzed according to the treatment they were randomized to receive.

6. STATISTICAL METHODS OF ANALYSIS

6.1 General Principles

The statistical analyses will be performed using SAS® Version 9.4 (or higher). All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by subject and visit/time point where appropriate. The summary tables will be stratified by, or have columns corresponding to, treatment groups (see section 6.1.1).

The total number of subjects in the treatment group (N) under the specified population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median, and maximum. Number of subjects with missing values will also be displayed, but only if non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data. The standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be displayed. The count [n] indicates the actual number of subjects in a particular category, which should always be less than or equal to the total number of subjects in the respective study group with known (non-missing) category [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise specified, all percentages will be expressed to one decimal place.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated.

Baselines will be defined separately for Part I and Part II.

- Part I Baseline is defined as the last assessment, scheduled or not, prior to the first dose of the study drug of the study drug in Part I, unless otherwise specified.
- Part II Baseline is defined as the last assessment, scheduled or not, prior to the first dose of the study drug in Part II. Part II baseline will be used in analysis of findings collected in Parts II, III and IV for subjects who were re-randomized in Part II to another treatment (i.e. SCD-044 [redacted] or [redacted] after being treated with Placebo in Part I or to SCD-044 [redacted] after being treated with SCD-044 [redacted] or [redacted] in Part I). Throughout this SAP, if the word "baseline" is used without qualification "Part I" or "Part II", it will refer to Part I baseline.

In by-visit summaries, only data collected on scheduled visits/timepoints will be summarized. Data from unscheduled assessments will be included in listings and may be used in determination of baseline if applicable.

Relative days will be calculated relative to date of first dose of the study drug. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug+1.

For assessment before the day of first dose of the study drug:

Relative Day = Date of Assessment – Date of First Dose of Study Drug.

All dates will be displayed in DDMMMYYYY format.

6.1.1 Treatment Groups

Data collected up to Week 16 visit will be analyzed by treatment groups based on the subject's treatment in Part I of the study:

- Placebo

- SCD-044 [redacted]
- SCD-044 [redacted]
- SCD-044 [redacted]

Efficacy data collected after Week 16 visit (i.e., Parts II-IV), as well as disposition and compliance in Parts II-IV, will be analyzed by treatment groups based on the responder status at the end of Part I (Week 16) (i.e., ≥ PASI50 or <PASI50), the subject's treatment in Part I and the subject's treatment in Part II of the study:

- Part I Responders
  - Placebo/SCD-044 [redacted]
  - Placebo/SCD-044 [redacted]
  - SCD-044 [redacted]
  - SCD-044 [redacted]
  - SCD-044 [redacted]
- Part I Non-Responders
  - Placebo/SCD-044 [redacted]
  - Placebo/SCD-044 [redacted]
  - SCD-044 [redacted]
  - SCD-044 [redacted]

Safety data collected after Week 16 visit (i.e., Parts II-IV) will be analyzed by treatment groups based on the subject's treatments in Part I and in Part II:

- Placebo/SCD-044 [redacted]
- Placebo/SCD-044 [redacted]
- SCD-044 [redacted]
- SCD-044 [redacted]
- SCD-044 [redacted]
- SCD-044 [redacted]
- SCD-044 [redacted]

Adverse events and concomitant medications will be additionally analyzed for the entire study. Details are provided in the sections 6.11.1 and 6.11.6.

6.1.2 Adjustment for multiplicity

No adjustment for multiplicity will be needed for the analysis of the primary and key secondary endpoints due to the step-down testing approach described below in this section. P-values for other endpoints, if calculated, will be presented nominally, without multiplicity adjustment. No inferences will be drawn from these p-values.

[redacted]

6.1.3 Handling of Withdrawals and Missed Data

In the primary analysis of the primary and the key secondary endpoint subjects with intercurrent events will be treated as non-responders and other missing values will be imputed using multiple imputation approach. See section 6.8.1 for more details. Last Observation Carried Forward (LOCF) and Active Treatment Worst Case (ATWC) imputations as well as tipping-point analysis will be explored in the sensitivity analyses (see section 6.8.2.2). All other endpoints will be summarized as collected without imputations and without any special handling for the intercurrent events.

6.2 Subject Disposition

Disposition will be summarized for Part I, Part II, Parts III/IV, and the study overall.

For Part I, the number of subjects who were screened, were screen failures, were randomized to treatment, included in the Safety, ITT and PP, completed Part I (i.e., attended Week 16 visit) and prematurely discontinued from the study during Part I (along with the reasons for discontinuation), as well as found to be non-responders and randomized to be discontinued after Part I will be presented. Additionally, if subject eligible to continue to Part II discontinues the study right after completion of Part I without being re-randomized for Part II, such subjects will also be summarized by reason for discontinuation.

For Part II, the summary will include the subjects who were re-randomized for Part II. It will present the number and percentage of subjects who were re-randomized to continue in Part II, completed Part II (i.e., attended Week 28 visit) and prematurely discontinued from the study during Part II (along with the reasons for discontinuation) as well as found to be non-responders and discontinued after Part II. Additionally, if a subject who is eligible to continue to Part III discontinues the study right after completion of Part II without receiving any study drug in Part III, such subjects will also be summarized by reason for discontinuation.

For Parts III/IV, the summary will include the subjects who were eligible to continue to Part III at Visit 16. It will present the number and percentage of subjects who were eligible to continue in Part III, completed Part III (i.e., attended Week 52 visit) and prematurely discontinued from the study during Part III (along with the reasons for discontinuation) and separately prematurely discontinued from the study during Part IV (along with the reasons for discontinuation).

For the study overall, the summary will present the number of subjects who were screened, were screen failures, were randomized to treatment, included in the Safety, ITT, and PP, attended the visits at Weeks 16, 28, 52 and 54, completed the study and prematurely discontinued from the study at any time (along with the reasons for discontinuation).

All disposition information will be listed. Also, a listing of enrollment details will provide the date of informed consent and inclusion/exclusion criteria not met, if any.

6.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will include:

- age
- sex
- race

- ethnicity
- baseline height, weight, and body mass index (BMI)
- time since psoriasis diagnosis (years)
- whether the subject took any prior biologic therapy for psoriasis
- whether the subject has scalp, palmoplantar, nail psoriasis or psoriatic arthritis (PsA) or other types of psoriasis.
- whether the subject meets Classification of Psoriatic Arthritis (CASPAR) criteria
- Baseline PASI score
- Baseline BSA affected %
- Baseline IGA

Descriptive statistics will be presented for continuous variables. Frequency counts and percentage will be presented for categorical variables. Height will be presented in centimeters, weight in kilograms and BMI in kg/m^2.

Age will be derived from Informed Consent Date and Date of Birth as the number of whole years between those two dates.

These analyses will be performed for the ITT population.

All demographic parameters and baseline characteristics will be presented in the by-subject listings.

6.4 Medical History

Medical history will be summarized by Medical Dictionary of Regulatory Activities (MedDRA), Version 25.0, System Organ Class and Preferred Term. One subject will be counted once for each applicable Preferred Term and System Organ Class. This summary will be performed for the ITT population. All medical history information will be listed.

6.5 Ophthalmological History

Number and percentage of subjects with each finding of past ocular history and each type of ocular surgery as collected at the Ophthalmological History eCRF will be presented by treatment group.

All ophthalmological history conditions and surgeries will be listed.

6.6 Protocol Deviations

Protocol deviations will be derived algorithmically as well as reported by sites. A subset of protocol deviation will be classified as affecting proper administration of the treatment or accurate evaluation of its effectiveness and thus excluding from the PP population. Specific deviation, their exclusion status and rules for their algorithmic detection are defined in the separate Protocol Deviations Specification document.

All reasons for exclusion from the PP population will be summarized by reason category and treatment group and listed. This analysis will be performed for the ITT population. The final

determination of which protocol deviations exclude subjects from the PP population will be made by the sponsor during the blinded data review prior to the database lock.

6.7 CASPAR Criteria

All subjects with a medical history of PsA reported at the screening or baseline will be assessed to establish if there is a diagnosis of PsA per the CASPAR criteria. The diagnosis of PsA will be done by a rheumatologist or an orthopedist, or a qualified trained designee (not applicable at sites where an independent assessor experienced in performing joint assessments is not available). According to CASPAR, the establishment of the diagnosis of PsA requires the presence of inflammatory joint disease (peripheral, axial or enthesitis) with at least three points from the following features: evidence of skin psoriasis (current psoriasis was assigned a score of 2, while history of psoriasis or familial history of psoriasis were assigned a score of 1 each, as were all the other features), psoriatic nail dystrophy, rheumatoid factor negativity, dactylitis, and characteristic radiological evidence.

Results from CASPAR criteria evaluation will be listed.

6.7.1 Study Drug Exposure and Compliance

Duration of exposure will be defined separately for each treatment group, by study part (Part I and Parts II/III) and overall. Duration of exposure in each study part will be calculated as [redacted] The date of the last dose in the study will be collected at the End of Study eCRF. For subjects staying on the same dose throughout the study, total duration of exposure in the study will be defined as the sum of their durations of exposure in Part I and Part II/III.

Total dose of SCD-044 will be calculated based on the number of tablets taken as collected at the Study Product Accountability eCRF. The strength of each tablet will be assumed to follow the protocol-defined [redacted] schedule. Average daily dose of SCD-044 will be calculated as Total dose taken / Duration of Exposure.

Compliance will be calculated for maintenance periods only and separately for Part I and Parts II/III as [Total number of tablets of any strength taken] / [Planned number of tablets] *100%.

Planned number of tablets will be defined as follows:

- For Part I maintenance period:
  - [redacted]
- For Part II/III maintenance period:
  - [redacted]

- [redacted]

Date of discontinuation will be defined as the date of early termination visit, if one occurred, otherwise the discontinuation date collected on the End of Study eCRF.

If Total number of tablets of any strength taken cannot be determined, the compliance will be missing.

Compliance in the maintenance periods will be classified as <75%, 75%-125% and >125%. Subjects with compliance <75% or >125% will be considered non-compliant with the study medication.

Duration of exposure, average daily dose and compliance will be summarized descriptively by treatment group for the Safety population.

Number and percentage of subjects who underwent re-[redacted] will be presented separately for Part I and Parts II/III by treatment group for the Safety population. Number of missed doses in the [redacted] period will be summarized descriptively separately for Part I and Parts II/III by treatment group for the Safety population.

6.8 Efficacy Analyses

6.8.1 Imputation of the primary and key secondary endpoints

All subjects in the ITT population with the following intercurrent events prior to Week 16 will be imputed as non-responders for both the primary endpoint and key secondary endpoint.

- taking prohibited medications prior to Week 16
- discontinuing from the study due to lack of efficacy, protocol deviation or AE prior to Week 16

Subjects who did not have intercurrent events prior to Week 16, and either do not have a Week 16 PASI assessment or do not have a PASI baseline will be referred to as “subjects missing at random” for the primary endpoint. Similarly, subjects who did not have intercurrent events prior to Week 16, and either do not have a Week 16 IGA assessment or do not have an IGA baseline will be referred to as “subjects missing at random” for the key secondary endpoint.

The PASI values of these subjects will be imputed using multiple imputations (MI) approach under the “missing at random” (MAR) assumption. For each subject who is “missing at random” in the ITT population 50 imputations will be performed using Fully Conditional Specifications (FCS) regression imputation model with the factors for gender, prior biologic therapy (Yes/No), PASI score at baseline and weeks 4, 8, 12 and 16. All subjects in the ITT population will be used in the model. Imputed PASI scores will be rounded to 1 decimal place and restricted to the range 0 to 72. For all imputed record PASI75 response will be calculated based on the imputed PASI value using the regular PASI75 definition, i.e. 75% reduction from baseline in the PASI score. See section 11.4.1 for sample SAS code.

The key secondary endpoint values (i.e. the binary outcomes of whether the subject achieved the IGA response or not) will also be imputed using multiple imputations (MI) approach under the “missing at random” (MAR) assumption. For each subject who is “missing at random” in

the ITT population 50 imputations will be performed using Fully Conditional Specifications (FCS) logistic regression imputation model with the factors for gender, prior biologic therapy (Yes/No), IGA grades at baseline and weeks 4, 8, and 12. All subjects in the ITT population will be used in the model. See section 11.4.2 for sample SAS code.

6.8.2 Analysis of the primary and key secondary endpoints

6.8.2.1 Primary analysis

The primary analysis will be performed on the ITT population.

For both primary and key secondary endpoint the number and percentage of subjects achieving the endpoint will be provided based on the subjects with observed endpoint or with intercurrent events (imputed as non-responders), i.e. excluding the subjects who are "missing at random".

The comparisons between each active group and the placebo group will be performed pairwise. Each comparison will be done using Cochran-Mantel-Haenszel (CMH) test stratified by gender and prior biologic therapy (Yes/No). If all strata have no subjects in one of the treatment groups, a value of 0.1 will be added to all cells in the corresponding table in order to prevent dividing by 0, as suggested in Greenland and Robins (1985). The Breslow-Day test with Tarone's adjustment for homogeneity of strata will also be performed.

This analysis will be performed on each multiple-imputed set of records and then the results will be pooled as described below.

The estimates of Mantel-Haenszel common risk (response rate) difference between each active dose group and placebo, along with 95% confidence interval, will be pooled assuming the difference is approximately normally distributed, using Rubin's rule as described in Ratitch, Lipkovich and O'Kelley (2013).

The CMH test statistics as well as the Breslow-Day test statistic will be pooled using the Wilson-Hilferty transformation method from Ratitch, Lipkovich and O'Kelley (2013) and the pooled p-value will be provided.

If the pooled p-value of the Breslow-Day test is ≥ 0.05, the treatment-by-strata interaction is not significant. In the case of heterogeneity between the strata, in-depth analysis will be conducted to understand the source of the interaction; CMH test without stratification will be used then instead of the stratified CMH test.

See sections 11.4.3, 11.4.4, 11.4.5 and 11.4.6 for sample SAS code.

Tests for superiority over placebo for the primary and the key secondary endpoint will be following the step-down approach as described in section 6.1.2.

6.8.2.2 Sensitivity analyses

The following sensitivity analyses will be performed to explore the effects of missing data on the primary endpoint and key secondary endpoint:

1. Analysis similar to the primary analysis on the ITT population, but without multiple imputations with "missing at random" endpoint values and values after intercurrent events imputed using Last Observation Carried Forward (LOCF) approach. For this analysis the latest available post-baseline assessment of PASI or IGA will be carried

forward to impute missing Week 16 assessments. Subjects with missing baseline or no post-baseline assessment prior to Week 16 will be excluded from this analysis. Additionally for subjects with intercurrent events the last available post-baseline assessment obtained prior to the start of the intercurrent event will be used to impute Week 16 assessment. If no such assessment is available, the subject will be excluded from analysis.

2. Analysis similar to the primary analysis on the ITT population, but without multiple imputations with "missing at random" endpoint values and values after intercurrent events imputed using Active Treatment Worst Case (ATWC) approach. For this analysis any subjects in the Placebo group with missing response or with an intercurrent event will be imputed as responders, while any subjects in any active treatment group with missing response or with an intercurrent event will be imputed as non-responders.
3. Tipping point analysis. This analysis will consist of a series of analyses similar to the primary analysis of the primary and key secondary endpoints with varying proportions of subjects who are "missing at random" imputed as responders or non-responders. The analysis will be performed for each active treatment group vs. placebo and for each combination of X1, the percentage of subjects "missing at random" in the placebo group and X2, the percentage of subjects "missing at random" in the active group. Both X1 and X2 will range from 0% to 100% in steps of 20%.

For each pair of (X1, X2), X1% of subjects will be randomly drawn from the subjects "missing at random" in placebo group and X2% of subjects will be randomly drawn from the subjects "missing at random" in the active group. These randomly selected X1% subjects in the placebo and X2% subjects in the active group will be imputed as responders. The remaining subjects "missing at random" will be imputed as non-responders. Analysis then will be conducted using the combined observed data and imputed data for each treatment group using the CMH test as described for the primary analysis in section 6.8.2.1. The random draw procedure will be repeated 49 times for each pair of (X1, X2) and the median p-value for the active vs. placebo comparison will be used for the conclusion. The estimate of the CMH common risk (response rate) difference between the treatment groups associated with the p-value selected as median will also be shown. If the same median p-value is obtained in more than one of the 49 random draws, the largest difference will be selected. The random seed for the draw will be preset as 441914 to ensure the analysis is repeatable and amenable to validation via double programming. If one pair of X1 and X2 is found to reverse the study conclusion (i.e., median p-value > 0.05 [tipping point analysis will be performed only if the primary analysis reached p-value $\leq$ 0.05]), then these parameters will be the tipping points.

6.8.2.3 Supplementary analyses

The following supplementary analyses will be performed:

1. Analysis similar to the primary analysis, but on the Per Protocol population using observed cases only with no imputations.
2. The primary and key secondary endpoint will be analyzed using generalized linear mixed model for repeated measures with fixed effects for treatment, visit (time

variable), treatment by visit interaction, gender and prior biologic therapy (yes/no). Visits 7, 8, 9 and 10 will be used. Visit is random effect within Subject with covariance structure. The model will be used to estimate the probability of response (expressed as percentage) at each visit with its 95% confidence interval. Odds ratio for response at Visit 10 (Week 16) for each active treatment vs. placebo with its 95% confidence interval will also be presented with the p-value for the hypothesis of no difference. See section 11.4.7 for details and sample SAS code.

6.8.2.4 Subgroup analyses

The primary analysis of the primary and key secondary endpoints will also be repeated by subgroups:

[redacted]

In the subgroup analysis by gender and prior biologic therapy the subgroup factor will not be used as stratification factor in the CMH test.

The Breslow-Day test will be performed for each subgrouping variables in order to verify the homogeneity of endpoints. In the case of sparse data non-stratified CMH test will be used instead of the stratified CMH.

6.8.3 Analysis of other endpoints

All other endpoints will be summarized using the ITT population.

6.8.3.1 Continuous endpoints

Continuous endpoints such as change from baseline and/or percent change from baseline in PASI, PSSD score, DLQI score, BSA involvement, Pain VAS, mNAPSI score will be summarized descriptively by visit and treatment group.

In the analyses of change from baseline and percent change from baseline above, Part II baseline will be used for the groups switching the treatment in Part II (Placebo/SCD-044 [redacted] Placebo/SCD-044 [redacted] SCD-044 [redacted] and SCD-044 [redacted] while Part I baseline will be used for the treatment groups staying on the same treatments throughout the study.

Change from baseline in PASI score will also be summarized with a Mixed Model for Repeated Measures (MMRM) that will include fixed effects for treatment, visit (time variable), treatment by visit interaction, gender, prior biologic therapy (yes/no), and Baseline value as a covariate. Visit is random effect within Subject with covariance structure. Unstructured covariance matrix will be assumed and Kenward-Roger method for computing the denominator degrees of freedom will be used. If the model fails to converge with the unstructured covariance matrix, the following covariance matrix types will be tried in order until convergence is achieved: heterogeneous Toeplitz (TOEPH), heterogeneous first-order auto-regressive (ARH(1)), Toeplitz (TOEP), first-order auto-regressive (AR(1)), compound symmetry (CS). Data up to Week 16 will be used in this analysis. The model will be used to estimate treatment LS Means of the endpoint at Week 16 as well as LS mean differences for

each SCD-044 dose vs. Placebo with 95% confidence interval and p-value for the hypothesis of no difference. These analyses will be considered supportive.

PASI total score, total percentage of BSA affected and Pain VAS are collected directly on the eCRF. DLQI, PSSD and mNAPSI scores are calculated as follows:

1. DLQI. The scoring of each question is as follows: Very Much or Yes = 3, A lot = 2, A little = 2, Not relevant or Not at all or No = 0. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.
2. PSSD. The questionnaire consists of 11 items scored using a 0-10 numerical rating scale. The summary score is the sum of item scores, and a higher score indicates more severe disease.
3. mNAPSI. The scale consists of 7 assessments for each fingernail. The total score is the sum of items scores for all assessments and all fingernails. It can range from 0 to 130 (maximum of 13 for each fingernail), with higher mNAPSI scores denoting more severe disease activity.

6.8.3.2 Binary endpoints

Binary endpoints include:

- PASI50, PASI75, PASI90, PASI100 responses (i.e. reduction of at least 50%, 75%, 90% and 100% from baseline in PASI)
- IGA response (achieving IGA score of “clear” or “almost clear” with at least two-grade reduction from baseline)
- achieving PGIC improvement,
- Scalp IGA response (achieving Scalp IGA score of “clear” or “almost clear” with at least two-grade reduction from baseline).
- mNAPSI response (achieving at least a 75% improvement from baseline in total fingernail mNAPSI)
- ACR20 response (see the definition in the next section)
- achieving PPPGA score of 0 or 1
- achieving DLQI scores of 0 or 1
- achieving ≥ 4-point improvement in Itch NRS from baseline
- achieving ≥ 4-point improvement in Scalp Itch NRS from baseline.

Note that for all binary endpoints above that involve change from baseline or percent change from baseline, Part II baseline will be used for the groups that switch treatment in Part II, while Part I baseline will be used for the groups that stay on the same treatment throughout the study.

Number and percentage of subjects achieving these endpoints will be presented by treatment group along with 95% confidence interval for percentages based on binomial proportion.

Additionally shift tables will be created for IGA presenting shifts from baseline to post-baseline visits in Part I and Part II separately.

6.8.3.3 American College of Rheumatology ACR20 Response Definition

ACR response assessments will be performed only in subjects who meet the CASPAR Criteria (see Section 6.7). The ACR components evaluations will be used to calculate the subject's ACR response criteria (ACR20 / 50 / 70). ACR20 response indicates a decrease of at least 20% in both the number of tender and swollen joint counts, as well as a 20% improvement in at least three of five scores of individual components:

1. Health Assessment Questionnaire of disability (HAQ-DI).
2. Patient global assessment of disease activity (PtGA) on VAS of 0 to 100.
3. Patient assessment of pain (PtAP) on VAS of 0 to 100.
4. Physician global assessment of disease activity (PGA) on a VAS of 0 to 100.
5. C-reactive protein (CRP) level, mg/dL.

In Part II changes in the ACR20 definition will be taken relative to the Part II baseline for groups that switch treatment in Part II, and relative to the Part I baseline for the other groups.

See appendix 11.3 for detailed instructions on calculating HAQ-DI score.

6.8.3.4 Categorical endpoints

Categorical endpoints include IGA, Scalp IGA, PPPGA, PGIC and PGIS. Number and percentage of subjects with each category of response will be presented by treatment group and visit. Additionally, for PGIS shifts from baseline to each post-baseline visit will be presented.

6.8.3.5 Time to PASI75 and IGA responses

Time to achieve PASI75 and time to achieve IGA response will be summarized separately for the Part I of the study, for the Parts II and III of the study for subjects re-randomized at Week 16 and for the study overall for subjects receiving the same treatment throughout the study.

In the analysis of Part I subjects will be analyzed by treatment groups based on the treatment that the subject received in Part I (see Section 6.1.1). Time to achieve PASI75 will be defined as the number of weeks from the day of the first dose of the study drug to the first PASI75 assessment in Part I (i.e., up to and including Week 16 visit) when PASI75 is achieved. For subjects who never achieve PASI75 in Part I the time will be censored at the last PASI75 assessment in Part I.

Similarly, time to achieve IGA response in Part I will be defined as the number of weeks from the day of the first dose of the study drug to the first IGA assessment in Part I (i.e., up to and including Week 16 visit) when IGA score of 'clear' or 'almost clear' with at least two-grade reduction from Baseline is achieved. For subjects who never achieve IGA response in Part I the time will be censored at the last IGA assessment in Part I.

The analysis of the Parts II and III will be conducted within subjects who were re-randomized at the start of Part II. In this analysis, subjects will be analyzed by treatment groups based on their treatments in Part II (see Section 6.1.1). Times will be defined similarly to the analysis of Part I, except they will start at the time of the switch to a new treatment in Part II and will be

censored at the last assessment in the study. Part II baseline will be used when determining PASI and IGA responses.

The analysis for the study overall will be conducted only for subjects who were initially randomized to any dose of SCD-044 and did not switch treatments during the study. In this analysis subjects will be analyzed by treatment groups based on their treatments in Part I. Times will be defined similarly to the analysis of Part I, except then will be censored at the last assessment in the study.

Quartiles of time to achieve PASI75 and time to achieve IGA response (based on the Kaplan-Meier method) with their 95% confidence intervals (using Brookmeyer and Crowley method with log-log transformation) will be calculated by treatment group.

6.8.3.6 Relationship between SCD-044 plasma concentrations and efficacy/PD endpoints

[redacted]

6.9 Pharmacokinetic Analyses

[redacted]

[redacted]

In addition, PK sample will be collected, if possible, approximately 1 hour within the onset of an AE related to bradycardia during the [redacted] monitoring.

PK concentrations will be summarized descriptively by visit, timepoint and treatment group, including CV%, geometric mean and geometric CV%.

Concentrations reported as below limit of quantification (BLQ) will be treated as 0 for the purposes of the summary if they precede quantifiable samples prior to the first measurable concentration or occur after the last quantifiable concentration. A BLQ concentration embedded between two quantifiable concentrations during the post-dose collections on Day 29 will be set to missing. Missing values will not be imputed.

PK parameters will be estimated using noncompartmental analysis with the software program WinNonLin version 8.4 or higher for subjects who had PK samples collected from pre-dose to 6 hours post-dose on Day 29 under protocol version 2. The parameters will include:

- maximum concentration (C_{max})
- time to maximum concentration (t_{max})
- Area under the concentration-time curve up to 6 hours (AUC_{0-6})
- Area under the concentration-time curve up to the last observed quantifiable concentration (AUC_{0-last}).

Pharmacokinetic parameters will be summarized descriptively by treatment group. However, PK parameters from subjects with emesis occurred within 5 hours post-dose on Day 29 will not be included into descriptive statistics.

6.10 Analyses of PD biomarkers

[redacted] blood sample will be collected for testing of:

- Cytokines in plasma/serum: [redacted]
- Cell types in blood:
  - [redacted]

Additional biomarkers may be included during the study.

[redacted]

6.11 Safety Analyses

All safety analyses will be performed on the Safety population.

6.11.1 Adverse Events

Adverse events will be coded using MedDRA, Version 25.0, AE coding system for purposes of summarization.

An AE will be considered as treatment-emergent (TEAE) if the date of onset is on or after the date of the first study drug administration. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the study drug start date. If the start date is partially missing, the AE will be considered treatment-emergent, unless the month and year (when available) rule out the possibility that the event occurred post start of study drug dosing.

A TEAE is defined as treatment-related if its relationship to study medication is recorded as "Possible", "Probable" or "Definite" on the eCRF. In case the relatedness was not assessed, the most conservative result (related) will be chosen for the analysis.

Cardiovascular AEs will be defined as AEs with MedDRA system organ class "Cardiac disorders" or "Vascular disorders".

Adverse events that are of special interest, that represent signs/symptoms of Progressive Multifocal Leukoencephalopathy (PML) or of Posterior Reversible Encephalopathy Syndrome (PRES) and that are cardiac arrhythmias will be marked on the eCRF.

AEs will be assigned to Part I or Parts II/III of the study based on the date of onset, i.e. AEs that start prior to the first dose of the Part II treatment will be assigned to the Part I and AEs that start on or after the date of the first Part II dose will be assigned to the Parts II/III. In case AE start date is partially known so that there exists an ambiguity whether the AE starts in Part I or Part II, it will be assigned to Part I.

In summaries of TEAEs a subject experiencing the same AE multiple times on the same treatment will only be counted once for that preferred term and treatment. Similarly, if a subject experiences multiple AEs within the same system organ class on the same treatment that subject will be counted only once in that system organ class and treatment. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class and treatment will be used. Similarly, when summarizing AEs by relationship to study drug, only the most related occurrence within the preferred term or system organ class and treatment will be selected for displays in summary tables.

All AE summaries will be presented in 3 ways:

1. For events in Part I only, using Part I treatment groups, with the additional groups SCD-044 Any Dose (including the three SCD-044 groups) and Total (including all subjects).
2. For events in Parts II/III/IV only, using Parts II/III/IV safety treatment groups, with the additional group Total.

3. For the entire study using only the subjects who stayed on the same treatment throughout the study, using the three active treatment groups with the additional group Total.

An overall summary for the Safety population will include, by treatment and overall, the number and percentage of subjects reporting at least 1 TEAE in the following categories:

- Any TEAE
- Treatment-related TEAE
- Serious TEAE
- Serious drug-related TEAE
- TEAE leading to discontinuation of the study medication
- Treatment-related TEAE leading to discontinuation of the study medication
- TEAE requiring temporary interruption of the study medication
- Treatment-related TEAE requiring temporary interruption of the study medication
- TEAE leading to death.
- TEAEs of special interest

Additional overall summary of cardiovascular TEAEs will include, by treatment and overall, the number and percentage of subjects reporting at least one cardiovascular TEAE in the following categories:

- Any cardiovascular TEAE
- Treatment-related cardiovascular TEAE
- Serious cardiovascular TEAE
- Cardiovascular TEAE leading to discontinuation of the study medication
- Cardiovascular TEAE leading to death.
- Cardiovascular TEAEs of special interest
- Cardiac arrhythmias

The following TEAE frequency tables will be prepared summarizing the number and percentage of subjects reporting at least one TEAE by MedDRA System Organ Class (SOC) and preferred term PT, by treatment group for the Safety population:

- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- Serious treatment-related TEAEs
- TEAEs leading to discontinuation of the study medication
- Treatment-related TEAEs leading to discontinuation of the study medication
- TEAE requiring temporary interruption of the study medication
- Treatment-related TEAE requiring temporary interruption of the study medication
- TEAEs occurring in ≥2% in any treatment group
- TEAEs of special interest
- Cardiac arrhythmias
- TEAEs with onset during the [redacted] period in Part I and in Part II
- TEAEs by Severity

- TEAEs by Relationship to Study Drug.

The tables for the [redacted] periods will be separated into sections for Week 1, Week 2 and Week 3 of [redacted] where the weeks are defined by the dates of the [redacted] visits (Week 1, Week 2 and Week 3 for Part I and Week 16, Week 17 and Week 18 for Part II). Only events occurring in each week in the treatment groups still undergoing [redacted] (including the Placebo group in Part I) will be included. In the Part II table five columns will be included: Placebo/SCD-044 [redacted] Placebo/SCD-044 [redacted] SCD-044 [redacted] SCD-044 [redacted] and Total as only these groups actually undergo [redacted] in Part II.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date and study day, stop date, intensity, outcome, action taken and causal relationship to the study drug. The adverse event onset will also be shown relative (in number of days) to the date of first administration of the study drug.

6.11.2 Laboratory tests

A central laboratory will be used for all assessments unless noted otherwise. Unscheduled laboratory assessments can be performed at discretion of the Investigator in response to AEs. The laboratory assessments include:

Hematology: at all study visits a blood sample will be collected for total and differential WBC count, Absolute Neutrophil count (ANC), ALC, Platelet count, Hemoglobin, Hematocrit, Mean Corpuscular Volume (MCV) testing. Additionally, total WBC count with differential counts including ALC and ANC counts will be performed pre-dose and at 1h, 2h, 4h and 6h post-dose on Day 29 (Week 4).

Lipid profile: at the study Visits 1, 2, 10 and 19 (Screening and study Weeks 0, 16, and 52) a blood sample will be collected for LDL, HDL and total cholesterol and Triglycerides testing.

Clinical chemistry: at the study Visits 1, 2, 7, 8, 10, 15, 16, and 19 (Screening and study Weeks 0, 4, 8, 16, 20, 28, and 52) a blood sample will be collected for sodium, potassium, chloride, calcium, magnesium, bicarbonate, phosphate, blood urea nitrogen, random glucose, albumin, total protein, alkaline phosphatase, creatinine, ALT, AST, gamma glutamyl transferase (GGT), total bilirubin, conjugated bilirubin testing.

Coagulation profile: at the study Visits 1, 2, 10, 16, and 19 (Screening and study Weeks 0, 16, 28, and 52) a blood sample will be collected for PT, INR, and aPTT testing.

Serology: at Screening visit a blood sample will be collected for: anti-VZV IgG, HIV antibodies, HBsAg, and HCV antibodies testing.

QuantiFERON Gold test: at Screening Visit a blood sample will be collected for TB antigens testing. [redacted]

Serum pregnancy test: at Screening Visit a blood sample will be collected for serum beta-hCG testing.

The following tests will be performed at a clinic site:

Urinalysis dipstick: at the study Visits 1, 2, 10, and 19 (Screening and study Weeks 0, 16, and 52) a urine sample will be collected for pH, specific gravity, protein, glucose, ketones, and blood testing.

Microscopic exam may be performed at the local or central laboratory at the discretion of the Investigator if the dipstick is positive (i.e. trace or above).

Urine Pregnancy Test: at the [redacted] a urine sample will be collected in women of childbearing potential for hCG testing.

A positive result should be confirmed by a serum beta-hCG test. A confirmed positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study drugs and the subject must be discontinued from the study.

C-reactive protein test (CRP): Test for CRP will be done for all subjects. At the study Visits 2, 10, 16, and 19 (study Weeks 0, 16, 28, and 52) a blood sample will be collected for CRP testing.

Rheumatoid Factor (RF): may be performed at study visit 1 or 2 at the local or central laboratory at the discretion of the Investigator to establish if there is a diagnosis of PsA per the Classification of Psoriatic Arthritis (CASPAR) criteria.

[redacted]

For Hematology, Chemistry profile the labs, which were abnormal and clinically significant at EOT, are needed at safety follow-up visit.

Hematology, chemistry (including lipid profile and CRP), coagulation and continuous urinalysis parameters and their changes from baseline will be summarized descriptively by visit and treatment group. For WBC and differentials (absolute counts and percentages) percent change from baseline will also be summarized.

Additionally, hematology (WBC and differentials) results obtained during Day 29 (Week 4) visit will be summarized by timepoint with changes and percent changes from pre-dose.

Shifts from baseline among the categories Normal (within the reference range), Low (below the reference range) and High (above the reference range) will be presented by visit.

In the analyses of change from baseline and shifts from baseline above, Part II baseline will be used for the groups that switched treatment in Part II, while Part I baseline will be used for the other treatment groups.

All results will be listed.

[redacted]

[redacted]

The number and percentage of subjects with pulse rate ≤40 bpm, ≤50 bpm and with decrease [redacted]

[redacted]

In the analyses of change from baseline above, Part II baseline will be used for the groups that switch treatment in Part II, while Part I baseline will be used for the other treatment groups.

All ECG findings will be listed.

6.11.5 Physical Examination

The investigator, sub-investigator or appropriately delegated designee will perform a physical examination, prior to the Subject starting study drug and at the end of treatment. The physical examination will include, at a minimum, examination of the Subject's general appearance, comprehensive skin examination, HEENT (head, eyes, ears, nose and throat), heart, lungs, musculoskeletal system, neurological system, lymph nodes, abdomen and extremities.

Each body system will be classified as normal, abnormal not clinically significant or abnormal clinically significant.

Number and percentage of subjects with normal, abnormal not clinically significant or abnormal clinically significant findings will be presented by body system, visit and treatment group.

All results will be listed.

6.11.6 Prior and Concomitant Medication

Prior and concomitant medication will be coded according to the World Health Organization – Drug Dictionary version MAR 01, 2022 and the Anatomical Therapeutic Chemical (ATC) classification system. Prior medications are defined as those taken before the first dose of the study drug (i.e., start and end date before the first dose of the study drug). Concomitant medications are defined as those taken at the time of or after the first dose of the study drug. Any medications that were started before the first dose of the study drug but continued after dosing will be considered a concomitant medication.

Medications concomitant with Part I will be defined as those taken at any time on or after the first study drug dose date in Part I and prior to the first study drug dose date in Part II. Medications concomitant with Part II/III/IV will be defined as those taken at any time on or after the first study drug dose in Part II.

All previous and concomitant medication will be listed by subject. Concomitant medications in Part I, in Parts II/III/IV and in the study overall will be summarized by treatment group, ATC class (highest level available) and preferred name. The summary for the study overall will include only subjects staying on the same treatment throughout the study. This analysis will be done for the Safety population.

All prior and concomitant medications will be listed.

6.11.7 Pulmonary Function Tests

At the study Visits 1 and 19 (Screening and study Week 52) pulmonary function tests (PFTs) will be performed, including assessment of FEV_1 and FVC. Spirometry will be performed in accordance with American Thoracic Society standards. The results will be compared to the predicted values based on factors such as age, gender, and ethnicity

Additional pulmonary assessments will be done in case of clinically significant abnormal findings on the PFTs or physical examination and at the discretion of the Investigator in subjects with respiratory complaints like dyspnea, shortness of breath, chest tightness, wheezing etc.

Spirometry parameters such as FEV_1, FEV_1 Percent Predicted, FVC, FVC Percent Predicted and FEV_1/FVC Ratio as well as their changes from baseline to Week 52 will be summarized descriptively by visit.

6.11.8 Ophthalmological Examination

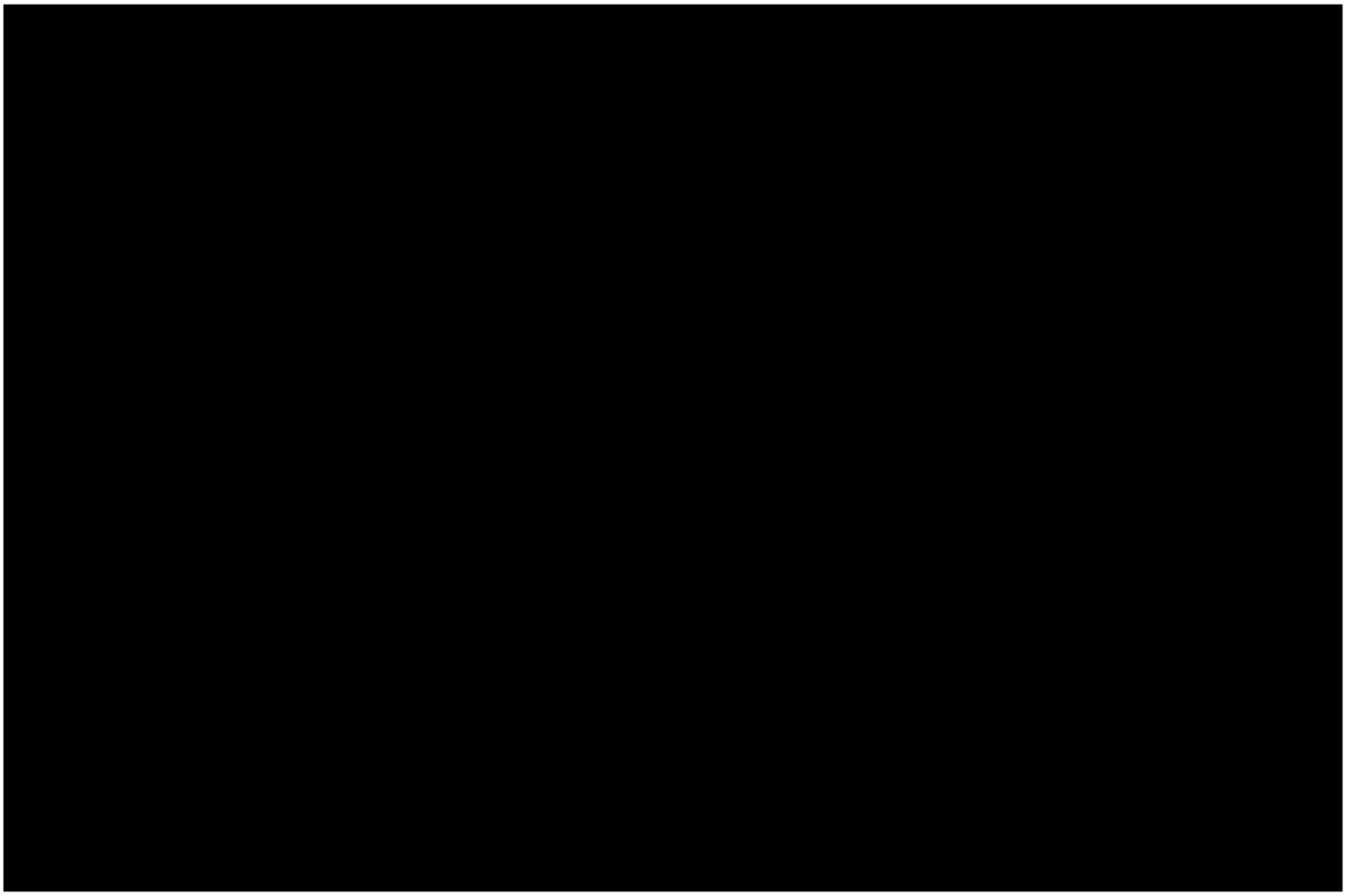
At the study Visits 1, 9 and 19 (Screening and study Weeks 12 and 52) a complete ophthalmologic examination will be performed by an ophthalmologist, including an ophthalmological history, best corrected visual acuity (Snellen chart), ophthalmoscopy (preferably slit-lamp) and Optical Coherence Tomography (OCT) assessment (measurement of central foveal thickness).

The following results of the ophthalmological examination will be summarized descriptively by eye (left or right), visit and treatment group:

- Best corrected visual acuity (Snellen denominator)
- OCT results: central fovea thickness

Number and percentage of subjects with presence of macular edema and/or uveitis will be presented by visit and overall across all visits (including both scheduled and unscheduled visits).

All ophthalmological examination data will be listed.



- The pulse rate 6 hours post-dose is <50 bpm and >10 bpm lower than the baseline value i.e., pre-dose value of that day
- The pulse rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum PD effect on the heart may not have occurred)
- The ECG 6 hours post-dose shows new onset second degree or higher AV block
- The ECG 6 hours post-dose shows a prolonged QTcF interval of ≥500 ms

Number and percentage of subjects requiring monitoring beyond 6 hours will be provided along with reasons, treatment group and visit as well as overall across all visits.

7. TIMING OF ANALYSES

7.1 Interim Analysis of Cardiac Safety

An unblinded analysis of the cardiac safety data will be performed by an unblinded study team after approximately 50 subjects complete the initial [redacted] period. The duration of in-clinic cardiac monitoring after first dose and/or certain dose escalation visits may be increased up to 24 hours if this review indicates new onset cardiac rhythm abnormalities after 6 hours of dosing that justify monitoring beyond 6 hours. Based on ongoing safety review by the Independent Safety assessor and Independent MM, recruitment of subjects may continue during review of cardiac monitoring results from these initial subjects.

A subset of tables and listings identified in a separate "Cardiac Safety Data Analysis Shell" document will be prepared. This analysis will include only the data from Part I of the study, i.e. findings collected and events starting up to the date of Week 16 visit of each subject.

7.2 DSBM Review of Cardiac Safety Data

An independent DSMB will review treatment initiation cardiac monitoring results from approximately first half of the randomized subjects and provide a recommendation if the cardiac monitoring in subsequent subjects could be reduced, for example, to assessment of only pre-dose ECGs.

The outputs required for DSMB are described in the DSMB charter. These outputs will be prepared both in the blinded and unblinded fashion. Unblinded output will be created by a separate unblinded team. Initially the DSMB will review the blinded outputs, and then unblinded if required.

7.3 Part I Analysis

Once the last subject completes Week 16 visit (or early termination prior to Week 16), the analysis will be conducted on all available data to evaluate the primary and key secondary efficacy outcomes. At this time all planned tables, listing and figures pertaining to Part I of the study will be created. This will be the final analysis for the primary efficacy endpoint. Investigational sites, subjects, and study team members directly involved in study activities will remain blinded to study treatment assignments until the last subject completes the follow-up period (Week 56). A separate document, The Blinding Maintenance and Communication Plan will provide further details related to unblinding of personnel involved in reporting activities

[redacted]

7.4 Final Analysis

When all subjects complete the study, the final analysis will be performed. At this time the randomization code will be released and the statistical and programming team that was blinded throughout the study will become unblinded. For the final analysis all planned tables, listings and figures will be created.

8. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Handling of intercurrent events is expanded in this SAP.

The endpoint of achieving DLQI score of 0 or 1 was added.

There are no other changes from the protocol-specified analyses.

9. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

See separate document with the table, figure and listing shells.

10. LITERATURE CITATIONS / REFERENCES

1. Study protocol: "A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of SCD-044 in the Treatment of Moderate to Severe Plaque Psoriasis", version 4.0, dated April 10, 2023
2. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med. 1990 Dec;9(12):1439-45.
3. Greenland S, Robins M. Estimation of a common effect parameter from sparse follow-up data. Biometrics. 1985;41(1):55-68.
4. Ratitch B., Lipkovich I. and O'Kelley M. Combining Analysis Results from Multiply Imputed Categorical Data. PharmaSUG 2013 – Paper SP03. Available online: https://www.lexjansen.com/pharmasug/2013/SP/PharmaSUG-2013-SP03.pdf