Official title: 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

Document: Study Protocol

NCT number: NCT04566666

Document date: 22 December 2023

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

Brief Title: A Phase IIb study to assess the efficacy and safety of SCD-044 in the treatment of moderate to severe plaque psoriasis

CLINICAL STUDY PROTOCOL

Protocol Number: SCD-044-19-14

Protocol Version Number: 4.2

Protocol Version Date: Dec 22, 2023

Study Managing Lead: Taro Pharmaceuticals U.S.A., Inc.

FDA IND: 144951

EU Ct No.: 2023-506477-35-00

UTN: U1111-1287-8390

Sponsor: Sun Pharmaceutical Industries Limited

Sun house, CTS no. 201 b/1
Western express highway, Goregaon (E)
Mumbai 400063; India

Developmental phase of study: 2b

PROTOCOL APPROVAL:

I am aware of, and agree to comply with, all of the procedures contained within this protocol and requirements of applicable regulatory agencies:

Study Managing Lead Representative [redacted]	Signature, Date: [redacted]
Medical Monitor [redacted]	Signature, Date: [redacted]
CRO Representative [redacted]	Signature, Date: [redacted]
Sponsor Representative and Medical Expert [redacted]	Signature, Date: [redacted]

CONTACT LIST

Study Managing Lead Representative:

[redacted]

Sponsor Medical Expert:

[redacted]

Independent Sponsor Medical Monitor:

[redacted]

Independent Medical Monitor:

[redacted]

Contract Research Organization (CRO):

[redacted]

Medical Monitor (MM)[America]

[redacted]

Contract Research Organization [Europe]

[redacted]

Medical Monitor (MM) [Europe]

[redacted]

Drug Labeling, Packaging and Shipping Facility [America]

[redacted]

Statistical Consultant:

[redacted]

Statistics and Data Management (DM):

[redacted]

Institutional Review Board (IRB) [America]

[redacted]

PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read and understand the foregoing protocol SCD-044-19-14 “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” and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR) and local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety, and welfare, of Subjects under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide copies of the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all Subject information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with Food and Drug Administration (FDA) regulations.

I will not enroll any Subjects into this protocol until IRB approval and Sponsor approval are obtained.

Principal Investigator	**Signature, Date**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Counts
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ACR	American College of Rheumatology
AST	Aspartate aminotransferase
ATWC	Active Treatment Worst Case
AUC	Area under the concentration-time curve
AV block	Atrioventricular block
BL	Baseline
BMI	Body Mass Index
bpm	beats per minute
BP	Blood Pressure
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
CFR	Code of Federal Regulations
Cmax	Maximum Concentration/Maximum Observed Concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COPD	Chronic obstructive pulmonary disease
CRA	Clinical Research Associate
CT	Computerized Tomography
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
Ctrough	lowest concentration reached by a drug before the next dose
DLQI	Dermatology Life Quality Index
DM	Data Management
DMARD	Disease Modifying Anti-rheumatic drug
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiography
ED	Early Discontinuation
EDC	Electronic Data Capture
e.g.	exempli gratia, “for example”, “such as”
EoS	End-of-Study
EOT	End of Treatment
EU	European Union
EU Ct No.	European Union Clinical Trial Register number
FEV	Forced expiratory volume
FDA	Food and Drug Administration
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire of Disability
HBsAg	Surface antigen of the hepatitis B virus (HBV)
hCG	Human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human immunodeficiency virus
hr	Hour
HR	Heart rate
hrs	Hours
HDL	High-density lipoproteins
ICF	Informed Consent Form

ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
IUD	Intrauterine Device
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
INR	International Normalized Ratio
IND	Investigational New Drug
IP (IMP)	Investigational (Medical) Product
IR	Infrared
IRT	Interactive Response Technology
ITT	Intent To Treat
IV	Intravenous
JC	John Cunningham virus
Kg	Kilogram
LDL	Low-density lipoprotein
LLN	Lower limit of normal
L/kg	Liter per kilogram
LOCF	Last Observation Carried Forward
MAD	Multiple Ascending Dose
MCV	Mean Corpuscular Volume
mg	Milligram
mL	Milliliter
mm	millimeter
MM	Medical Monitor
MMRM	Mixed Model Repeated Measures
Mm Hg	millimeter of mercury
msec	millisecond
mNAPSI	modified Nail Psoriasis Severity Index
NCE	New Chemical Entity
NDA	New Drug Application
ng	Nanogram
NK cell	Natural Killer cell
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OC	Observed Cases
OCT	Optical Coherence Tomography
OTC	Over-The-Counter
p.o.	Per Oral
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PFT	Pulmonary Function Test
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PtGA	Patient Global Assessment of Disease Activity
PtA-P	Patient Assessment of Pain
PI	Principal Investigator
PK	Pharmacokinetics
PL	Placebo
PML	Progressive Multifocal Leukoencephalopathy
PRES	Posterior Reversible Encephalopathy Syndrome
PP	Per Protocol
PPPGA	Palmoplantar Physician Global Assessment
PsA	Psoriatic Arthritis
PSSD	Psoriasis Symptoms and Signs Diary
PT	Prothrombin time
aPTT	Activated partial thromboplastin time
PUVA	psoralen and ultraviolet A

RF	Rheumatoid Factor
SAP	Statistical Analysis Plan
QRS	A combination of the Q wave, R wave and S wave
QT	QT Interval (the time from the start of the Q wave to the end of the T wave)
QTcF	QT corrected Fridericia's formulas
SAE	Serious Adverse Event
S1P	Sphingosine-1-phosphate
S1PR1	Sphingosine-1-phosphate Receptor 1
SPARC	Sun Pharma Advanced Research Company Limited
SPIL	Sun Pharmaceutical Industries Ltd.
SUSAR	Suspected Unexpected Serious Adverse Reactions
t1/2	Half-Life
TB	Tuberculosis
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TIA	Transient Ischemic Attack
Tmax	Time to Maximum Plasma Concentration
VAS	Visual Analogue Scale
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
UTN	Universal Trial Number
UV-B	type B ultraviolet
WBC	White Blood Cell
µg/mL	Microgram Per Milliliter
µg•h/mL	Microgram Times Hour Per Milliliter
µM	Micro Molar
VZV	Varicella Zoster Virus

STUDY SYNOPSIS

Protocol Number: SCD-044-19-14

Title of Study: 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

Study Managing Lead: Taro Pharmaceuticals U.S.A., Inc.

Sponsor: Sun Pharmaceutical Industries Ltd.

IND: 144951

Start of the study: in North and Latin America: [redacted] [first participant enrolled]
in Europe: [redacted]

End of the study: the study is expected to be concluded upon final collection of data for all outcome measures and adverse events, including safety follow up (last participant's last visit).

Investigational Products:
SCD-044 Tablets [redacted] (low dose)
SCD-044 Tablets [redacted] (intermediate dose)
SCD-044 Tablets [redacted] (high dose)
SCD-044 Tablets [redacted]

Control: Placebo of SCD-044 product

Treatment Duration: The study treatment period will last up to 52 weeks

Dose and Mode of Administration: Once daily according to a randomization scheme and titration schedule.

Objectives:

Primary Objective:

- 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.

Secondary Objectives:

- 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
- To characterize the pharmacokinetics (PK) of SCD-044 in subjects with

moderate to severe plaque psoriasis

Tertiary Objectives:

- 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

Exploratory Objectives:

- To examine the pharmacodynamic/pharmacokinetic (PK/PD) relationship between SCD-044 plasma concentrations and PASI response
- [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 (PtA-P)
- To evaluate the effect of SCD-044 on blood-based biomarkers.

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 titration schedule:

- **Part I:** 16 weeks: Subjects will be randomized to placebo, Low dose [redacted] Intermediate dose [redacted] or High dose [redacted] of SCD-044 [redacted] to assess primary and secondary endpoints at 16 weeks
- **Part II:** Week 16 to Week 28:

  At Week 16, subjects initially randomized to a treatment group will be re-randomized or discontinued from the study based on the PASI response as follows:

  - Subjects initially randomized to placebo with a response of:

    [redacted] will be re-randomized to Intermediate dose, High dose, [redacted]

    [redacted] will be re-randomized to Intermediate dose or High dose [redacted]

  - Subjects originally randomized to Low dose and Intermediate dose arms with a response of:

    [redacted] will be switched to High dose [redacted]

    [redacted] will remain on their assigned dosing regimen

  - Subjects originally randomized to High dose arm with a response of:

    [redacted] will remain on their assigned dosing regimen

Re-randomized subjects continuing in the study will stay on their assigned dosing regimen until the end of Part II (Week 28). [redacted]

- **Part III:** Week 28 to Week 52: Subjects with a response of [redacted] at Week 28 will be discontinued from the study. Subjects with a response of [redacted] at Week 28 will continue their existing dosing regimen until the end of Part III.
- **Part IV:** Week 52 to Week 56; After Week 52 (or early termination of study treatment prior to Week 52), the study treatment will be stopped, and all subjects will enter the follow-up period to monitor safety and tolerability for 4 weeks following the last dose of study treatment. During the follow-up period, subjects should continue study approved concomitant medications only. However, they may be placed on appropriate therapies for safety concerns or significant worsening of psoriasis based on the judgment of the Investigator.

Clinical evaluations will be performed at:

[redacted]

On-site Visit 1: Screening Visit (Week ≥ -4 / Day -28 to -1);
On-site Visit 2: Baseline Visit (Week 0 / Day 1; before 12 noon);
On-site Visit 7: [redacted]
On-site Visit 8: [redacted]
On-site Visit 9: [redacted]
On-site Visit 10: [redacted]
On-site Visit 14: [redacted]
On-site Visit 15: [redacted]
On-site Visit 16: [redacted]
On-site Visit 17: [redacted]
On-site Visit 18: [redacted]
On-site Visit 19: End of treatment visit (Week 52 / Day 365 ± 3 Days; before 12 noon);
On-site Visit 20: Follow-up visit (Week 56 / Day 393 ± 3 Days);

[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.

Study Population:

Key Inclusion Criteria

1. Males and non-pregnant non-lactating females ≥ 18 years of age providing written informed consent prior to any study-related procedures.
2. Diagnosis of predominantly plaque psoriasis for ≥ 6 months as determined by subject interview and confirmation of diagnosis through physical examination by Investigator
3. Subject is a candidate for phototherapy or systemic therapy for plaque psoriasis.*

   *Note: Subjects are required to be candidates for systemic/phototherapy, however no such therapy will be allowed during the study. Please refer to exclusion criteria 3
4. Moderate to severe plaque psoriasis at Screening and Baseline defined as:
   - BSA involvement of ≥ 10%
   - PASI score of ≥ 12
   - IGA of at least moderate disease (≥ 3)

Key Exclusion Criteria

1. Female subjects who are pregnant, nursing or planning to become pregnant during the study participation or within 6 months of completing the study.
2. Predominantly non-plaque forms of psoriasis like erythrodermic psoriasis, pustular psoriasis, medication-induced or medication exacerbated psoriasis, or new-onset guttate psoriasis.
3. Anticipated requirement of topical therapy, phototherapy, or systemic therapy for psoriasis [redacted] during the study.

4. [redacted]
5. [redacted]
6. Known organ complications of diabetes mellitus such as reduced renal function, significant retinal pathology, or neuropathy.
7. History or presence of uveitis
8. Any of the following pulmonary conditions:
   - History of or active severe respiratory disease, including COPD, tuberculosis, or pulmonary fibrosis
   - Severe asthma or asthma requiring regular treatment with oral steroids
   - Forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values at screening
9. Use of the medications listed below within the indicated washout period prior to Baseline visit:

- Any prior treatment with lymphocyte-depleting therapies (e.g., anti-CD4 antibodies, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
- Any prior treatment with lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, other S1PR agonists)
- Treatment with ustekinumab within 6 months, secukinumab within 5 months, etanercept within 4 weeks and any other biologics within 12 weeks or 5 half-lives whichever is longer
- Systemic immunosuppressive therapy (e.g., Tacrolimus) within 4 weeks
- Treatment with Disease Modifying Anti-rheumatic drugs (DMARDs) within 4 weeks
- Oral systemic psoriasis therapy (e.g., cyclosporine, methotrexate, acitretin, fumaric acid esters, apremilast) within 4 weeks
- Phototherapy (e.g., UV-B light phototherapy, PUVA (Psoralen and ultraviolet A) therapy, tanning salon or home-administered UV-B) within 4 weeks
- Oral or injectable corticosteroids within 4 weeks
- Treatment with a non-biologic investigational agent within 4 weeks (or 5 half-lives whichever is longer)
- Topical psoriasis treatment within 2 weeks prior to randomization
- Treatment with JAK inhibitors within 4 weeks prior to randomization

Number of Subjects:

Approximately 240 subjects will be enrolled in the study in a 1:1:1:1 ratio to the following treatment groups:

- Placebo of SCD-044
- SCD-044 Tablets [redacted] (Low dose)
- SCD-044 Tablets [redacted] (Intermediate dose)
- SCD-044 Tablets [redacted] High dose

At the beginning of Part III (Week 28 to Week 52) subjects will be discontinued from the study or will continue their existing dosing regimen based on their PASI response.

A subset of eligible subjects will participate in photographic evaluation

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

Approximately the same number of subjects who have prior exposure to biologics therapy for psoriasis will be enrolled between treatment groups.

Criteria for Evaluation:

Following assessments will be performed by the Investigator according to the schedule of assessments:

Efficacy:

- Psoriasis Area and Severity Index (PASI), Investigator's Global Assessment (IGA), BSA, Scalp IGA (for subjects with Scalp psoriasis), modified Nail Psoriasis Severity Index (mNAPSI) (for subjects with nail psoriasis), Palmoplantar Physician Global Assessment (PPPGA) (for subjects with Palmoplantar Psoriasis).

- For subjects with PsA: Tender and Swollen Joint Count assessment and Physician's Global Assessment (PGA) of Disease Activity.

  * Note: For subjects with PsA, assessments will be made by an independent joint assessor experienced in performing psoriatic arthritis joint assessments. Assessments will not be performed at sites where an independent assessor experienced in performing psoriatic arthritis joint assessments is not available.
- Subjects will be asked to complete DLQI, PSSD, PGIS, PGIC, and Itch Numeric Rating Scale (NRS).
- Subjects with PsA will also be asked to complete Health Assessment Questionnaire of Disability (HAQ-DI), Patient Assessment of Pain (PtA-P), Patient Global Assessment of Disease Activity (PtGA).
- Laboratory assessment: Serum C - reactive protein (CRP).
- A subset of eligible subjects will participate in photographic evaluation.

Safety:

- Vital signs
- Physical examination
- Monitoring of all adverse events (AEs)
- Laboratory assessments: Hematology, Clinical chemistry, Lipid Profile, Urinalysis, Pregnancy test, Coagulation profile, Serology at screening: anti-VZV IgG, HIV antibodies, HBsAg, HCV antibodies, and QuantiFERON Gold.
- ECG
- Pulmonary assessments: Pulmonary function tests (PFTs) will include assessment of FEV1 and FVC.
- Ophthalmological assessments: A complete ophthalmologic examination will be performed by an ophthalmologist; this will include an ophthalmological history, best corrected visual acuity, ophthalmoscopy, and Optical Coherence Tomography (OCT) assessment (measurement of central foveal thickness).

Pharmacokinetics:

- Pre-dose (trough) PK samples will be collected within 1 hour prior to dosing on weeks 16, 20, 28, and 52 visits.

  In addition, PK sample will be collected, if possible, approximately 1 hour within the onset of an adverse event [redacted] during on-site visits [redacted]

  Under the Protocol version 2.0 approximately [redacted] have completed PK sampling [redacted] post-dose on [redacted]

  [redacted]

  PK samples collected only from the active treatment groups will be analysed in an unblinded manner.

Pharmacodynamics:

- [redacted]. The exploratory pharmacodynamics biomarkers include cytokines in plasma/serum and cell types in blood

Photography (Optional):

- Photography is an optional procedure in the study and will be performed only at selected centres. Photographs will be used for visual evaluation only and will not be included in any analyses

Study Endpoints:

Primary:

- Proportion of subjects with at least 75% improvement in PASI (PASI75) at Week 16

Key Secondary:

- Proportion of subjects achieving IGA of “clear” (0) or “almost clear” (1) with at least two-grade reduction from baseline to Week 16

Other Secondary:

- Percent change from Baseline in mean PASI score at Weeks 12, 16, 20, 28 and 52
- PASI75 response rate at Weeks 12, 20, 28, and 52
- PASI50, PASI90, and PASI100 response rate at Weeks 12, 16, 20, 28, and 52
- Change from Baseline in PSSD score at Weeks 16, 20, 28, and 52
- Change from Baseline in DLQI score at Weeks 16, 20, 28, and 52
- Proportion of subjects with IGA score of “clear” or “almost clear” with at least two-grade reduction from baseline to Weeks 12, 20, 28, and 52
- Time to achieve PASI75 response
- Time to achieve IGA response of “clear” or “almost clear” with at least two-grade reduction from baseline
- Change from baseline in BSA involvement at Weeks 12, 16, 20, 28, and 52
- Change from baseline in PGIS at Weeks 16, 20, 28, and 52
- Proportion of subjects with improvement in PGIC at Weeks 16, 20, 28, and 52
- PASI50 and PASI75 response rate at Week 4
- [redacted]
- Steady state C_{trough} concentrations of SCD-044 at the dose levels evaluated in the study population
- Frequency, type, and severity of adverse events (AEs)

Tertiary

- Proportion of subjects with Scalp IGA “clear” or “almost clear” with at least two-grade reduction from baseline at Weeks 16, 20, 28, 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 16, 20, 28, and 52
- Proportion of psoriatic arthritis subjects who achieve ACR20 response at Weeks 16, 20, 28, and 52.
- Proportion of subjects with PPPGA score of 0 or 1 at Weeks 16, 20, 28, and 52 among subjects with a baseline PPPGA score of ≥3.

Exploratory

- Relationship between SCD-044 plasma concentrations and PASI response
- [redacted]
- Relationship between SCD-044 plasma concentrations and change in lymphocyte counts
- Proportion of subjects achieving ≥ 4-point improvement in NRS from baseline at Weeks 16, 20, 28, 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 16, 20, 28 and 52 among subjects with a baseline Scalp Itch NRS of ≥4
- Change from baseline in subject global assessment of PtA-P at Weeks 16, 20, 28, and 52 among subjects with PsA at baseline
- Level of lymphocyte sub-types and cytokines in blood/plasma/serum.

Other exploratory analyses may be performed based on available data. The Intent-to-Treat Population (ITT) will be used for all efficacy analyses.

Statistical Methods:

The primary and key secondary efficacy variables will be analysed using a Cochran-Mantel-Haenszel (CMH) test, stratified by gender and prior biologic therapy (Yes/No), and using the Intent-to-Treat (ITT) Population.

[redacted].

The Mantel-Haenszel common risk (response rate) difference between each SCD-044 dose group and placebo, along with 95% Confidence Interval, will be estimated. Subjects with missing values will be imputed using non-responder imputation (NRI).

Summary of Subjects who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

Concomitant medication

The start and stop date of concomitant medication use during the study will be provided in the data set in addition to the reason for the medication use.

Safety Analyses

Safety analyses will be conducted on the Safety Population. Safety Incidence of all adverse events reported during the study will be summarized by treatment group, severity, and relationship to study drug.

Summary of Subjects who Screen Fail

Reasons for removal of subjects during screening will be summarized.

1. INTRODUCTION AND BACKGROUND

Psoriasis is an immune-mediated inflammatory skin disease that affects approximately 125 million people in Europe, the USA and Japan.[1] The most common type of psoriasis affecting 90% of patients is plaque psoriasis, which is characterized by the presence of raised, thick red lesions covered by silver or white scales most commonly affecting the knees and elbows but can appear anywhere on the body.[1] The red plaques are due to dilation of blood vessels, while the silver or white scales result from the rapid proliferation of keratinocytes. Thus, psoriatic patients have lesioned or involved skin as well as areas of uninvolved skin with normal appearance. The disease is chronic, cycling between periods of exacerbation and remission.[1] Despite reports implicating a genetic association with the disease, published studies have established several psoriatic triggers including stress, medications (e.g., lithium, antimalarials, indomethacin, quinidine, beta blockers), injury or infection.[1-3]

Many affected individuals with psoriasis can be treated with topical agents including creams, sprays, lotions, and foams; however, up to one third of patients with severe psoriasis require other therapies such as ultraviolet (UV) light therapy, biologics, or systemic medications (e.g., methotrexate and oral retinoids).[1,3,5,6]

The treatment of moderate to severe chronic plaque psoriasis remains challenging due to issues relating to efficacy and safety. Biologics are reported having higher efficacy in treatment of chronic plaque psoriasis. However, treatment with biologics needs injections and multiple visits to the clinical facility. Hence, there is a probability of poor adherence to therapy, which may reduce the actual therapeutic benefit.

[redacted] there remains an unmet medical need for developing a safer and effective oral therapy for treating subjects with chronic plaque psoriasis

Sun Pharmaceutical Industries Limited. (SPIL) is developing a Sphingosine-1-phosphate receptor 1 (S1PR1) agonist, SCD-044 (Vibozilimod)[i], to treat moderate to severe plaque psoriasis. SCD-044 is a potent S1P1R and [redacted] S1P5R agonist, devoid of any activity on S1P2 or S1P3 receptors and is [redacted] at S1P4 receptor.

S1PR1 modulation and the resulting lymphocyte sequestration have the potential for treating multiple autoimmune and chronic inflammatory diseases, including psoriasis. Ponesimod, another S1PR1 agonist has been found to be effective in the treatment of plaque psoriasis.[11]

SCD-044 has shown efficacy in preclinical models of psoriasis. SCD-044 demonstrated a clinically meaningful reduction in lymphocyte counts with an acceptable safety profile in the Phase I study. The reduction in lymphocyte count is anticipated to result in therapeutic benefit in the treatment of 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.

[redacted].

2. OBJECTIVES

The objectives of this study are as follows:

Primary Objective:

- 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.

Secondary Objectives:

- 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
- To characterize the pharmacokinetics (PK) of SCD-044 in subjects with moderate to severe plaque psoriasis

Tertiary Objectives:

- 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

Exploratory Objectives:

- To examine the pharmacodynamic/pharmacokinetic (PK/PD) relationship between SCD-044 plasma concentrations and PASI response
- To examine the PK/PD relationship between SCD-044 plasma concentrations and [redacted] parameters [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 (PtA-P)
- To evaluate the effect of SCD-044 on blood-based biomarkers.

3. STUDY OVERVIEW

Start of the study: in North and Latin America: [redacted]
in Europe: [redacted]

End of the study: the study is expected to be concluded upon final collection of data for all outcome measures and adverse events, including safety follow up (last participant's last visit).

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 titration schedule.

- **Part I:** 16 weeks; Subjects will be randomized to placebo, Low dose [redacted] Intermediate dose [redacted] or High dose [redacted] of SCD-044 [redacted] to assess primary and secondary endpoints at Week 16
- **Part II:** Week 16 to Week 28:

  At Week 16, subjects initially randomized to a treatment group will be re-randomized or discontinued from the study based on the PASI response as follows:

  - Subjects initially randomized to placebo with a response of:

[redacted] will be re-randomized to Intermediate dose, High dose, [redacted] respectively

[redacted]: will be re-randomized to Intermediate dose or High dose [redacted]

- Subjects originally randomized to Low dose and Intermediate dose arms with a response of:

  [redacted] will be switched to High dose [redacted],

  [redacted]: will remain on their assigned dosing regimen

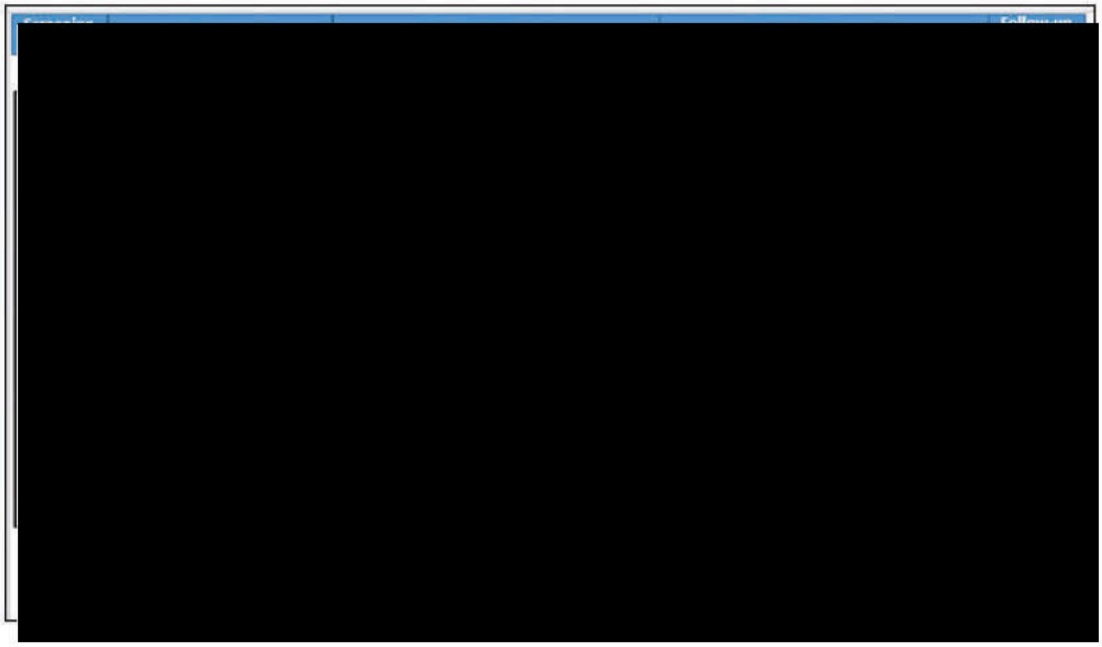
- Subjects originally randomized to High dose arm with a response of:

  [redacted]: will remain on their assigned dosing regimen

[redacted].

Re-randomized subjects continuing in the study will stay on their assigned dosing regimen until the end of Part II (Week 28). [redacted]

- **Part III:** Week 28 to Week 52: Subjects with a response of [redacted] at Week 28 will be discontinued from the study. Subjects with a response of [redacted] at Week 28 will continue their existing dosing regimen until the end of Part III.
- **Part IV:** Week 52 to Week 56: After Week 52 (or early termination of study treatment prior to week 52) the study treatment will be stopped and all subjects will enter the follow-up period to monitor safety and tolerability for 4 weeks following the last dose of study treatment. During the follow-up period, subjects should continue study-approved concomitant medications only. However, they may be placed on appropriate therapies for safety concerns or significant worsening of psoriasis based on the judgment of the Investigator.



Clinical Evaluations will be performed at:

[redacted]

On-site Visit 1: Screening Visit (Week ≥ -4 / Day -28 to -1);
On-site Visit 2: Baseline Visit (Week 0 / Day 1; before 12 noon);
On-site Visit 7: [redacted]
On-site Visit 8: [redacted]
On-site Visit 9: [redacted]
On-site Visit 10: [redacted]
On-site Visit 14: [redacted]
On-site Visit 15: [redacted]
On-site Visit 16: [redacted]
On-site Visit 17: [redacted]
On-site Visit 18: [redacted]
On-site Visit 19: End of Treatment Visit (Week 52 / Day 365 ± 3 Days);
On-site Visit 20: Follow-up Visit (Week 56 / Day 393 ± 3 Days);

[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 COVID-19 pandemic, [redacted] may have assessments done at home or remote visit. Remote visits must be discussed and consulted with the CRO's and the Sponsor's medical monitor 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 [redacted] Subjects that have remote assessments or delayed visits [redacted] will be recorded in the source documents 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 gender and prior biologic therapy for psoriasis. Approximately the same number of male and female subjects will be enrolled between treatment groups. A maximum of [redacted] of randomized subjects may have prior exposure to biologics therapy for psoriasis. Approximately the same number of subjects who have prior exposure to biologics therapy for psoriasis will be enrolled between treatment groups.

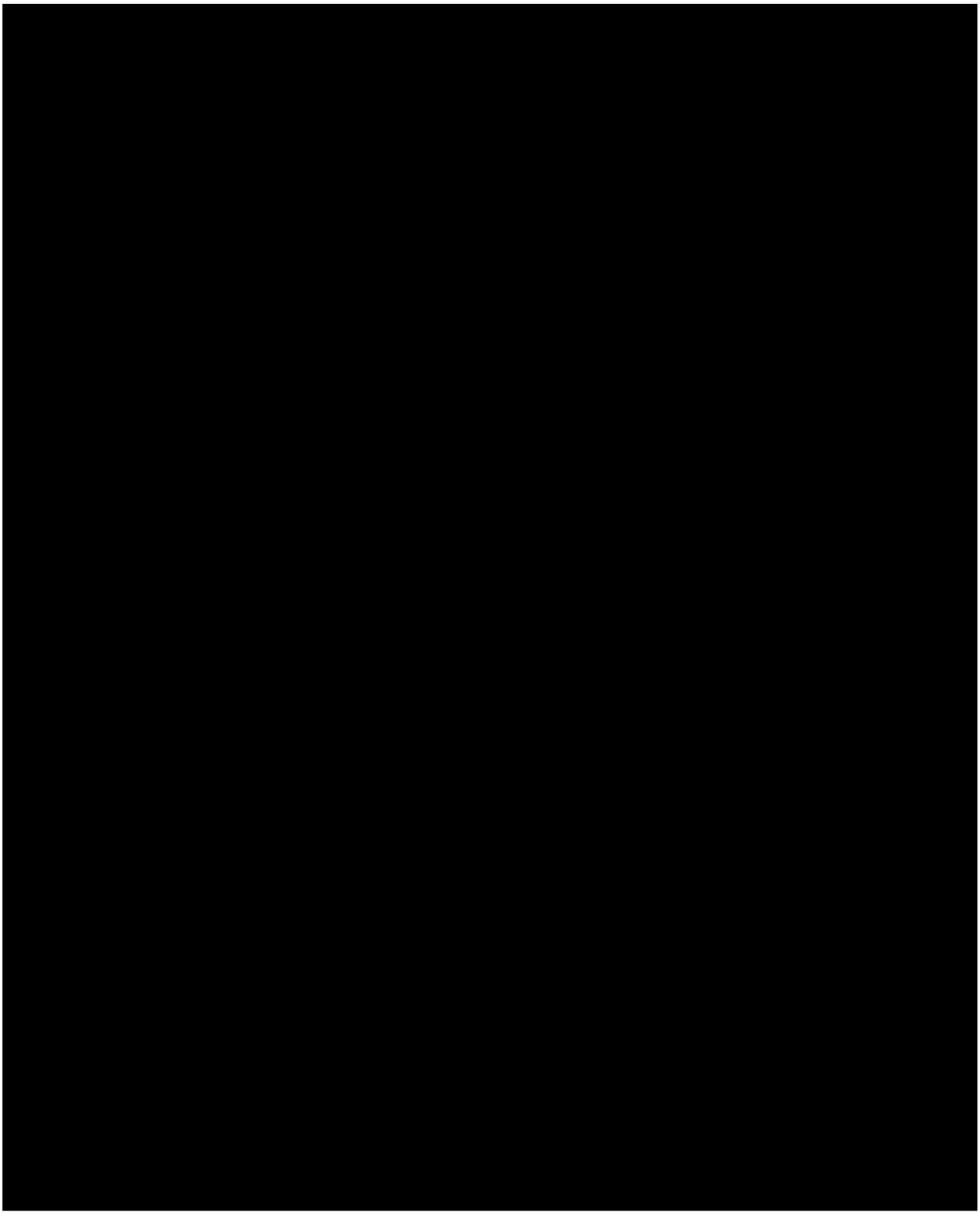
The assigned Investigational Product will be administered orally once a day. Subjects will be required to use diaries to document the date of study treatments, any missed treatments and the occurrence of all adverse events.

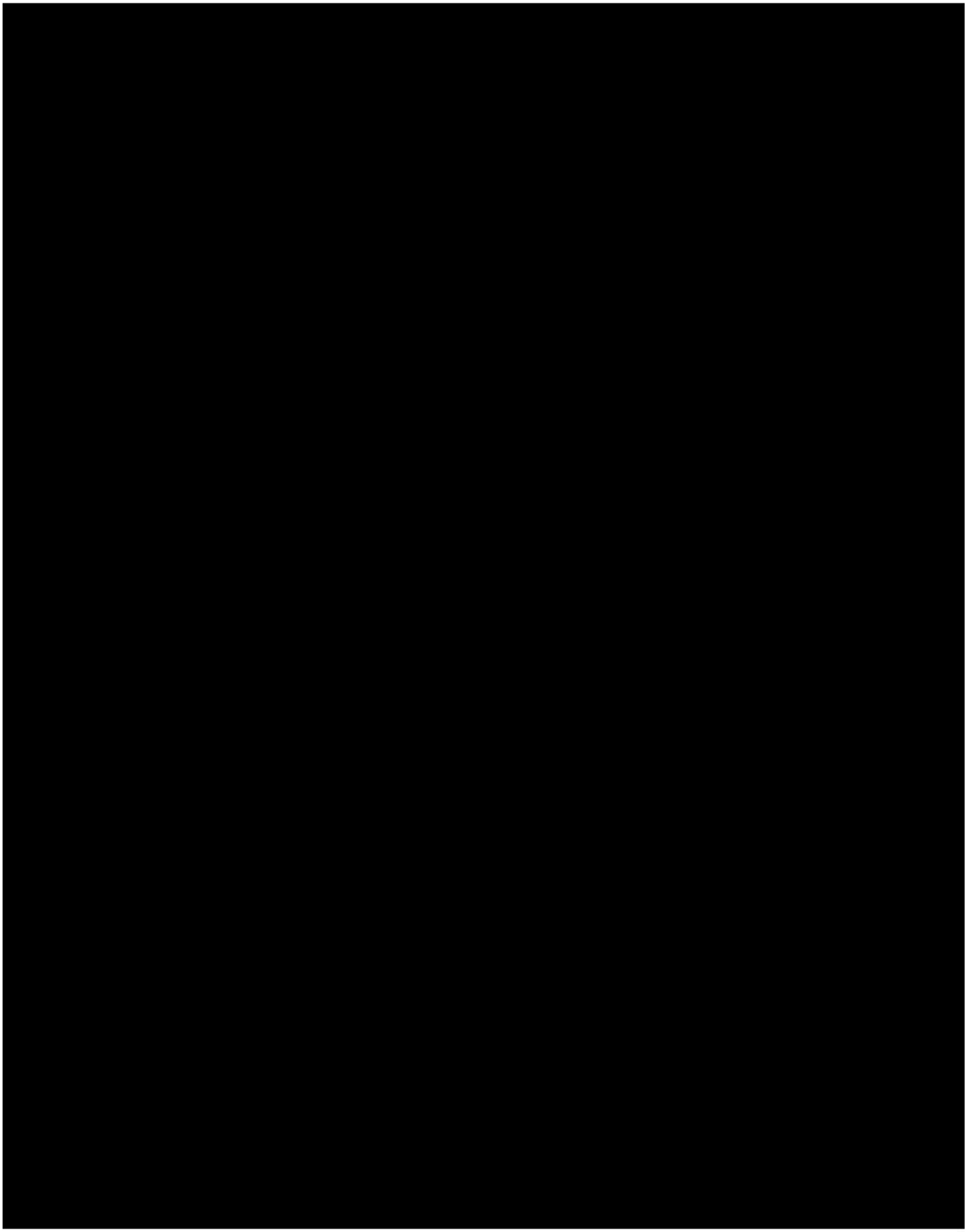
The duration of each subject's participation in the study will be approximately 56 weeks (393 days).

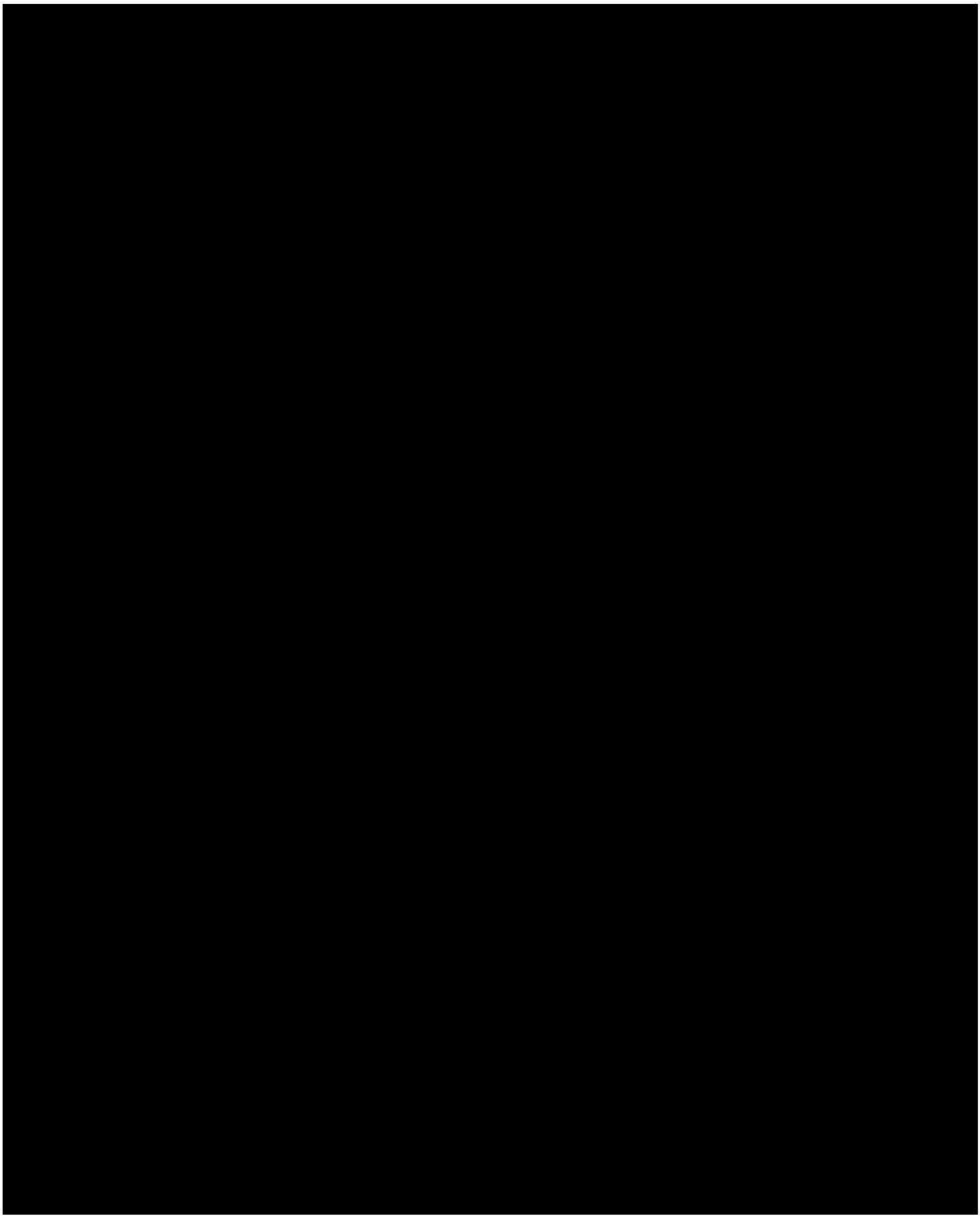
If the Principal Investigator determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure and the subject may be treated using the standard care.

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.

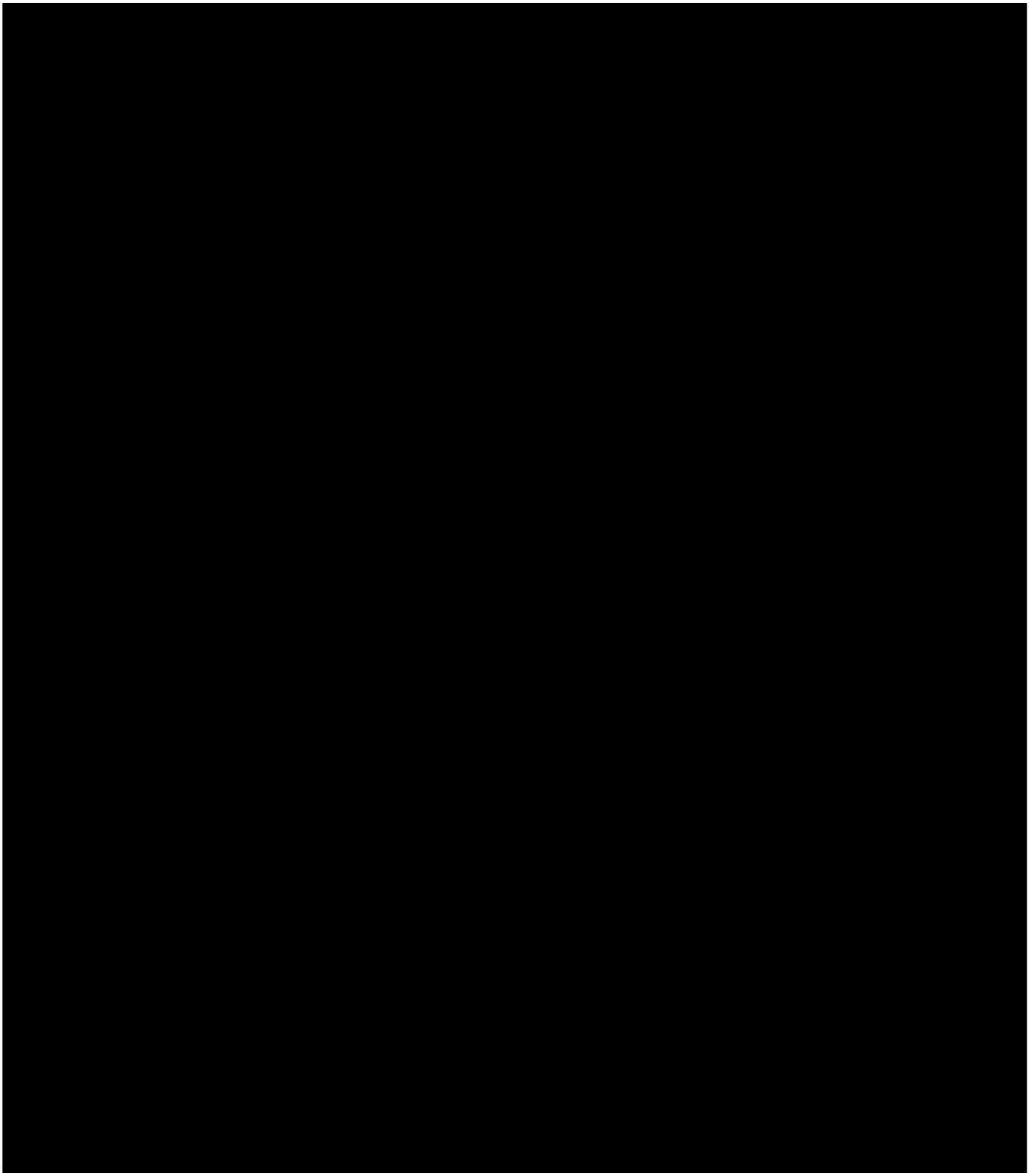
[redacted]

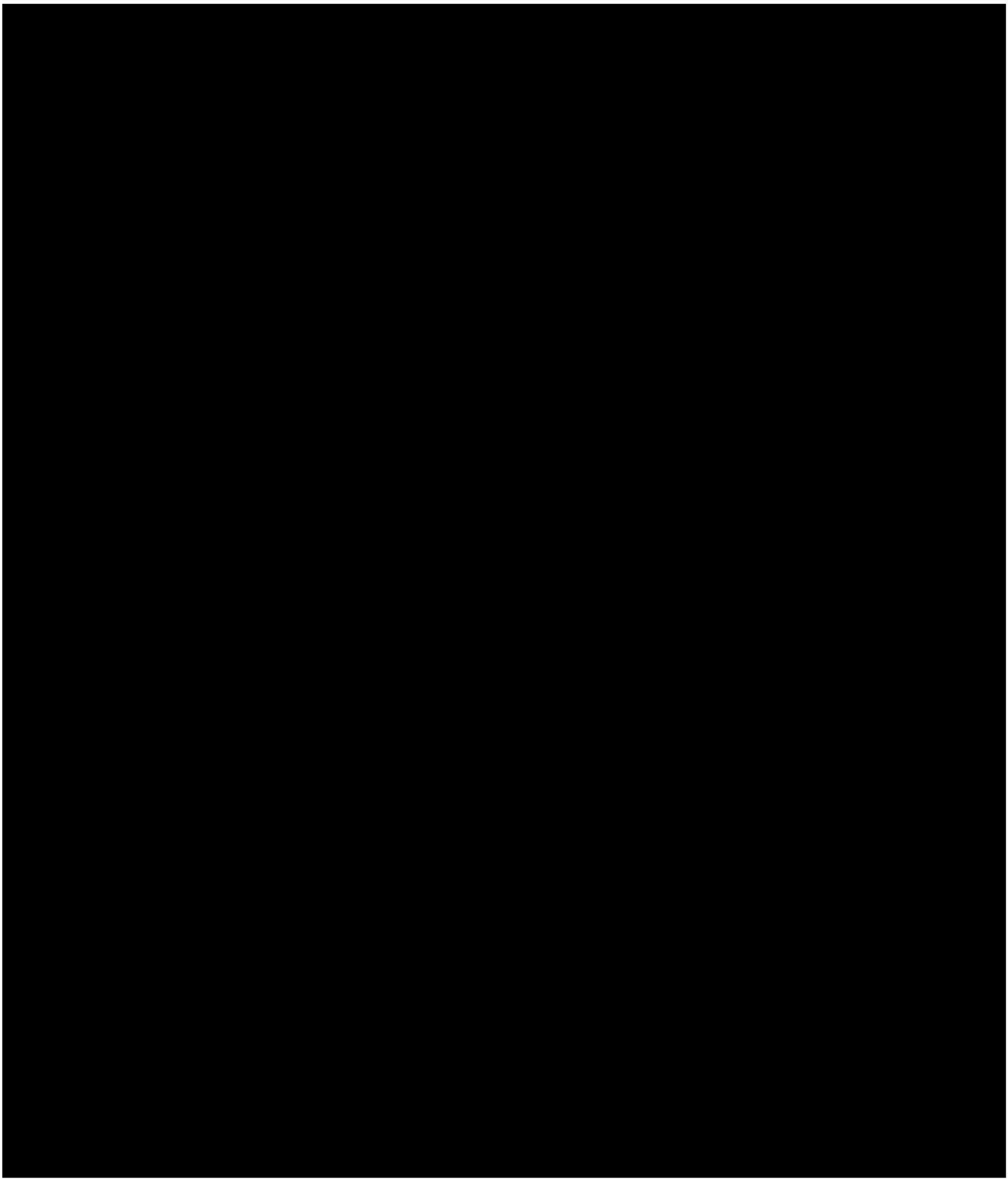


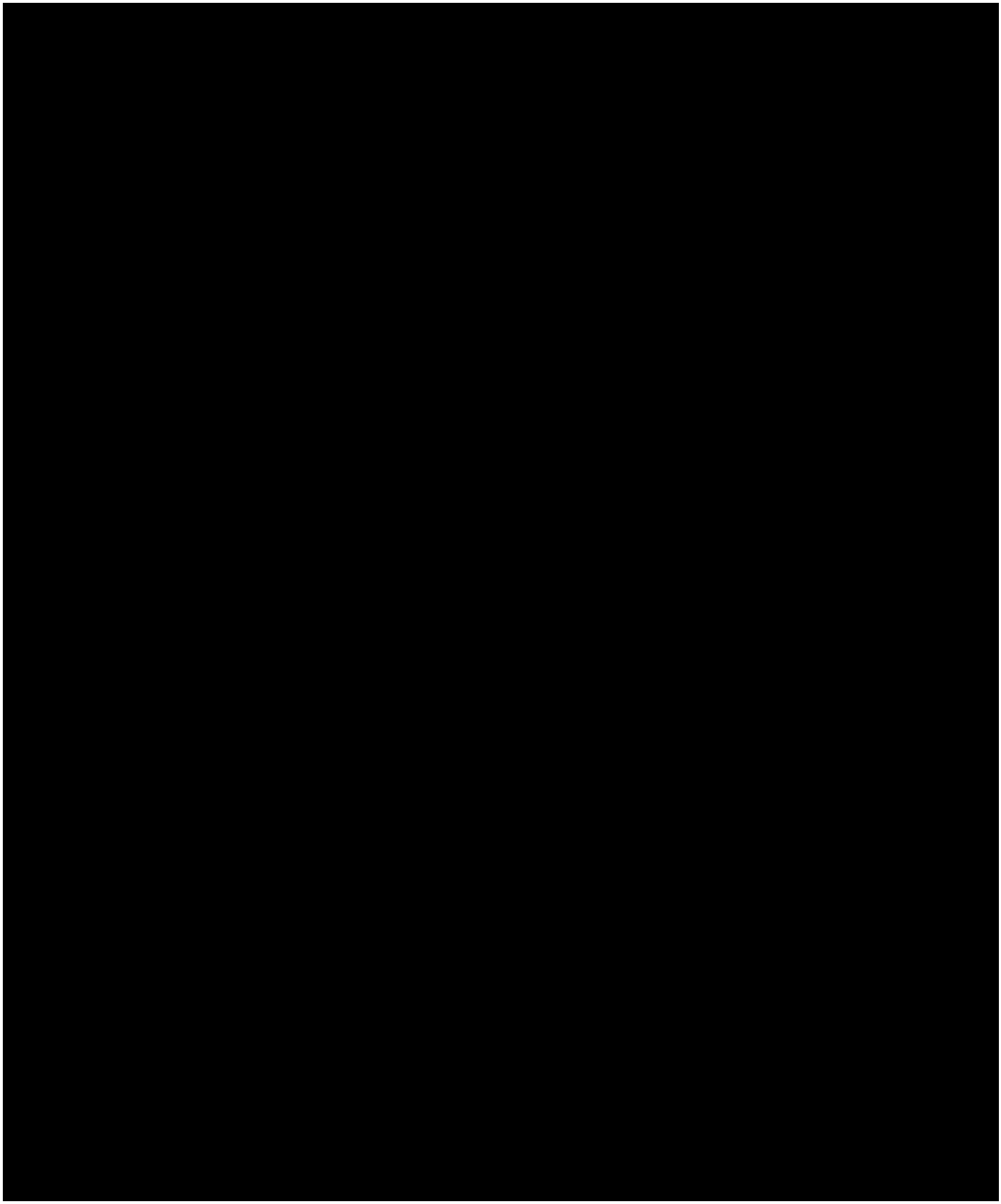




[redacted]







4. STUDY POPULATION

4.1 Number of Subjects

Approximately 240 subjects will be enrolled in the study in a 1:1:1:1 ratio to the following treatment groups: [redacted]

The number of subjects contributed by a site will not exceed approximately [redacted] of total study population unless approved by the Sponsor. Enrolment in a country other than USA will be limited to approximately [redacted] unless approved by the Sponsor.

4.2 Inclusion Criteria

1. Males and non-pregnant non-lactating females ≥ 18 years of age providing written informed consent prior to any study-related procedures.
2. Diagnosis of predominantly plaque psoriasis for ≥ 6 months as determined by subject interview and confirmation of diagnosis through physical examination by Investigator
3. Subject is a candidate for phototherapy or systemic therapy for plaque psoriasis.*
   *Note: subjects are required to be candidates for systemic/phototherapy, however no such therapy will be allowed during the study. Please refer to exclusion criteria 3
4. Moderate to severe plaque psoriasis at Screening and Baseline defined as:
   - BSA involvement of ≥ 10%
   - PASI score of ≥ 12
   - IGA of at least moderate disease (≥ 3)
5. Negative evaluation for tuberculosis (TB) within 4 weeks prior to initiating IMP, defined as a negative QuantiFERON test. Subjects with a positive or 2 successive indeterminate QuantiFERON tests are allowed if they have all of the following:
   - No history of active TB or symptoms of TB
     - A posterior-anterior (PA) chest radiogram or chest computerized tomography (CT) Scan (with associated report available at the site) performed within 3 months of Screening with no evidence of active TB or of any other pulmonary infectious diseases)
   - If prior latent TB infection, must have history of adequate prophylaxis (per local standard of care)
   - If presence of latent TB is established, then treatment according to local country guidelines must have been followed for 4 weeks, prior to inclusion in the study. A maximum of 2 QuantiFERON tests are allowed. A re-test is only permitted if the first is indeterminate; the result of the second test will then be used.
6. Subjects must be in good health and free from any clinically significant disease, including but not limited to, known hypersensitivity to similar products or excipients, conditions that may interfere with the evaluation of plaque psoriasis. Such conditions include, but are not limited to atopic or contact dermatitis, eczema, tinea corporis, and psoriasis other than stable plaque psoriasis (e.g., erythrodermic, exfoliative or pustular psoriasis).
7. Willing to refrain from using all study prohibited medications during the treatment period.

8. Female subjects of childbearing potential, in addition to having a negative pregnancy test (serum at Screening Visit, urine at Baseline Visit), must be willing to use a *highly effective* form (failure rate of less than 1% per year when used consistently and correctly) of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered *highly effective* methods of birth control: combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation (oral, intra-vaginal or transdermal), progestogen-only hormonal contraceptives associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS); bilateral tubal ligation, vasectomized male partner and complete sexual abstinence with a 2nd *highly effective* method of birth control should the subject become sexually active.

   Notes:

   - For the purpose of this study, a female is considered of childbearing potential i.e. fertile following menarche and until becoming post-menopausal unless permanently sterile. The methods of permanent sterilization are hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without any other medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is in-sufficient [CTFG guidelines (Clinical Trials Facilitation and Coordination Group CTFG 21/09/2020 Version 1.1]
   - Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. A sterile sexual partner is NOT considered an adequate form of birth control.
   - Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success
   - Sexual abstinence is considered a highly effective method only if the subject refrains from heterosexual intercourse during the entire period of the contraception requirement i.e., from first dose administration to 30 days after the last administration of study drug. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

9. All male subjects must agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 30 days after the last administration of study drug. Complete sexual abstinence is a "*highly effective*" method of birth control and acceptable for this study. Female partners should use an acceptable method of birth control as described in the above Item Number 8.

   Notes: For the purpose of this study, a male is considered fertile following puberty unless permanently sterile by bilateral orchidectomy [CTFG guidelines (Clinical Trials Facilitation and Coordination Group CTFG 21/09/2020 Version 1.1].

10. Willing and able to understand and comply with the requirements of the protocol, including attendance at the required study visits.
11. Documentation of positive varicella zoster virus (VZV) IgG antibody status. [redacted]
12. To participate in whole body photography, the subject must be willing to give written informed consent for whole body photography and be able to adhere to the procedures involved. A subject unwilling to consent for whole body photography may still be included in the trial.

4.3 Exclusion Criteria

1. Female subjects who are pregnant, nursing or planning to become pregnant during the study participation or within 6 months of completing the study.
2. Predominantly non-plaque forms of psoriasis like erythrodermic psoriasis, pustular psoriasis, medication-induced or medication exacerbated psoriasis, or new-onset guttate psoriasis.

3. Anticipated requirement of topical therapy, phototherapy, or systemic therapy for psoriasis [redacted] during the study.
4. [redacted]
5. [redacted]
6. Known organ complications of Diabetes mellitus such as reduced renal function, significant retinal pathology, or neuropathy.
7. History or presence of uveitis
8. Any of the following pulmonary conditions:
   - History of or active severe respiratory disease, including COPD, tuberculosis, or pulmonary fibrosis
   - Severe asthma or asthma requiring regular treatment with oral steroids
   - Forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values at screening
9. Use of the medications listed below within the indicated washout period prior to Baseline visit:
   - Any prior treatment with lymphocyte-depleting therapies (e.g., anti-CD4 antibodies, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
   - Any prior treatment with lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, other S1PR agonists)

- Treatment with ustekinumab within 6 months, secukinumab within 5 months, etanercept within 4 weeks and any other biologics within 12 weeks or 5 half-lives whichever is longer
- Systemic immunosuppressive therapy (e.g., Tacrolimus) within 4 weeks
- Treatment with Disease Modifying Anti-rheumatic drugs (DMARDs) within 4 weeks
- Oral systemic psoriasis therapy (e.g., cyclosporine, methotrexate, acitretin, fumaric acid esters, apremilast) within 4 weeks
- Phototherapy (e.g., UV-B light phototherapy, PUVA (Psoralen and ultraviolet A) therapy, tanning salon or home-administered UV-B) within 4 weeks
- Oral or injectable corticosteroids within 4 weeks
- Treatment with a non-biologic investigational agent within 4 weeks (or 5 half-lives whichever is longer)
- Topical psoriasis treatment within 2 weeks prior to randomization
- Treatment with JAK inhibitors within 4 weeks prior to randomization

10. Laboratory abnormalities at screening:
    - [redacted]
    - Any other laboratory abnormalities, which, in the opinion of the Investigator will expose the subject to undue risk, prevent the subject from completing the study or will interfere with the interpretation of the study results. Out of range laboratory results at screening not specified above should have been assessed as clinically non-significant by the Investigator and confirmed by the Medical Monitor (MM) as acceptable for participation in the study
11. Presence of any infection or history of infection requiring treatment with systemic antibiotics within 2 weeks prior to Screening, or severe infection (e.g., pneumonia, cellulitis, bone or joint infections) requiring hospitalization or treatment with IV antibiotics within 8 weeks prior to Screening.
12. Positive human immunodeficiency virus (HIV) test result, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) test result. Subjects with a positive HCV test are allowed if HCV RNA is negative
13. Prior malignancy, or concurrent malignancy (excluding successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma with no evidence of recurrence within 5 years or carcinoma in situ of the cervix that has been adequately treated).
14. Subject who has received live viral or bacterial vaccination within 4 weeks prior to Screening, or who intends to receive live viral or bacterial vaccination during the study.
15. Presence of macular edema at Screening (subjects with a history of macular edema are allowed provided they do not have macular edema at Screening Visit)
16. Consumption of excessive amounts of alcohol (greater than 2 drinks per day) or use drugs of abuse (including, but not limited to, cannabinoids, cocaine, and barbiturates).
17. Presence of autoimmune disorder other than Psoriasis
18. Documented organ transplantation
19. History or presence of clinically relevant, hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric, or other systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study
20. History of alcohol abuse
21. History of substance abuse in the previous year, in the opinion of the Investigator
22. History of attempted suicide.
23. History of or currently active primary or secondary immunodeficiency.

24. Engagement in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold.
25. Participation in an investigational drug study (i.e., Subjects have been treated with an investigational drug) within 30 days prior to screening. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.
26. Presence of excessive hair, tattoos, pigmentation, extensive scarring, pigmented lesions, or sunburn in the treatment area, which could make the affected plaque psoriasis BSA difficult to visualize.
27. Previous enrolment in this study.
28. The subject or a family member is among the personnel of the investigational site or Sponsor designee staff directly involved with this trial.
29. Subjects who are members of the same household with subjects participating or previously enrolled in this study

4.4 Prohibited Medications, Procedures, and Activities

Medication necessary for the health and well-being of the subject are permitted provided the subject has been at a stable dose for 30 days prior to screening/baseline. The use of any medication that could affect the course of psoriasis is prohibited during the entire study period. Subjects will be advised to refrain from making any significant change in the use of consumer products during the study (including moisturizers, new brands of make-up, creams, ointments, lotions, and powders) applied on or near the treatment area.

The following are prohibited during this study**:**

1. Use of new or changes in use of hormonal contraceptives
2. Analgesics, including NSAIDS and Acetaminophen, within [redacted] before scheduled study visits.
3. Topical psoriasis treatment.
   [redacted]
4. Oral systemic psoriasis therapy (e.g., cyclosporine, methotrexate, acitretin, fumaric acid esters, apremilast)
5. Phototherapy (e.g., UV-B light phototherapy, PUVA therapy, tanning salon, home-administered UVB), or excessive exposure to the sun
6. Oral or injectable corticosteroids
7. Biologic agents
8. Class Ia or III antiarrhythmic drugs (e.g. quinidine, disopyramide, amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, ajmaline, procainamide)
9. Drugs that cause QT prolongation and/or with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin)
10. Medications that may cause AV block and suppress AV conduction (e.g. Beta blockers, carbamazepine, non-dihydropyridine calcium-channel blockers, or cardiac glycosides)
11. Medications that may decrease heart-rate such as calcium channel blockers (verapamil or diltiazem), digoxin, ivabradine, anticholinesteratic agents or pilocarpine
12. Lymphocyte-depleting therapies (e.g., Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
13. Lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, other S1PR agonists)

14. Disease modifying anti-rheumatic drugs.
15. Immunosuppressive agents (e.g., Methotrexate, Azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus)
16. Immunosuppressive procedures that deplete lymphocytes (e.g., total body irradiation, bone marrow transplantation).
17. JAK inhibitors

4.5 Permitted Medications

1. Non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics given to treat psoriatic arthritis (PsA) only if the subject was on a stable dose for at least 4 weeks prior to Day 1 and is expected to maintain a stable dose for the first 16 weeks of the study. NSAIDs should not be used within [redacted] before scheduled study visits.
2. Analgesics: Acetaminophen may be used by the subject PRN except within [redacted] before scheduled study visits.
3. [redacted]

4.6 Precautions

The following precautions are to be taken during this study:

- [redacted]
- [redacted]

The therapeutic class of S1P agonists carries following known and/or potential risks:

- Bradyarrhythmia and atrioventricular conduction delays
- Hypotension
- Increased blood pressure
- Increased risk of infections
- Macular edema
- Decline in pulmonary function
- Liver injury
- Progressive multifocal leukoencephalopathy (PML)
- Posterior reversible encephalopathy syndrome (PRES)

If an adverse reaction suggesting Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Principal Investigator should assess the Subject's condition as soon as possible (i.e., during an Unscheduled Visit) and determine whether treatment should be

discontinued. If the Subject is discontinued from the study during an Unscheduled Visit, procedures from Early Discontinuation should be followed and the visit will be referred to as an Early Discontinuation Visit.

4.7 Subject Disposition and Discontinuation

Investigators are urged to enroll only those eligible Subjects who are likely to complete the entire study and who are willing to comply with the protocol-specified procedures. It is the right and duty of the Investigator to interrupt the treatment of any Subject whose health or well-being may be threatened by continuation in this study, or who may be experiencing unmanageable factors that may interfere with the study procedures and/or the interpretation of study results. Such Subjects should be withdrawn from the study rather than continued under a modified regimen.

Subjects will be removed from the study for any of the following reasons:

- If the Subject withdraws his or her consent for any reason; (note: if reason of discontinuation is due to COVID 19 related reasons this is to be noted.)
- If the Subject's condition has worsened to the degree that the Principal Investigator feels it is unsafe for the Subject to continue in the study;
- If the Subject's drug code is unblinded (on a case-by-case basis in consultation with the MM);
- If an adverse event occurs for which the Subject desires to discontinue treatment or the Principal Investigator determines that it is in the Subject's best interest to be discontinued;
- If there is a significant protocol violation;
- If the Subject is lost to follow-up;
- If the Subject becomes pregnant;
- If the Subject becomes a prisoner or become involuntarily incarcerated;
- Any other reason that may affect the outcome of the study or the safety of Subjects
- Termination of the study by the IRB; or
- Termination of the study by the Sponsor.

Additional reasons for Subjects to be removed from the study:

- Diagnosis of new onset of a Malignancy
- Diagnosis of Cryptococcal central nervous system (CNS) infection.
- Diagnosis of Progressive multifocal leukoencephalopathy (PML)
- Diagnosis of Posterior reversible encephalopathy syndrome (PRES)
- [redacted]
- On a case-by-case basis in consultation with independent MM in case of use of prohibited medications
- Clinically significant abnormalities that put the subject safety at risk if continued in the study including but not limited to
  - [redacted]

[redacted]

- [redacted]

Medical Monitor/Sponsor notification is required before removing/discontinuing subjects for any of the reasons noted above, as soon as possible.

The Principal Investigator must strive to follow the Subjects that are discontinued for any of the above reasons due to safety until the adverse event has resolved, becomes clinically insignificant, is stabilized or the Subject is lost to follow-up.

A significant protocol violation is defined as any Subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy.

The reasons for a Subject discontinuation will be documented. If a Subject is discontinued from the study for any reason, the procedures scheduled for Early Discontinuation will be completed and any outstanding data and study drug should be collected if possible. Data, in addition to the reason for discontinuation and the date of removal, will be documented.

Before a Subject is considered to be lost to follow-up, the Principal Investigator will document all (at least three) attempts to reach the Subject twice by telephone and will send a certified follow-up letter.

If a Subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a Subject, the Principal Investigator must strive to follow the Subject until the adverse event has resolved, becomes clinically insignificant, is stabilized or the Subject is lost to follow-up. [redacted]

Subjects who drop out after randomization will not be replaced.

4.8 Criteria to Discontinue Study

The entire trial may be discontinued by the sponsor pertaining to lack of efficacy, safety, feasibility or unspecified strategic or business reasons.

The Data Safety Monitoring Board (DSMB) may make a recommendation for discontinuation of the trial based on safety assessments of treated subjects when there is no justification for exposing additional subjects to additional potential risks by continuing the trial. The DSMB may recommend discontinuation of the study if the safety profile of SCD-044 is anticipated to be significantly inferior to other drugs in the class.

[redacted]

4.9 Meals and Refreshments

No consumption of energy drinks, alcohol, or caffeine-containing products, or the start, stop or change in dose of any prescription or over-the-counter (OTC) medication will be allowed during the housing at dose titration visits.

No excessive sodium consumption (>2,400 mg/day or >1 teaspoon equivalent/day) in food or beverage, and no caffeine containing beverages and foods (e.g., tea, coffee, cola drinks, and chocolate) and grapefruit containing beverages may be taken by subjects during the housing at dose titration visits.

5. SAFETY AND TOLERABILITY EVALUATIONS

Safety monitoring in this study will be performed by:

- Site PI (blinded). PI will identify a local ophthalmologist and a pulmonologist for screening or consultation, as necessary,
- [redacted]
- [redacted]
- Study Medical Monitor (blinded) will be available to consult on enrollment, medical questions, discontinuation, safety evaluations,
- [redacted]
- [redacted]
- Data Safety Monitoring Board (see Section 12.6).

[redacted]

5.1 Medical History

A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to evidence of hypertension, lipid disorders, obesity, heart attack, stroke, congestive heart failure, kidney disease, auto immune disease and diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

5.2 Physical Examination

The Investigator, sub-Investigator or appropriately delegated designee, (Physician's Assistant, Advanced Registered Nurse Practitioner, or Registered Nurse as per local regulations) 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.

Height and weight will be measured without shoes.

At the study Visits 1, 10, and 19 (Screening and study Weeks 16, and 52) the Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes).

5.3 Vital Signs

Vital signs, including blood pressure*, pulse rate**, respiratory rate and oral body temperature, will be documented at every on-site visit. Vital signs will be measured after the Subject has rested in a seated or supine position for at least 5 minutes. [redacted]

** The same arm should be used if triplicate measurements are required for blood pressure.*

*** Pulse rate will be measured once by counting the number of heart beats over 60 seconds (the pulse rate should not be extrapolated after counting for part of 60 seconds).*

5.4 Pregnancy Test

All female Subjects of childbearing potential will undergo serum beta-human chorionic gonadotropin (hCG) testing at Screening. [redacted]

For the purpose of this study, a female is considered of childbearing potential i.e. fertile following menarche and until becoming post-menopausal unless permanently sterile. The methods of permanent sterilization are hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without any other medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is in-sufficient. [Per CTFG guidelines (Clinical Trials Facilitation and Coordination Group CTFG 21/09/2020 Version 1.1).

Women of childbearing potential, in addition to having a negative pregnancy test, must be willing to use a *highly effective* form (failure rate of less than 1% per year when used consistently and correctly) of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered *highly effective* methods of birth control: combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation (oral, intra-vaginal, or transdermal) progestogen-only hormonal contraceptive associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS); bilateral tubal ligation, vasectomized male partner, complete sexual abstinence with a 2nd *highly effective* method of birth control should the subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control. Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. Subjects who had used hormonal contraception and stopped must have stopped no less than three months prior to the study.

5.5 Laboratory assessments

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 on-site study visits a blood sample will be collected for total and differential WBC count, Absolute Neutrophil count (ANC), Absolute Lymphocyte count (ALC), Platelet count, Hemoglobin, Hematocrit, Mean Corpuscular Volume (MCV) testing.

[redacted]

[redacted]

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. [redacted]

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 central laboratory at the discretion of the Investigator if the dipstick is positive (i.e. trace or above).

Urine Pregnancy Test: [redacted] a urine sample will be collected in women of childbearing potential for hCG testing (see section 5.4). [redacted] The safety team will take confirmation of the result through scheduled phone calls.

[redacted]

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 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.[12]

[redacted]

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

5.6 Pulmonary assessments

[redacted] pulmonary function tests (PFTs) will be performed, including assessment of FEV1 and FVC. Spirometry will be performed in accordance with American Thoracic Society standards.[13] The results will be compared to the predicted values based on factors such as age, gender, and ethnicity. The ATS standardized report form will be used as a source to record spirometry readings.[14,15,16]

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.

5.7 Ophthalmological assessments

[redacted] 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).

A comprehensive eye examination by an ophthalmologist must be scheduled immediately for any subject who complains of any visual disturbance. Subjects will be instructed to contact the site for any problems with vision. The results of this test will be provided to the sites' Independent Safety Assessor (unblinded team).

If there is a suspicion of macular edema, additional assessments like fluorescein angiogram may be performed at the discretion of the ophthalmologist. Subjects who develop blurred or changed vision (redness, pain, light sensitivity, blurred vision, and dark floating spots in the field of vision), that may be indicative of uveitis (based on Standardization of Uveitis Nomenclature (SUN) Working Group) or macular edema will have follow up ophthalmic examinations every month or as per the discretion of the ophthalmologist. [redacted]

5.8 Concomitant medications

Concomitant medications, including the use of non-drug treatments/therapies, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A record of concomitant medications taken by the Subject is to be obtained using generic name, if known, with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on a regular basis, including acetaminophen, should be recorded.

5.9 Adverse Events (AEs) and Adverse Events of Special Interest (AESI)

Any AEs occurring after signing Informed Consent should be reported. An adverse event is defined as any untoward medical occurrence (sign, symptom or clinically significant abnormal laboratory finding) regardless of severity in a subject or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. All adverse events, whether observed by an Investigator or Study Coordinator or reported by the subject, whether related to study drug or not related to study drug, shall be documented on Subject records, together with details, i.e. date of onset, description of the AE, the duration and intensity of each episode, the action taken, the relationship to the investigational product and the degree of severity, the seriousness, date of resolution, and the outcome.

After first dose, AEs (including AESIs and cardiac arrhythmias) should only be reported to and assessed by the independent safety team.

Following are Adverse Events of Special Interest (AESI):

- Serious Infections
- New onset malignancy
- [redacted]
- New Onset Macular edema
- PML and PRES

5.10 Query for Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare viral disease of the brain caused by a common infection called the John Cunningham (JC) virus. Up to 85% of adults in the general population have the JC virus. The virus usually remains dormant in the lymph nodes, bone marrow, or kidneys throughout life. If the immune system becomes severely compromised for any reason, the virus can be reactivated.

At each study Visit starting from Screening, the subject will be assessed for initial symptoms of PML:

- clumsiness or loss of coordination
- sensory loss
- difficulty walking
- changes in vision
- facial drooping
- personality changes
- memory problems and mental slowness
- trouble speaking
- weak muscles
- changes in thinking
- confusion
- progressive weakness on one side of the body

Symptoms can progress rapidly to include complications such as dementia, seizures, or coma. PML is a life-threatening medical emergency and usually leads to death or severe disability over weeks or months.

At each study visit, subjects will be instructed to immediately contact their doctor and stop treatment with the study drug if they experience any symptoms of PML. Subjects should also be instructed that typical symptoms associated with PML are diverse and progress over days to weeks.

5.11 Query for Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) may occur due to a number of causes, predominantly malignant hypertension, eclampsia and some medical treatments.

At each study visit starting from screening the subject will be assessed for symptoms of PRES:

- headache
- confusion or altered mental state
- seizures

- changes in vision

The symptoms tend to resolve after a period of time, although visual changes sometimes remain. Symptoms of PRES may be sudden and are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage.

At each study visit, subjects will be instructed to immediately contact their doctor and stop treatment with the study drug if they experience any symptoms of PRES. Subjects will also be informed that delayed treatment could lead to permanent neurological sequelae.

5.12 ECG

- the end of treatment visit 19 (study week 52) before the pre-dose PK sample
- if needed, at the discretion of the independent medical monitor, post-treatment follow up visit.

All 12-lead ECGs will be recorded after the subject is rested in supine position for at least 5 minutes.

[redacted]

Pre-dose:

Vital Signs (supine): Vital signs, including blood pressure, pulse rate, respiratory rate and oral body temperature will be documented before administration of the study drug. To establish an accurate baseline measurement, systolic and diastolic blood pressure will be measured after the Subject is rested for at least 5 minutes.

Pulse rate will be measured once by counting the number of heart beats over 60 seconds (the pulse rate should not be extrapolated after counting for part of 60 seconds).

If needed, at the independent safety assessor's discretion, pulse rate and BP may be measured in triplicate (at 1-2 minute intervals using the same arm for each repeat). The lowest pre-dose value of supine pulse rate and BP (based on the systolic BP) will be taken as the visit baseline measure and used for comparison to post-dose values.

Orthostatic (postural) vital signs: orthostatic (postural) vital signs, including blood pressure and pulse rate will be obtained 2-5 minutes after a subject stands ([redacted] If needed, at the independent safety assessor's discretion, pulse rate and BP may be measured in triplicate (at 1-2 minute intervals).[18]

[redacted]

ECG: a predose 12-lead ECG using an appropriate device [redacted]) will be obtained.

[redacted]

HR/ECG monitoring: [redacted] ECG recording using an appropriate device [redacted]) will be performed [redacted]

[redacted]

[redacted]

[redacted]

Pulse rate will be measured once by counting the number of heart beats over 60 seconds (the pulse rate should not be extrapolated after counting for part of 60 seconds).

If needed, at the independent safety assessor's discretion, pulse rate and BP may be measured in triplicate (at 1-2 minute intervals using the same arm for each repeat).The lowest post-dose values of HR and BP (based on the systolic BP) will be taken as the measures for the corresponding time point.

Orthostatic (postural) vital signs: orthostatic (postural) vital signs, including blood pressure and pulse rate 2-5 minutes after a subject stands, will be documented [redacted] If needed, at the independent safety assessor's discretion, pulse rate and BP may be measured in triplicate (at 1-2 minute intervals).

[redacted]

The treatment period should not be extended beyond 52 weeks due to missed doses or treatment interruption periods. Subjects whose condition worsens should be re-evaluated by the Investigator and management reconsidered.

[redacted]

[redacted]

Pulmonary Function Tests (PFTs):

Unscheduled PFTs should be performed in subjects with respiratory symptoms such as dyspnea, shortness of breath, chest tightness, wheezing after an assessment by the Investigator. The Investigator shall decide if additional assessment by a pulmonologist is needed based on results of the PFTs. A decision on the study treatment interruption and/or discontinuation shall be taken in consultation with the pulmonologist, the Independent Safety Assessor and the independent MM.

Ophthalmological examination:

Unscheduled comprehensive eye examination should be performed in subjects with visual disturbances.

[redacted]

Infections:

In the case of suspected or confirmed serious infection, the Investigator should report the event as an AESI to the CRO MM and independent MM within 24 hours. Treatment interruption and/or

discontinuation can be considered in consultation with the independent safety assessor and the independent MM.

Progressive multifocal leukoencephalopathy (PML):

If PML is suspected, the study treatment should be withdrawn until PML has been excluded, and the subject should immediately receive emergency care for proper diagnosis and/or treatment.

If PML is diagnosed, the subject should be discontinued from the study and followed up for safety according to Section 10.

Posterior reversible encephalopathy syndrome (PRES):

If PRES is suspected, the study treatment should be withdrawn until PRES has been excluded.

If a subject develops any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the Investigator or the independent safety assessor and the independent MM should promptly schedule a complete physical and neurological examination and should consider a magnetic resonance imaging (MRI).

At the discretion of the Investigator, the subject may also be referred to emergency care for proper diagnosis and/or treatment.

If PRES is diagnosed, the subject should be discontinued from the study and followed up for safety according to Section 10.

[redacted]

Medical Monitor/Sponsor notification is required before removing subjects for any of the reasons noted above at the earliest.

The Principal Investigator must strive to follow the subjects who are discontinued for any of the above-mentioned reasons due to safety until the adverse event has resolved, becomes clinically insignificant, is stabilized or the subject is lost to follow-up.

[redacted]

6 STUDY EVALUATIONS

6.1 Efficacy

Efficacy assessments should be performed by the Investigator or a designee who is appropriately trained and experienced in the assessment of psoriasis patients.

[redacted]

[redacted]

IGA assessments should be done by the Investigator before performing other efficacy assessments and after obtaining the subject questionnaires.

The ACR components (Tender and Swollen Joint Count and PGA) assessments are to be performed by an independent Investigator rheumatologist or an orthopaedist, or a qualified trained designee. The PsA assessments are not applicable at sites where an independent assessor experienced in performing joint assessments is not available.

Subjects who worsen beyond their scores at baseline will be described in the safety evaluation.

6.1.1 Dermatology Life Quality Index (DLQI) [19]

At the study visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) subjects will be asked to complete a 10-item questionnaire to measure how much the skin problem has affected subject's life over the past week. (Appendix IV) The scoring of each question is as follows:

Response	Score
Very much | Yes	3
A lot	2
A little	1
Not relevant | Not at all | 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:

Total score	Effect on patient's life
0 – 1	no effect at all
2 – 5	small effect
6 – 10	moderate effect
11 – 20	very large effect
21 – 30	extremely large

6.1.2 Psoriasis Symptoms and Signs diary (PSSD) [20]

At the study visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) subjects will be asked to complete an 11-item questionnaire to assess symptoms and patient-observable signs in psoriasis in the past week using a 0-10 numerical rating scale. (Appendix V) Summary scores range from 0 to 100, and a higher score indicates more severe disease.

6.1.3 Patient Global Impression of Severity (PGIS) [21]

At the study Visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) subjects will be asked to assess their overall impression of disease severity over the past week using a scale of None, Mild, Moderate or Severe. (Appendix VI)

6.1.4 Patient Global Impression of Change (PGIC) [21]

At the study visits 10, 15, 16, and 19 (study Weeks 16, 20, 28, and 52) subjects will be asked to assess if there has been an improvement or decline in clinical status using a 5-point scale depicting a patient's rating of overall improvement. (Appendix VII)

6.1.5 Itch Numeric Rating Scale (itch NRS)

At the study Visits 2, 10, 15, 16, and 19 (study weeks 0, 16, 20, 28, and 52) subjects will be asked to assess severity of itching due to psoriasis perceived over past 24 hours at the moment of scoring on

an 11-point scale anchored at 0, representing 'No itch' and 10, representing 'Worst itch imaginable'. (Appendix VIII)

6.1.6 Scalp Itch Numeric Rating Scale (scalp itch NRS) – *for subjects with Scalp psoriasis*

At the study Visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) subjects will be asked to assess severity of itching of the scalp due to psoriasis perceived over past 24 hours at the moment of scoring on an 11-point scale anchored at 0, representing 'No scalp itch' and 10, representing 'Worst scalp itch imaginable'. (Appendix VIII)

6.1.7 Health Assessment Questionnaire of disability (HAQ-DI) – *for subjects with PsA*

The HAQ-DI is a component of American College of Rheumatology (ACR) response Assessments. ACR response assessments will be performed only in subjects who meet the CASPAR Criteria. (see 6.1.16) The ACR components evaluations will be used to calculate the subject's ACR response criteria (ACR20 / 50 / 70)

At the study Visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) the subject will assess their general disability using the HAQ-DI questionnaire. The HAQ-DI is designed to assess patients' usual abilities using their usual equipment. The time frame for the disability questions is the past week and scoring within each section is from 0 (without any difficulty) to 3 (unable to do). (Appendix IX) A higher score indicates greater disability.

6.1.8 Patient Global Assessment of Disease Activity (PtGA) – *for subjects with PsA*

The PtGA is a component of American College of Rheumatology (ACR) response Assessments. ACR response assessments will be performed only in subjects who meet the CASPAR Criteria. (see 6.1.16) The ACR components evaluations will be used to calculate the subject's ACR response criteria (ACR20 / 50 / 70)

At the study visits 2, 10, 15, 16, and 19 (study weeks 0, 16, 20, 28, and 52) the subject will assess their current ('today') global status of PsA using a Visual Analogue Scale (VAS) of 0 to 100. (Appendix X)

6.1.9 Patient Assessment of Pain (PtA-P) – *for subjects with PsA*

The PtA-P is individual measurement and also a component of American College of Rheumatology (ACR) response Assessments. PtA-P assessments will be performed only in subjects who meet the CASPAR Criteria. (see 6.1.16)

At the study visits 2, 10, 15, 16, and 19 (study weeks 0, 16, 20, 28, and 52) the subject will assess their pain due to PsA using a Visual Analogue Scale (VAS). It is a subjective measure of pain. It is a continuous scale, 100 mm in length, anchored by 2 verbal descriptors, one for each symptom extreme ("no pain" and "worst pain imaginable"). Subjects are asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The distance along the line from the "no pain" marker is then measured with a calibrated ruler giving a pain score out of 100. (Appendix XI)

6.1.10 Investigator's Global Assessment (IGA)

At Screening and Baseline, to be eligible for inclusion in the study, subjects must have a definite clinical diagnosis of psoriasis of at least moderate severity (IGA score ≥ 3) as an overall assessment of all psoriatic lesions.

[redacted] the Investigator will perform an average assessment of all psoriatic lesions based on erythema, scale, and induration. The static IGA determines psoriasis severity at a single point in time, without taking the baseline disease condition into consideration. The following scale will be used for the IGA:

Table 1: Investigator's Global Assessment (IGA)

Score	Grade	Description
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]

6.1.11 Scalp IGA – *for subjects with Scalp psoriasis*

Scalp IGA assessments will be performed only in subjects with scalp psoriasis.

At the study Visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) the Investigator will perform an overall assessment of all scalp psoriasis lesions. The static Scalp IGA determines psoriasis severity at a single point in time, without taking the baseline disease condition into consideration. The following scale will be used for the Scalp IGA:

Table 2: Scalp Investigator's Global Assessment (IGA)

Score	Grade	Description
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]

6.1.12 Palmoplantar Physician Global Assessment (PPPGA) – ***for subjects with Palmoplantar psoriasis***

Palmoplantar Physician Global Assessment (PPPGA) will be performed only in subjects with palmoplantar psoriasis. [22]

At the study visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) the Investigator will perform an overall assessment palmoplantar involvement with a 5-point scale. The static PPPGA determines psoriasis severity at a single point in time, without taking the baseline disease condition into consideration. The following scale will be used for the PPPGA:

Table 3: Palmoplantar Physician Global Assessment (PPPGA)

Score	Grade	Description
0	[redacted]	[redacted]
1	[redacted]	[redacted]

Score	Grade	Description
2	[redacted]	
3	[redacted]	
4	[redacted]	

6.1.13 Psoriasis Area and Severity Index (PASI) evaluation

At Screening and baseline, to be eligible for inclusion in the study, subjects must have a definite clinical diagnosis of psoriasis of at least moderate severity (PASI score ≥ 12) as an overall assessment of all psoriatic lesions.

[redacted] the Investigator will perform psoriasis severity using PASI evaluations. The PASI is a measure of the average redness (erythema), thickness (induration), and scaliness (scaling) of psoriatic skin lesions (each graded on a 0–4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks). The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. Investigators will perform the efficacy assessments of PASI based on the guidance provided in the training module of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA module) (Appendix III)

PASI scores will be used to calculate the subject's PASI response criteria (PASI50, PASI75, PASI90, and PASI100). PASI75 response indicates an improvement in PASI score by at least 75% as compared with a baseline value.

The following PASI scale will be used to evaluate the severity of clinical signs:

Table 4: Psoriasis Area and Severity Index (PASI): Severity

	Severity			
Score	**Grade**	**Redness** (Erythema)	**Thickness** (Induration)	**Scaliness** (scaling)
0	[redacted]			
1	[redacted]			
2	[redacted]			
3	[redacted]			
4	[redacted]			

The total PASI score is calculated as follows (to be performed programmatically by DM):

Area	PASI Clinical Signs Severity Score			Total Severity Score	Extent*	Weighting factor	Total
	Redness	Thickness	Scaliness				
Head and neck	+	+	=	x	x	0.1	=
Arms	+	+	=	x	x	0.2	=
Trunk	+	+	=	x	x	0.3	=
Legs	+	+	=	x	x	0.4	=
				Total PASI Score (sum of above)			=

*the Extent of area involving psoriasis is assigned according to the table below:

Extent	% affected
0	0 (noninvolvement)
1	< 10%
2	10 – 29%
3	30 – 49%
4	50 – 69%
5	70 – 89%
6	90 – 100%

6.1.14 Body Surface Area (BSA)

At Screening and Baseline, to be eligible for inclusion in the study, Subjects must have a definite clinical diagnosis of psoriasis of at least moderate severity (BSA involvement ≥ 10%) as an overall assessment of all psoriatic lesions. The handprint method will be used to estimate % BSA.

[redacted] the Investigator will assess % BSA affected with psoriasis using instructions in Appendix II.

6.1.15 Modified Nail Psoriasis Severity Index (mNAPSI) – *for subjects with Nail psoriasis*

Modified Nail Psoriasis Severity Index assessments will be performed only in subjects with nail psoriasis. [23]

[redacted] the Investigator will perform an assessment of each affected finger nail abnormality. The mNAPSI produces a numeric score that can range from 0 to 130 (maximum of 13 for each fingernail), with higher mNAPSI scores denoting more severe disease activity. The following scale will be used for the mNAPSI:

Table 5: Modified Nail Psoriasis Severity Index (mNAPSI)

Nail abnormality	Score and Description
Onycholysis and oil-drop (salmon patch) dyschromia	0 = No onycholysis or oil drop dyschromia present 1 = 1–10% of the nail has onycholysis or oil-drop dyschromia 2 = 11–30% of the nail has onycholysis or oil-drop dyschromia 3 = > 30% of the nail has onycholysis or oil-drop dyschromia
Pitting	0 = No pitting 1 = 1–10 pits 2 = 11–49 pits 3 = ≥ 50 pits
Nail plate crumbling	0 = No crumbling 1 = 1–25% of the nail has crumbling 2 = 26–50% of the nail has crumbling 3 = > 50% of the nail has crumbling
Leukonychia	0 = Absent 1 = Present
Splinter hemorrhages	0 = Absent

Nail abnormality	Score and Description
	1 = Present
Hyperkeratosis	0 = Absent 1 = Present
Red spots in the lunula	0 = Absent 1 = Present

6.1.16 CASPAR Classification Criteria for Psoriatic Arthritis

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 Classification of Psoriatic Arthritis (CASPAR) criteria. [12] 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

Table 6: CASPAR Classification Criteria for Psoriatic Arthritis

Required criterion (must be Yes)	
• inflammatory joint disease (peripheral, axial or enthesitis)	
and additional categories (must have 3 points or more)	
1. Evidence of skin psoriasis (*select the option that assigns the most points, (e.g., if both current psoriasis and family history, select current psoriasis*)	
• Current	2 points
• personal history	1 point
• family history	1 point
2. Psoriatic nail dystrophy *(onycholysis, pitting, and hyperkeratosis)*	1 point
3. Negative test results for rheumatoid factor	1 point
4. Dactylitis	
• current inflammation of an entire digit	1 point
• history of dactylitis recorded by a rheumatologist	1 point
5. Radiological evidence of juxta-articular new bone formation *(Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiograph of hands and feet)*	1 point

6.1.17 Tender and Swollen Joint count – ***for subjects with PsA***

The tender and swollen joint count is a component of American College of Rheumatology (ACR) response Assessments. ACR response assessments will be performed only in subjects who meet the CASPAR Criteria. (See 6.1.16) The ACR components evaluations will be used to calculate the subject's ACR response criteria (ACR20 / 50 / 70)

At the study Visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) tender and swollen joint counts will be performed by an independent Investigator rheumatologist or qualified trained designee.

Joint count includes the majority of joints affected in PsA, 68 for tenderness and 66 for swelling. It includes the temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist (including the carpometacarpal and intercarpal joints as 1 unit), metacarpophalangeal (MCP), proximal interphalangeal (PIP), DIP, hip, knee, talotibial, midtarsal (including subtalar), metatarsophalangeal, and interphalangeal joints of the toes (proximal and distal joints of each toe is counted as 1 unit) for assessment of tenderness. The 66 joints to be examined for swelling are the same as those of tenderness, except the hip joints are not included. The assessments will be performed using instructions in Appendix XII and tender and swollen joint numbers will be recorded in a Joint Count Scoring Sheet.

6.1.18 Physician Global Assessment of Disease Activity (PGA) – *for subjects with PsA*

The PGA is a component of American College of Rheumatology (ACR) response assessments. ACR response assessments will be performed only in subjects who meet the CASPAR Criteria. (see 6.1.16) The ACR components evaluations will be used to calculate the subject's ACR response criteria (ACR20 / 50 / 70)

At the study Visits 2, 10, 15, 16, and 19 (study Weeks 0, 16, 20, 28, and 52) the status of the subject's PsA will be assessed by an independent Investigator rheumatologist or qualified trained designee using a VAS of 0 to 100. The subject will be assessed according to how their current arthritis is. The VAS will be anchored with verbal descriptors of "No Disease Activity" to "Maximum Disease Activity" (Appendix XIII)

6.1.19 American College of Rheumatology (ACR) response Assessments

ACR response assessments will be performed only in subjects who meet the CASPAR Criteria. (See 6.1.16) 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 (PtA-P) 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.

ACR50 and ACR70 are the same measurements with improvement levels defined as 50% and 70% respectively.

6.2 Pharmacokinetics

Blood (approximately 4 ml) will be collected for each PK sample. Pre-dose (trough) PK samples (within one hour before dosing) will be collected at study Visits 10, 15, 16, and 19 (study Weeks 16, 20, 28, and 52).

In addition, PK sample will be collected, if possible, approximately 1 hour within the onset of an adverse event related to bradycardia during on-site visits with dose titration monitoring.

PK samples collected only from the active treatment groups will be analysed in an unblinded manner.

The plasma samples collected at above-mentioned time points may be used for assay of metabolites, if required.

[redacted]

6.3 Pharmacodynamic (PD) biomarkers

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

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

Additional biomarkers may be included during the study.

[redacted]

Subjects who are withdrawn permanently from study drug but remain in the study should not have any more PD biomarker samples taken.

6.4 Photography (Optional)

Photography is an optional procedure in the study. Only at selected centers that have the ability and expertise taking digital photographs, the subjects will be asked if they want to participate in the photography portion of this study. The subject must indicate in the informed consent form if he/she consents to photography in the study. At the study Visits 2, 10, and 19 (study Weeks 0, 16, and 52), photography will be performed of the overall body. Photographs will be used for visual evaluation only and will not be included in any analyses. Details of photographic evaluation including handling, labeling and transfer of photographs will be included in a photography manual.

7 STUDY VISITS

At study visits the efficacy assessments have to be performed in the following order:

- the patient-rated questionnaires like DLQI, itch NRS, PtA-P, HAQ-DI, must be completed prior to the Investigator assessments
- Investigator Global assessment (IGA) for Psoriasis, Scalp only IGA, PPPGA, PGA for Psoriatic arthritis must be completed prior to other efficacy assessments
- PASI, BSA, mNAPSI, remaining components of ACR assessment in PsA subjects.

ACR20 assessments will be performed by an Independent Joint Assessor (independent Investigator rheumatologist or an orthopedist, or a qualified trained designee). ACR20 assessments are not applicable at sites where an independent assessor experienced in performing joint assessments is not available. The subject and his/her caregiver will be instructed to take care not to discuss aspects of the subject's treatment with the Investigator or the joint assessor.

The Central Independent MM will inform the Safety Assessor at the site if alert values are met for ALC and if repeat tests or dose interruption are needed because of laboratory abnormalities or because of findings from dose titration monitoring.

If necessary due to the 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 CRO's and the Sponsor's medical monitor before planning. Scheduled blood collection (for these visits only) may be waived if the individual subjects have not had clinically significant changes or undesired trend in laboratory or chemistry values

prior to Visit 15. Remote assessments or delayed Visits 17 or 18 will be recorded in the source documents and noted as a minor protocol deviation.

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 case report form 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).

7.1 FOR ALL SUBJECTS [redacted]

See Study Visit Schedule

On-site Visit 1: Screening Visit (Week ≥ -4 / Day -28 to -1);
On-site Visit 2: Baseline Visit (Week 0 / Day 1; before 12 noon);
On-site Visit 7: [redacted];
On-site Visit 8: [redacted]);
On-site Visit 9: [redacted]
On-site Visit 10: [redacted]);
On-site Visit 14: ([redacted]
On-site Visit 15: [redacted]
On-site Visit 16: [redacted]
On-site Visit 17: [redacted]
On-site Visit 18: [redacted]
On-site Visit 19: End of Treatment Visit (Week 52 / Day 365 ± 3 Days; before 12 noon);
On-site Visit 20: Follow-up Visit (Week 56 / Day 393 ± 3 Days);

Phone or in person contacts may be scheduled for [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]

For on-site visits conducted in the morning, study drug administration should be done in a clinic to ensure dosing before 12:00 (noon).

7.1.1 On-site Visit 1: Screening Visit (Week ≥-4 / Day -28 to -1)

Potential subjects will be screened during a 4-week period prior to randomization. CRO/Sponsor's approval is required on a case-by-case basis for an extension of the Screening Period to obtain all test results and to re-screen a subject. [redacted] The new informed consent/assent is not required, unless an amended or revised informed consent/assent is introduced during the study.

The following procedures will be performed at Screening:

1. **Written informed consent will be obtained**. Subjects must have provided IRB approved written informed consent. Subjects will be given the approved ICF describing the study and any risks associated with participation. The subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the subject might have regarding the study or study-related procedures. If the subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. The ICF must be signed by the subject before any protocol assessments can be undertaken.
2. Demographics will be collected, including date of birth, gender, race and ethnicity.
3. A compliance with applicable inclusion and exclusion criteria will be reviewed. (See Sections 4.2, 4.3)
4. After confirming the eligibility, the subject will be assigned a screening number.

5. A complete medical history will be obtained for the Subject's current and past medical conditions, including a complete list of current and past (within the previous 30 days) medications. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity*, heart attack, stroke, congestive heart failure, kidney disease, and auto immune disease and diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal. (See Section 5.1)

   * Obesity = BMI ≥30 (as defined by Metropolitan Life Insurance Company Chart)

6. A physical examination will be performed. At a minimum, the physical examination will include the following: height, weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
7. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
8. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
9. Blood samples will be collected for Hematology, Lipid Profile, Chemistry, Coagulation profile, Serology, QuantiFERON Gold test, and Serum pregnancy test for women of childbearing potential (See Sections 5.5 and 5.4)
10. Any AEs occurring after signing Informed Consent should be reported (See Section 5.9)
11. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
12. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
13. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.12)
14. A pulmonary function test will be performed or scheduled with an external expert (See Section 5.6)
15. An ophthalmologic examination including OCT will be performed or scheduled with an external expert (See Section 5.7)
16. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
17. The overall status of the Subject's psoriasis will be assessed using the IGA. (See Section 6.1.10). To be included in the study, subjects must have plaque psoriasis with moderate (3) score or higher.
18. Psoriasis Area Severity Index (PASI) will be evaluated. To be included in the study, subjects must have plaque psoriasis with PASI score 12 or higher (See Section 6.1.13)
19. Body Surface Area (BSA) involvement will be assessed. To be included in the study, subjects must have plaque psoriasis with BSA involvement 10% or higher (See Section 6.1.14)
20. Evaluate CASPAR criteria for diagnosis of PsA; may include assessment of rheumatoid factor and/or X-ray (See Section 6.1.16).
21. The following will be dispensed during Screening visit:
    - A diary card to record health changes and concomitant medication
22. On-site Visit 2 (Study Day 1; before 12 noon) will be scheduled and the Subject will be instructed to bring the subject diary with him or her to this visit.

7.1.2 On-site Visit 2: Baseline Visit (Week 0 / Day 1; before 12 noon)

If the Screening assessment was completed more than 2 weeks prior:

1. A physical examination will be performed. At a minimum, the physical examination will include the following: height, weight, assessment of general appearance, comprehensive skin examination,

HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)

2. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
3. A blood sample(s) will be collected for Hematology, Lipid Profile, Chemistry, and Coagulation (See Section 5.5)
4. CASPAR criteria – *for subjects with PsA* (See Section 6.1.16)

The following procedures will be performed at Baseline:

5. Compliance with the inclusion and exclusion criteria, including results of laboratory evaluations, a pulmonary function test, and an ophthalmologic examination will be reviewed.
6. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
7. After confirming the eligibility, the Subject will be assigned a randomization number using Interactive Response Technology (IRT). (see Section 8.4.1)
8. The Subject's diary provided at the previous visit will be collected and reviewed.
9. A medical history will be updated with any changes of the Subject's health since the previous study visit. (See Section 5.1)
10. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
11. A blood sample will be collected for PD biomarkers sample (See Section 6.3)
12. A blood sample will be collected for C-reactive protein (CRP) – (See Section 5.5)
13. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
14. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
15. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
16. Subject Reported Assessments will be collected for:
    - Dermatology Life Quality Index (DLQI) (See Section 6.1.1)
    - Psoriasis Symptoms and Signs Diary (PSSD) (See Section 6.1.2)
    - Patient Global Impression of Severity (PGIS) (See Section 6.1.3)
    - Itch Numeric Rating Scale (itch NRS) (See Section 6.1.5)
    - Scalp Itch Numeric Rating Scale (scalp itch NRS) – *for subjects with Scalp psoriasis* (See Section 6.1.6)
    - Health Assessment Questionnaire of disability (HAQ-DI) – *for subjects with PsA* (See Section 6.1.7)
    - Patient Global Assessment of Disease Activity (PtGA) – *for subjects with PsA* (See Section 6.1.8)
    - Patient Assessment of Pain (PtA-P) – *for subjects with PsA* (See Section 6.1.9)
17. Focused Area Assessments will be performed for:
    - Investigator's Global Assessment (IGA) (See Section 6.1.10)
    - Scalp Investigator's Global Assessment (Scalp IGA) – *for subjects with Scalp psoriasis* (See Section 6.1.11)
    - Palmoplantar Physician Global Assessment (PPPGA) – *for subjects with Palmoplantar Psoriasis* (See Section 6.1.12)
    - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)
    - Body Surface Area (BSA) (See Section 6.1.14)
    - modified Nail Psoriasis Severity Index (mNAPSI) – *for subjects with Nail psoriasis*

Following will be assessed by an independent assessor (See Section 6.1.15)
- Tender and Swollen Joint Count – *for subjects with PsA* (See Section 6.1.17)
- Physician Global Assessment of Disease Activity (PGA) – *for subjects with PsA* (See Section 6.1.18)

18. A whole-body photography – *for subjects consenting for photography* (See Section 6.4)
19. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
20. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results
21. Study drug administration in a clinic before 12 noon (See Section 8.5)

[redacted]

23. A general safety review before discharge

[redacted]

7.1.3 On-site Visit 7: Visit ([redacted])

The following procedures will be performed at Visit 7:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
2. Focused Area Assessments will be performed for:
    - Investigator's Global Assessment (IGA) (See Section 6.1.10)
    - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)

The following procedures will be performed by an independent safety team:

3. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
4. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
5. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
6. The Subject's diary provided at the previous visit will be collected and reviewed.
7. The returned study drugs will be counted
8. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)

9. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
10. A blood sample(s) will be collected for (See Section 5.5):
    - Hematology (total WBC count with differential counts including ALC and ANC)
    - Chemistry
11. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results

The following procedures will be performed prior a subject discharged from a clinic:

12. The following will be dispensed during Visit 7:
    - The study drug assembled for Visit 7
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
13. A general safety review before discharge
14. [redacted]

7.1.4 On-site Visit 8: Visit ([redacted])

The following procedures will be performed at Visit 8:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
2. Focused Area Assessments will be performed for:
    - Investigator's Global Assessment (IGA) (See Section 6.1.10)
    - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)

The following procedures will be performed by an independent safety team:

3. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
4. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
5. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
6. The Subject's diary provided at the previous visit will be collected and reviewed.
7. The returned study drugs will be counted
8. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
9. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
10. A blood sample(s) will be collected for Hematology and Chemistry (See Section 5.5)

11. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results

The following procedures will be performed prior a subject discharged from a clinic:

12. The following will be dispensed during Visit 8:
    - The study drug assembled for Visit 8
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
13. A general safety review before discharge
14. [redacted]

7.1.5 On-site Visit 9: Visit [redacted]

The following procedures will be performed at Visit 9:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
2. Focused Area Assessments will be performed for:
    - Investigator's Global Assessment (IGA) (See Section 6.1.10)
    - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)
    - Body Surface Area (BSA) (See Section 6.1.14)

The following procedures will be performed by an independent safety team:

3. An ophthalmologic examination including OCT will be performed or scheduled with an external expert (See Section 5.7)
4. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
5. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
6. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
7. The Subject's diary provided at the previous visit will be collected and reviewed.
8. The returned study drugs will be counted
9. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
10. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
11. A blood sample will be collected for Hematology (See Section 5.5)
12. A blood sample will be collected for PD biomarkers sample (See Section 6.3)
13. Independent Safety Assessor review:
    - Safety Lab Alerts

- [redacted]
- As available
    i. Lab results
    ii. Exam results

The following procedures will be performed prior a subject discharged from a clinic:

14. The following will be dispensed during Visit 9:
    - The study drug assembled for Visit 9
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
15. A general safety review before discharge
16. [redacted].

7.1.6 On-site Visit 10: Visit [redacted]

The visit 10 must be scheduled in a morning to allow the dosing before 12 noon.

The following procedures will be performed at Visit 10:

1. Subject Reported Assessments will be collected for:
    - Dermatology Life Quality Index (DLQI) (See Section 6.1.1)
    - Psoriasis Symptoms and Signs Diary (PSSD) (See Section 6.1.2)
    - Patient Global Impression of Severity (PGIS) (See Section 6.1.3)
    - Patient Global Impression of Change (PGIC) (See Section 6.1.4)
    - Itch Numeric Rating Scale (itch NRS) (See Section 6.1.5)
    - Scalp Itch Numeric Rating Scale (scalp itch NRS) – *for subjects with Scalp psoriasis* (See Section 6.1.6)
    - Health Assessment Questionnaire of disability (HAQ-DI) – *for subjects with PsA* (See Section 6.1.7)
    - Patient Global Assessment of Disease Activity (PtGA) – *for subjects with PsA* (See Section 6.1.8)
    - Patient Assessment of Pain (PtA-P) – *for subjects with PsA* (See Section 6.1.9)
2. Focused Area Assessments will be performed for:
    - Investigator's Global Assessment (IGA) (See Section 6.1.10)
    - Scalp Investigator's Global Assessment (Scalp IGA) – *for subjects with Scalp psoriasis* (See Section 6.1.11)
    - Palmoplantar Physician Global Assessment (PPPGA) – *for subjects with Palmoplantar Psoriasis* (See Section 6.1.12)
    - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)
    - Body Surface Area (BSA) (See Section 6.1.14)
    - modified Nail Psoriasis Severity Index (mNAPSI) – *for subjects with Nail psoriasis*

    Following will be assessed by an independent assessor (See Section 6.1.15)
    - Tender and Swollen Joint Count – *for subjects with PsA* (See Section 6.1.17)
    - Physician Global Assessment of Disease Activity (PGA) – *for subjects with PsA* (See Section 6.1.18)
3. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
4. IRT system consulted for re-randomization and selection of kit
5. A whole body photography – *for subjects consenting for photography* (See Section 6.4)

The following procedures will be performed by an independent safety team:

6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
7. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
8. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
9. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
10. The Subject's body weight will be measured while the Subject is lightly clothed (e.g., no coat or shoes)
11. The Subject's diary provided at the previous visit will be collected and reviewed.
12. The returned study drugs will be counted
13. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
14. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
15. A blood sample will be collected for Hematology, Lipid Profile, Chemistry, and Coagulation profile (See Section 5.5)
16. A blood sample will be collected for PD biomarkers sample (See Section 6.3)
17. A blood sample will be collected within one hour before dosing for PK testing (See Section 6.2)
18. A blood sample will be collected for C-reactive protein (CRP) – (See Section 5.5)
19. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results
20. Study drug administration in a clinic before 12 noon (See Section 8.5)
21. [redacted]
22. A general safety review before discharge
23. On-site Visit 14 (Study Day 134 ±1 Day) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used packs), and Subject diary with him or her to this visit.
24. [redacted]

- [redacted]
- [redacted]

7.1.7 On-site Visit 14: Visit [redacted]

The following procedures will be performed by an independent safety team at Visit 14:

1. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
2. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
3. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
4. The Subject's diary provided at the previous visit will be collected and reviewed.
5. The returned study drugs will be counted
6. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
7. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
8. A blood sample will be collected for Hematology (See Section 5.5)
9. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results
10. The following will be dispensed during Visit 14:
    - The study drug assembled for Visit 14
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
11. A general safety review before discharge
12. [redacted]

7.1.8 On-site Visit 15: Visit ([redacted])

The following procedures will be performed at Visit 15:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
2. Subject Reported Assessments will be collected for:
    - Dermatology Life Quality Index (DLQI) (See Section 6.1.1)
    - Psoriasis Symptoms and Signs Diary (PSSD) (See Section 6.1.2)
    - Patient Global Impression of Severity (PGIS) (See Section 6.1.3)
    - Patient Global Impression of Change (PGIC) (See Section 6.1.4)

- Itch Numeric Rating Scale (itch NRS) (See Section 6.1.5)
- Scalp Itch Numeric Rating Scale (scalp itch NRS) – *for subjects with Scalp psoriasis* (See Section 6.1.6)
- Health Assessment Questionnaire of disability (HAQ-DI) – *for subjects with PsA* (See Section 6.1.7)
- Patient Global Assessment of Disease Activity (PtGA) – *for subjects with PsA* (See Section 6.1.8)
- Patient Assessment of Pain (PtA-P) – *for subjects with PsA* (See Section 6.1.9)

3. Focused Area Assessments will be performed for:
    - Investigator's Global Assessment (IGA) (See Section 6.1.10)
    - Scalp Investigator's Global Assessment (Scalp IGA) – *for subjects with Scalp psoriasis* (See Section 6.1.11)
    - Palmoplantar Physician Global Assessment (PPPGA) – *for subjects with Palmoplantar Psoriasis* (See Section 6.1.12)
    - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)
    - Body Surface Area (BSA) (See Section 6.1.14)
    - modified Nail Psoriasis Severity Index (mNAPSI) – *for subjects with Nail psoriasis*

    Following will be assessed by an independent assessor (See Section 6.1.15)
    - Tender and Swollen Joint Count – *for subjects with PsA* (See Section 6.1.17)
    - Physician Global Assessment of Disease Activity (PGA) – *for subjects with PsA* (See Section 6.1.18)

<u>The following procedures will be performed by an independent safety team:</u>

4. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
5. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
6. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
7. The Subject's diary provided at the previous visit will be collected and reviewed.
8. The returned study drugs will be counted
9. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
10. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
11. A blood sample(s) will be collected for Hematology and Chemistry (See Section 5.5)
12. A blood sample will be collected within one hour before dosing for PK testing (See Section 6.2)
13. Study drug administration in a clinic before 12 noon (See Section 8.5)
14. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results

<u>The following procedures will be performed prior a subject discharged from a clinic:</u>

15. The following will be dispensed during Visit 15:
    - UPT to be performed at home at week 24 – *for female Subjects of childbearing potential* (see section 5.4)
    - The study drug assembled for Visit 15
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
16. A general safety review before discharge
17. [redacted]
18. A phone call will be scheduled at the study week 24 to collect information on the study drug use, UPT, health changes and concomitant medication.

7.1.9 On-site Visit 16: Visit ([redacted])

The following procedures will be performed at Visit 16:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
2. Subject Reported Assessments will be collected for:
    - Dermatology Life Quality Index (DLQI) (See Section 6.1.1)
    - Psoriasis Symptoms and Signs Diary (PSSD) (See Section 6.1.2)
    - Patient Global Impression of Severity (PGIS) (See Section 6.1.3)
    - Patient Global Impression of Change (PGIC) (See Section 6.1.4)
    - Itch Numeric Rating Scale (itch NRS) (See Section 6.1.5)
    - Scalp Itch Numeric Rating Scale (scalp itch NRS) – *for subjects with Scalp psoriasis* (See Section 6.1.6)
    - Health Assessment Questionnaire of disability (HAQ-DI) – *for subjects with PsA* (See Section 6.1.7)
    - Patient Global Assessment of Disease Activity (PtGA) – *for subjects with PsA* (See Section 6.1.8)
    - Patient Assessment of Pain (PtA-P) – *for subjects with PsA* (See Section 6.1.9)
3. Focused Area Assessments will be performed for:
    - Investigator's Global Assessment (IGA) (See Section 6.1.10)
    - Scalp Investigator's Global Assessment (Scalp IGA) – *for subjects with Scalp psoriasis* (See Section 6.1.11)
    - Palmoplantar Physician Global Assessment (PPPGA) – *for subjects with Palmoplantar Psoriasis* (See Section 6.1.12)
    - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)
    - Body Surface Area (BSA) (See Section 6.1.14)
    - modified Nail Psoriasis Severity Index (mNAPSI) – *for subjects with Nail psoriasis*

    Following will be assessed by an independent assessor (See Section 6.1.15)
    - Tender and Swollen Joint Count – *for subjects with PsA* (See Section 6.1.17)
    - Physician Global Assessment of Disease Activity (PGA) – *for subjects with PsA* (See Section 6.1.18)

The following procedures will be performed by an independent safety team:

4. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
5. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)

6. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
7. The Subject's diary provided at the previous visit will be collected and reviewed.
8. The returned study drugs will be counted
9. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
10. A blood sample(s) will be collected for Hematology, Chemistry, and Coagulation profile (See Section 5.5)
11. A blood sample will be collected for PD biomarkers sample (See Section 6.3)
12. A blood sample will be collected within one hour before dosing for PK testing (See Section 6.2)
13. A blood sample will be collected for C-reactive protein (CRP) – (See Section 5.5)
14. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)

<u>If Subject eligible to continue the study drug dosing based on PASI response ≥75</u>

15. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results
16. Study drug administration in a clinic before 12 noon (See Section 8.5)
17. The following will be dispensed during Visit 16:
    - The study drug assembled for Visit 16
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
18. A general safety review before discharge
19. [redacted]

<u>If Subject discontinue from the study drug dosing based on PASI response <75</u> (*the visit is to be reported as End of Treatment*<u>)</u>

15. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results
16. The following will be dispensed during Visit 16:
    a. A diary card with instructions and to record health changes and concomitant medication
17. A general safety review before discharge

18. [redacted]

7.1.10 On-site Visit 17: Visit ([redacted])

The following procedures will be performed at Visit 17:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)

The following procedures will be performed by an independent safety team:

2. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
3. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
4. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
5. The Subject's diary provided at the previous visit will be collected and reviewed.
6. The returned study drugs will be counted
7. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
8. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
9. A blood sample will be collected for Hematology (See Section 5.5)
10. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results

The following procedures will be performed prior a subject discharged from a clinic:

11. The following will be dispensed during Visit 17:
    - UPT to be performed at home at week 36 – *for female Subjects of childbearing potential* (see section 5.4)
    - The study drug assembled for Visit 17
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
12. A general safety review before discharge
13. [redacted]
14. A phone call will be scheduled at the study week 36 to collect information on the study drug use, UPT, health changes and concomitant medication.

7.1.11 On-site Visit 18: Visit ([redacted])

The following procedures will be performed at Visit 18:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)

The following procedures will be performed by an independent safety team:

2. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
3. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
4. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
5. The Subject's diary provided at the previous visit will be collected and reviewed.
6. The returned study drugs will be counted
7. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
8. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
9. A blood sample will be collected for Hematology (See Section 5.5)
10. Independent Safety Assessor review:
    - Safety Lab Alerts
    - [redacted]
    - As available
        i. Lab results
        ii. Exam results

The following procedures will be performed prior a subject discharged from a clinic:

11. The following will be dispensed during Visit 18:
    - 2 UPT to be performed at home at weeks 44 and 48 – *for female Subjects of childbearing potential* (see section 5.4)
    - The study drug assembled for Visit 18
    - A diary card with instructions and to record the study drug use, health changes and concomitant medication
12. A general safety review before discharge
13. Visit 19 (Study Day 365 ± 3 Days; before 12 noon) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used packs) and Subject diary with him or her to this visit.
14. Phone calls will be scheduled at the study weeks 44 and 48 to collect information on the study drug use, UPT, health changes and concomitant medication.

7.1.12 On-site Visit 19: End of Treatment Visit (Week 52 / Day 365 ± 3 Days; before 12 noon)

The visit 19 must be scheduled in a morning to allow the dosing before 12 noon.

The following procedures will be performed at Visit 19:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
2. Subject Reported Assessments will be collected for:
    - Dermatology Life Quality Index (DLQI) (See Section 6.1.1)
    - Psoriasis Symptoms and Signs Diary (PSSD) (See Section 6.1.2)

- Patient Global Impression of Severity (PGIS) (See Section 6.1.3)
- Patient Global Impression of Change (PGIC) (See Section 6.1.4)
- Itch Numeric Rating Scale (itch NRS) (See Section 6.1.5)
- Scalp Itch Numeric Rating Scale (scalp itch NRS) – *for subjects with Scalp psoriasis* (See Section 6.1.6)
- Health Assessment Questionnaire of disability (HAQ-DI) – *for subjects with PsA* (See Section 6.1.7)
- Patient Global Assessment of Disease Activity (PtGA) – *for subjects with PsA* (See Section 6.1.8)
- Patient Assessment of Pain (PtA-P) – *for subjects with PsA* (See Section 6.1.9)

3. Focused Area Assessments will be performed for:
   - Investigator's Global Assessment (IGA) (See Section 6.1.10)
   - Scalp Investigator's Global Assessment (Scalp IGA) – *for subjects with Scalp psoriasis* (See Section 6.1.11)
   - Palmoplantar Physician Global Assessment (PPPGA) – *for subjects with Palmoplantar Psoriasis* (See Section 6.1.12)
   - Psoriasis Area Severity Index (PASI) (See Section 6.1.13)
   - Body Surface Area (BSA) (See Section 6.1.14)
   - modified Nail Psoriasis Severity Index (mNAPSI) – *for subjects with Nail psoriasis*

   Following will be assessed by an independent assessor (See Section 6.1.15)
   - Tender and Swollen Joint Count – *for subjects with PsA* (See Section 6.1.17)
   - Physician Global Assessment of Disease Activity (PGA) – *for subjects with PsA* (See Section 6.1.18)
4. A whole body photography – *for subjects consenting for photography* (See Section 6.4)

The following procedures will be performed by an independent safety team:

5. A physical examination will be performed. At a minimum, the physical examination will include the following: height and weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
6. The Subject's diary provided at the previous visit will be collected and reviewed.
7. The returned study drugs will be counted
8. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
9. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
10. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
11. A blood sample(s) will be collected for Hematology, Lipid Profile, Chemistry, and Coagulation profile (See Section 5.5)
12. A blood sample will be collected for PD biomarkers sample (See Section 6.3)
13. A blood sample will be collected within one hour before dosing for PK testing (See Section 6.2)
14. A blood sample will be collected for C-reactive protein (CRP) – (See Section 5.5)
15. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.12)
16. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.

17. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
18. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
19. A pulmonary function test will be performed or scheduled with an external expert (See Section 5.6)
20. An ophthalmologic examination including OCT will be performed or scheduled with an external expert (See Section 5.7)
21. Study drug administration in a clinic before 12 noon (See Section 8.5)
22. Independent Safety Assessor review:
    - Safety Lab Alerts
    - 12-lead ECG
    - As available
        i. Lab results
        ii. Exam results

The following procedures will be performed prior a subject discharged from a clinic:

23. The following will be dispensed during Visit 19:
    - A diary card with instructions and to record health changes and concomitant medication
24. A general safety review before discharge
25. Visit 20 (Study Day 393 ± 3 Days) will be scheduled and the Subject will be instructed to bring the Subject diary with him or her to this visit.

7.1.13 On-site Visit 20: Follow-up Visit (Week 56 / Day 393 ± 3 Days or 4 weeks after End of Treatment)

The following procedures will be performed at Visit 20:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)

The following procedures will be performed by an independent safety team:

2. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
3. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
4. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
5. The Subject's diary provided at the previous visit will be collected and reviewed.
6. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
7. A blood sample(s) will be collected, if needed for Hematology, Chemistry, and Coagulation profile that were abnormal and clinically significant at Visit 19 (EOT) (See Section 5.5)
8. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
9. A 12-lead electrocardiogram (ECG) will be performed, if needed (See Section 5.12)
10. Independent Safety Assessor review:

- If performed, 12-lead ECG
- Safety Lab Alerts
- As available
    i. Lab results
    ii. Exam results

11. A general safety review before discharge

[redacted]

[redacted]

[redacted]

7.1.15 Unscheduled Visits and Early Discontinuation Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Principal Investigator will determine whether additional visits are needed.

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 (additional procedures may be performed as needed):

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)

<u>The following procedures will be performed by an independent safety team:</u>

2. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.8)
3. The occurrence of all AEs & AESIs will be assessed and documented following the procedures in Sections 5.9, 10.1, and 10.3.
4. A query for PML (progressive multifocal leukoencephalopathy) will be performed (See Section 5.10)
5. A query for PRES (Posterior reversible encephalopathy syndrome) will be performed (See Section 5.11)
6. Independent Safety Assessor review:
    - As available:
        i. Lab results
        ii. Exam results

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.

If 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 treatment failure and a standard of care treatment may be advised at the Principal Investigator's discretion.

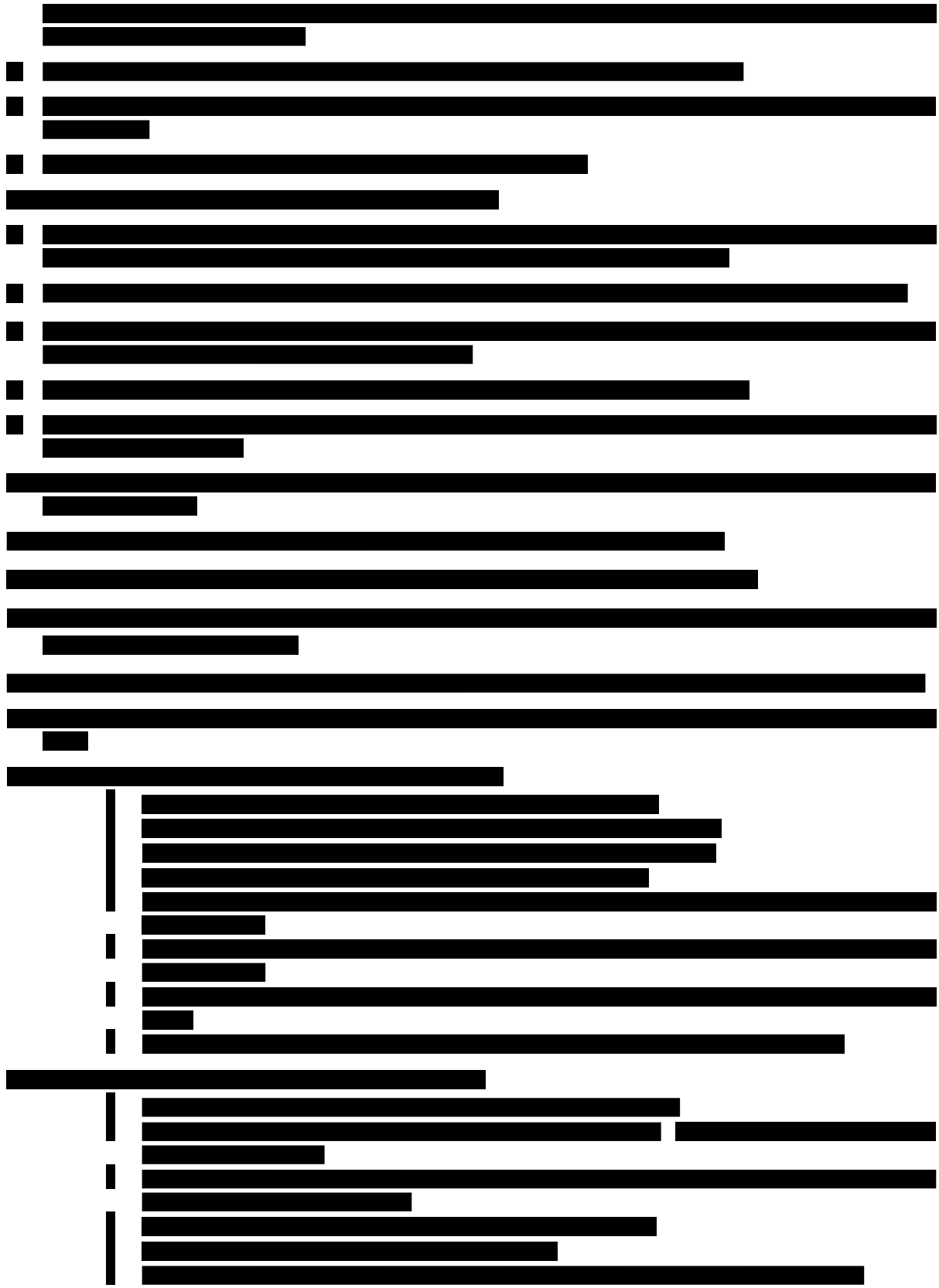
Subjects who are discontinued early from the study must attend the Follow-up visit 4 weeks after the date of Early Discontinuation.

[redacted]

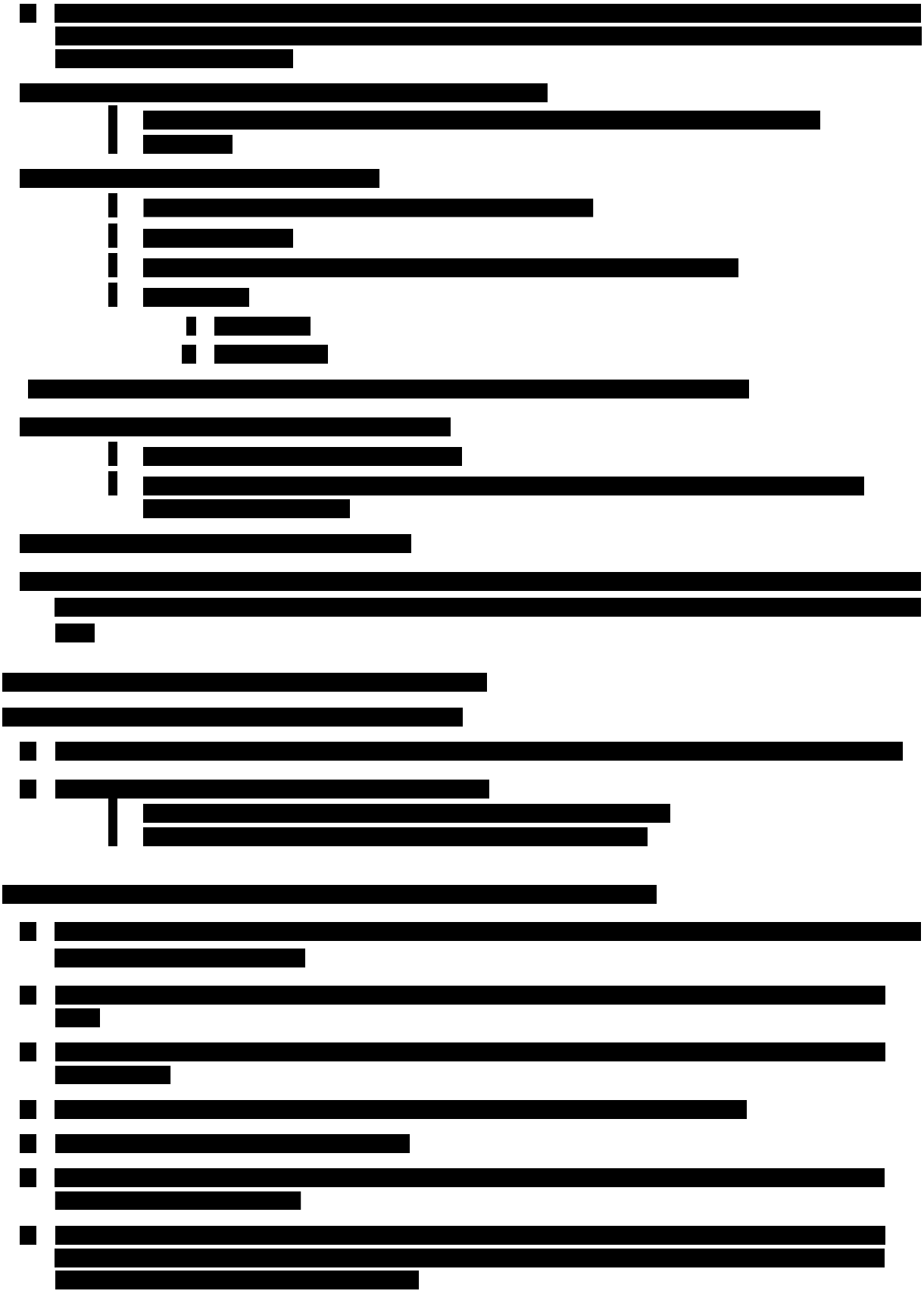
[redacted]

For subjects requiring cardiac monitoring the Baseline visit must be scheduled in a morning to allow the dosing before 12 noon.

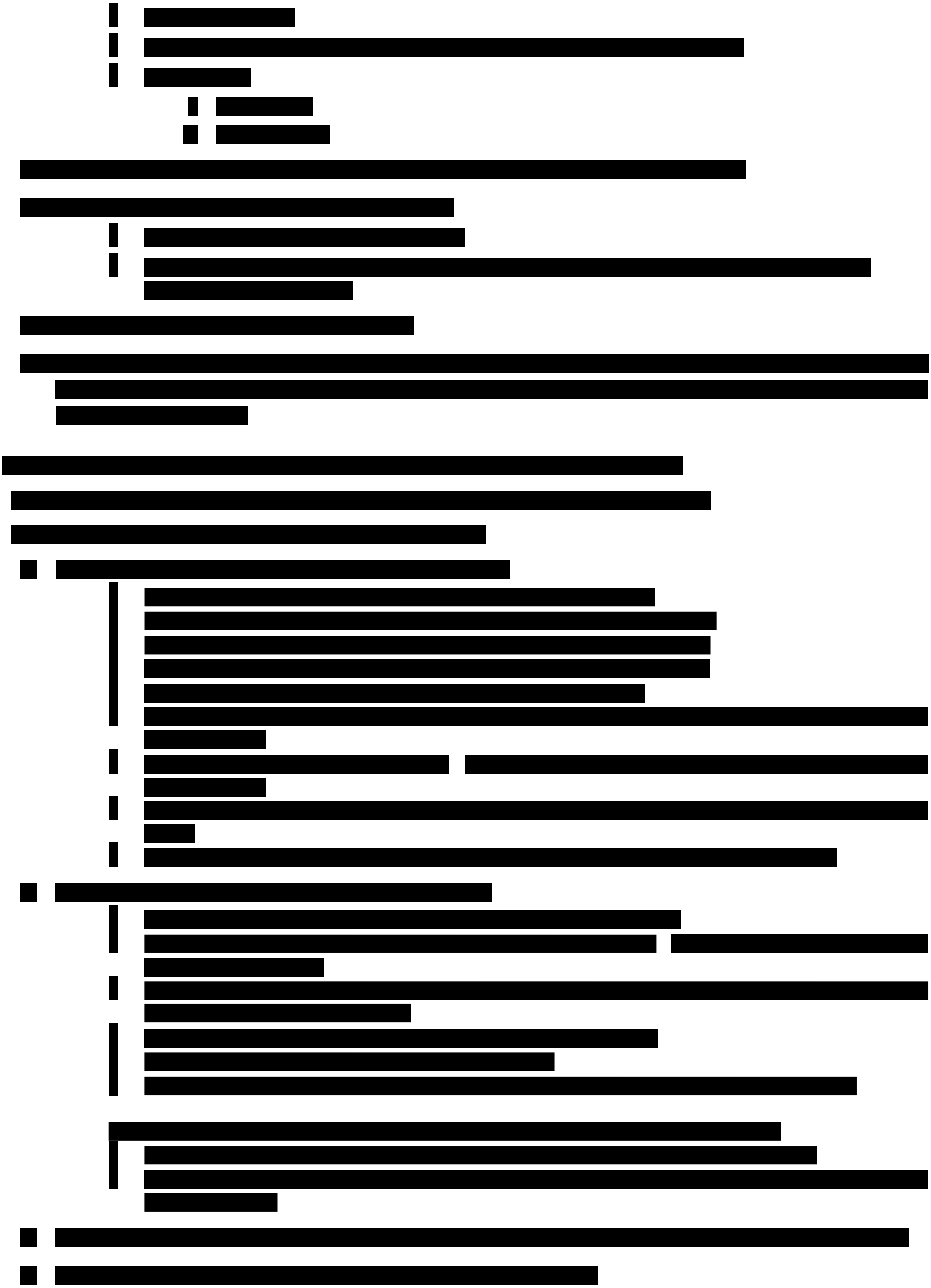
[redacted]



[redacted]

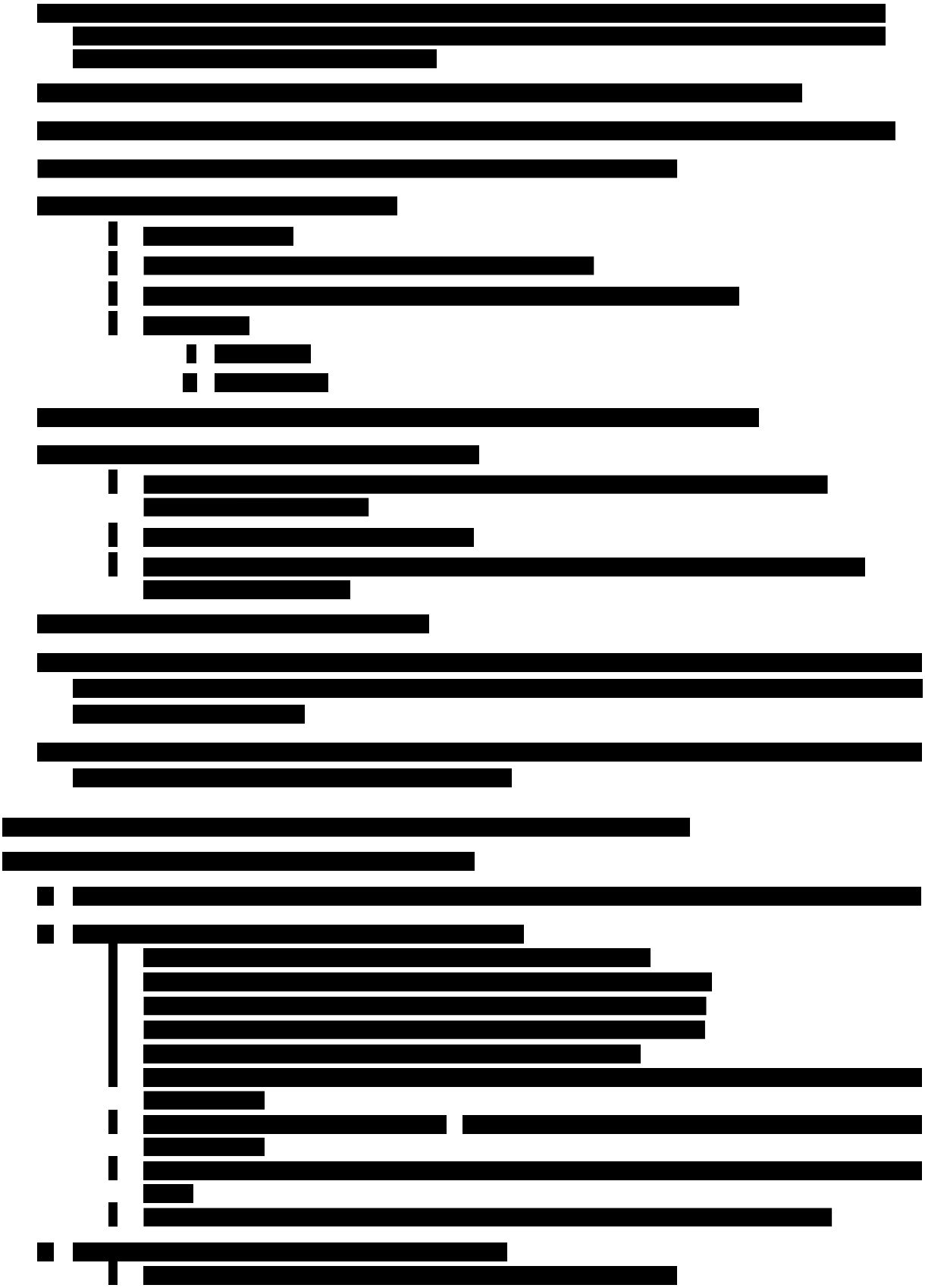


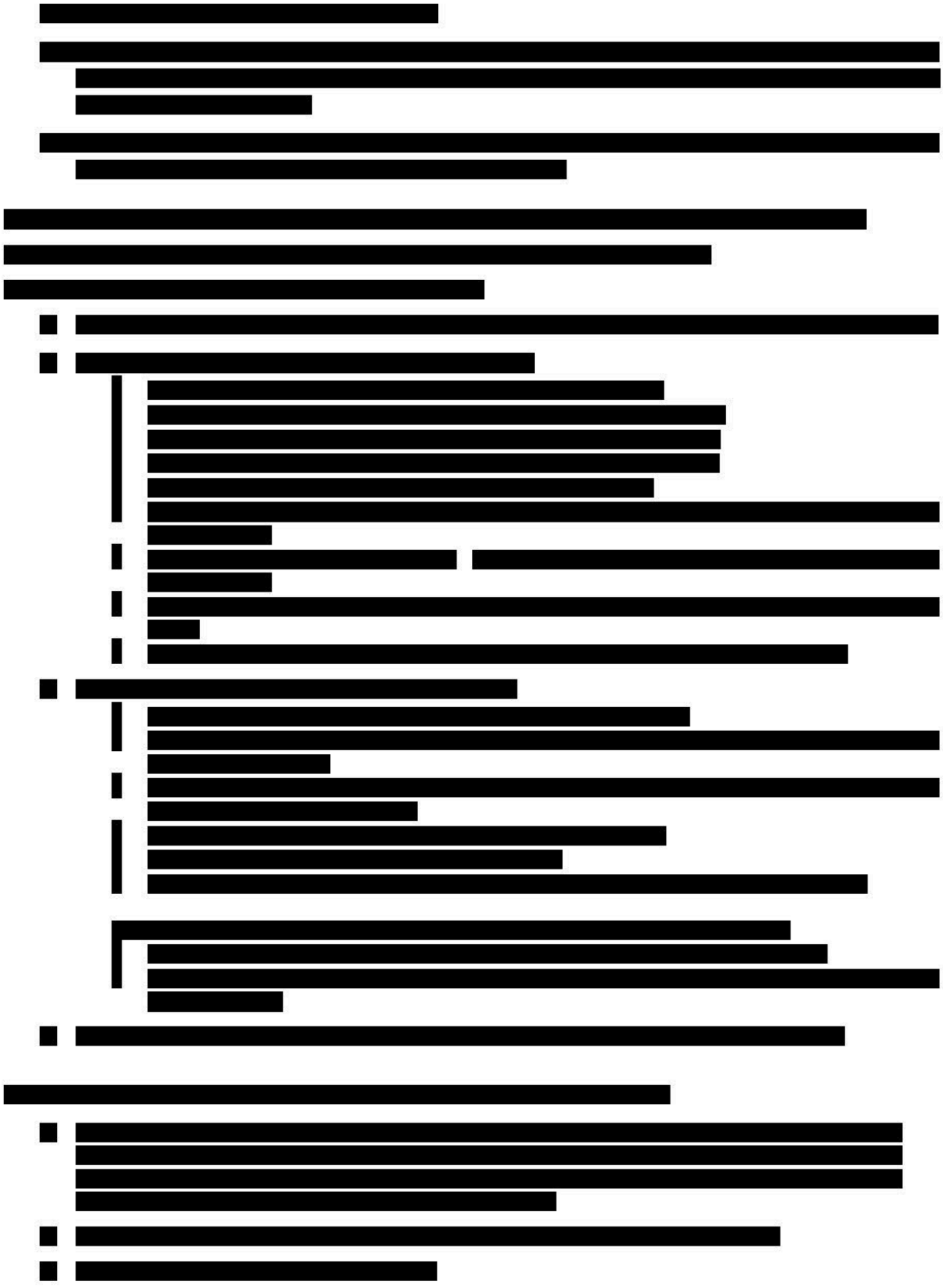
[redacted]



5. [redacted]

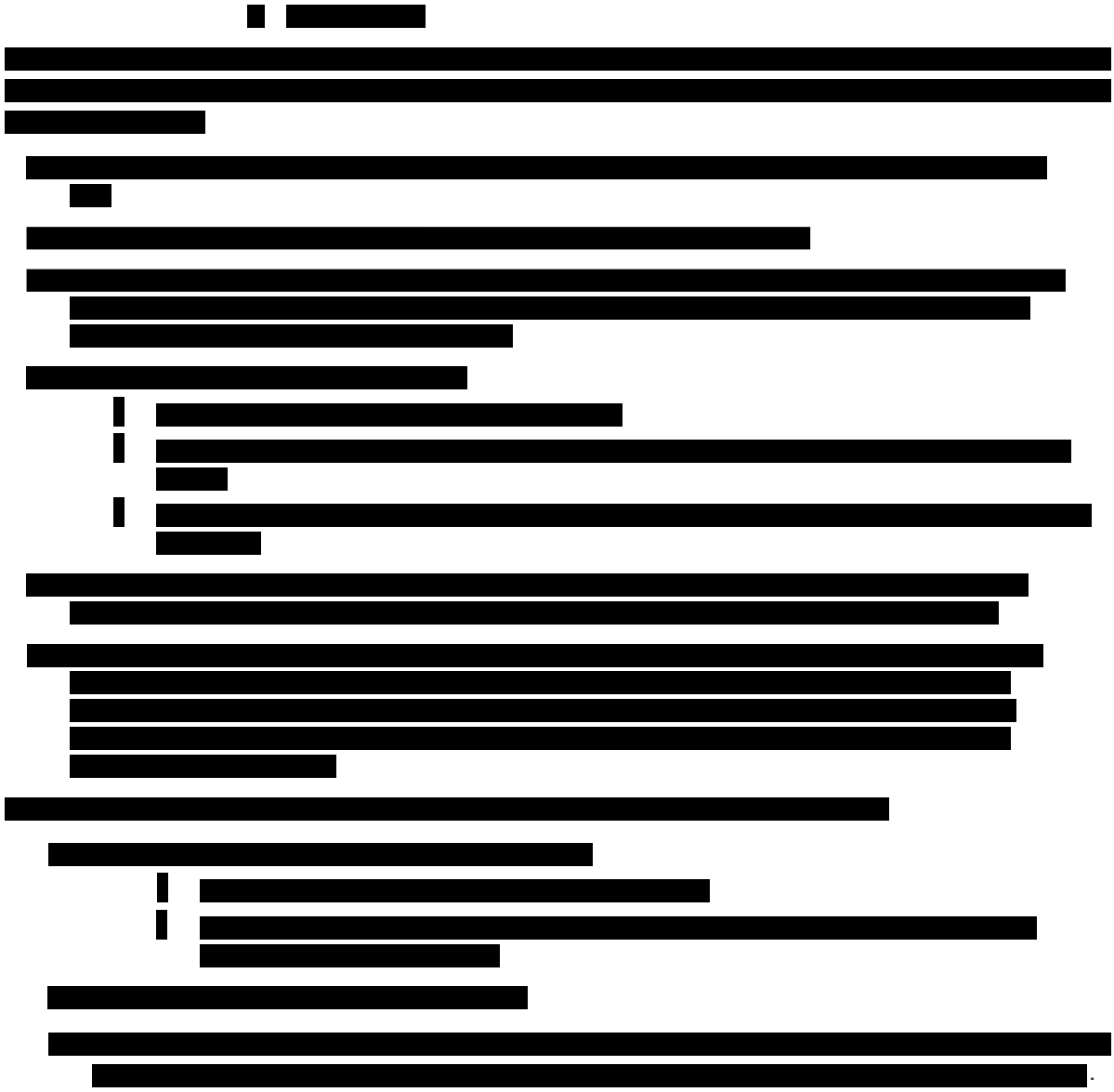
2. [redacted]





[redacted]

[redacted]



8 INVESTIGATIONAL PRODUCT

8.1 Description

All study medications will be dispensed by and returned to a qualified dispenser designated by the Principal Investigator. The investigational product will be dispensed only from the institution(s) approved by an Institutional Review Board.

The Investigational Product will be supplied by the Sponsor. The following treatments will be self-administered or administered by the subject's caregiver during this study.

Investigational Products:	SCD-044 Tablets [redacted] (low dose) SCD-044 Tablets [redacted] (intermediate dose) SCD-044 Tablets [redacted] (high dose) SCD-044 Tablets [redacted]
Control:	Placebo of SCD-044 product

8.2 Storage Conditions

All study products should be stored in a limited access area, at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

8.3 Packaging and Labeling

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. Only one Subject number will be assigned to each Subject. The Subject will maintain the same number throughout the study. The Investigational Product will be identically labeled and packaged such that neither the Subject nor any Investigator can identify the treatment.

[redacted]

Each bottle will be labeled with a two-part, double blind label and will display the following text: "content statement, protocol number, subject number, instructions for use and storage, Sponsor's name, an investigational use statement and warnings: "Keep out of reach of children". Part 2 of the label will contain a **sealed copy of the randomization scheme** (as a scratch off portion of the product label). This label should be detached from the container **prior to dispensing to the Subject and retained at the study site**, to be opened in case of medical emergency only. Where possible, the Medical Monitor should be contacted before breaking the blind for any Subject. The Sponsor must be notified in the event the blind is broken.

Details of the IMP packaging and labelling for the European region will be separately described in the IMP manual.

8.4 Treatment Assignment

The subject study identification number will correspond to a computer-generated randomization schedule assigning that number to one of the study treatment groups in Part I. The randomization scheme will be generated so that the placebo, low, intermediate, and high dose products are assigned [redacted].

[redacted]

Randomization will be stratified by gender and prior biologic therapy for psoriasis.

8.4.1 Randomization

The subject numbers at the site will be assigned by an Interactive Response Technology (IRT) using global data across all sites and identification numbers available at a site. IRT randomization will be stratified by gender and prior biologic therapy for psoriasis. In Part II the study treatment may be reassigned according to the randomization scheme and based on the subject's PASI score at Week 16 (visit 10) [redacted].

8.5 Administration of Investigational Product

At study Visits 2 through 18, Investigational Product will be dispensed to randomized subjects along with a diary. Each subject will also receive written study instructions, which detail the proper

administration method of the Investigational Product and general study instructions.

The study medication should be taken once daily, preferably at the same time each day before 12 noon with or without food. The doses should be taken with approximately 240 mL (8 oz.) of water.

Investigational Product will be used for 365 consecutive days.

Subjects will be required to use diaries to document the date and time of doses, any missed doses, and the occurrence of all adverse events.

At each visit during the study, the Investigator or designee should review proper use of the Investigational Product.

Missed doses:

Subjects should be instructed that if they forget to take a dose, they can take the dose within 4 hours of the normal dosing time; otherwise they should take their next dose at the regular time on the following day. If the subject vomits the tablet, he/she should be instructed not to take another tablet on the same day, but to take the next dose at the regular time on the following day.

[redacted]

8.6 Assessment of Compliance

Compliance with scheduled use of Investigational Product will be determined from the subject's diary. Subjects will be instructed to bring their daily diary and used and unused study drug containers at all

scheduled visits or Early Discontinuation Visit to allow for tablet count and compliance checks. Subjects will also be asked to record in a daily diary the date and time at which they took the study drug. In addition, subjects will be instructed to document all AEs on the diary.

If the subject does not return the Diary, Subject-reported dosing compliance will be recorded in the source notes and will be used to derive compliance between those visits.

For scheduled visits greater than 4 weeks apart, subjects will be called (at w24, w36, w44, w48) and asked about compliance with study drug.

Starting with the first dose at Baseline, only the independent safety team should review compliance and dispensing/returning of diary and study drug use.

8.7 Investigational Product Accountability

It is the responsibility of the Principal Investigator to ensure that the current disposition of the Investigational Product is maintained at each study site where Investigational Product is inventoried and dispensed. When a drug shipment is received at a study site, the Principal Investigator or the Principal Investigator's designee must inventory the drug and sign the receipt form provided with the shipment. The receipt form should be emailed as per instructions provided on the receipt. A copy of the receipt should remain at the site.

The Investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-Investigators.

A Drug Accountability Log will assist study site staff in maintaining inventory records of study drug.

Subjects must return used, partially used or unused Investigational Product so that any remaining drug supplies can be accounted for and noted in the Drug Accountability Log.

A certified copy of the Drug Accountability Log will be collected by the study monitor at the conclusion of the study and the original should remain at the study site.

8.8 Return of Clinical Supplies

All used and unused containers of Investigational Product may be returned to the Drug Labeling, Packaging and Shipping Facility for destruction or be destructed at the site after study close-out and final drug accountability is reconciled.

9. STATISTICAL METHODS

9.1 Scientific and Statistical Considerations of the Study Design

[redacted]

9.1.1 Rationale for the Selected Subject Population

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

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]

9.1.2 Rationale for Dose Selection

[redacted]

9.1.4 Rationale for the Use of Comparator

A placebo control arm is included to demonstrate that the investigational products are active and as a

parameter that the study is sufficiently sensitive to detect differences between products.

9.1.5 Rationale for Study Endpoints

The primary end-point will be the proportion of subjects with at least a 75% improvement in Psoriasis Area and Severity Index (PASI75) at Week 16. Duration of 16 Weeks is considered adequate to detect a clinically meaningful difference between placebo and active treatment and is consistent with previous studies in this indication. Proportion of subjects achieving Investigator's Global Assessment (IGA) of "clear" or "almost clear" with at least a two-grade reduction from baseline to Week 16 will be a key secondary end-point. It is anticipated that only a limited proportion of randomized patients will meet baseline criteria for assessment of efficacy in scalp psoriasis, nail psoriasis, psoriatic arthritis and palmar plantar psoriasis. Hence assessments of efficacy in these subsets are designated as tertiary end-points.

9.1.6 Rationale for the Overall Study Design

[redacted]. The primary and key secondary endpoints are based on efficacy assessments at Week 16 (end of Part 1). The study involves evaluation of efficacy and safety over a longer duration of up to 52 weeks. This long term evaluation comprises Parts 2 and 3 of the study.

[redacted]

[redacted]

9.3 Blinding 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. The placebo and tablets for all strengths of SCD-044 look alike which ensures blinding. The Investigational Product will be identically labeled and packaged such that neither the Subject nor any Investigator can identify the treatment. The Drug Labeling, Packaging and Shipping facility will hold the randomization code throughout the conduct of the study to minimize bias. A sealed copy of the randomization scheme (as a scratch off portion of the product label attached to the drug accountability page) will be retained at the study site. In the event of an emergency, the Subject-specific treatment may be identified; however, every effort should be made to maintain the blind. Where possible, the Medical Monitor should be

contacted before breaking the blind for any subject. The Sponsor must be notified in the event the blind is broken.

The treatment assignments will remain blinded until the final database is closed.

The following safety professionals will be allowed to be unblinded as necessary on a case by case basis:

If SUSAR requires unblinding by a Regulatory Agency, a designated member of the Sponsor's safety team will be un-blinded on case-by-case basis by receiving the randomization directly from the study unblinded statistical consultant.

9.4 Significance Level

Tests for superiority over placebo for the primary and the key secondary endpoint will be conducted using a hierarchical closed testing step-down approach to preserve the overall Type I error rate of 0.05.

9.5 Datasets to be analyzed

Three analysis populations will be used in the analysis of the clinical data:

1. A Safety Population subject is any individual who was randomized into the study and dispensed study drug.
2. The ITT Population includes all randomized subjects regardless of whether they received the investigational product.
3. The Per Protocol (PP) Population includes all ITT subjects who meet all inclusion/exclusion criteria and have no protocol violations that affect proper administration of the treatment or accurate evaluation of its effectiveness.

Additionally, the Screen Fail subjects will be summarized, including reasons for removal.

9.6 Demographics and Baseline/Randomization Characteristics

Demographic and baseline/randomization characteristics will be summarized descriptively by treatment group for the ITT, PP, and Safety Populations.

9.7 Safety Assessment

Safety Assessments will include vital signs, physical examination, adverse events (AEs), laboratory tests, ECG monitoring, pulmonary function tests, ophthalmologic exams.

The safety of SCD-044 will be evaluated by:

- Incidence, seriousness and severity of all adverse events
- Shifts from baseline in hematology and laboratory tests
- Incidence of AEs of special interest (AE-SI)
- [redacted]

[redacted]

The extent of exposure will be summarized using descriptive statistics. No inferential analyses are planned.

Incidence of all adverse events reported during the study will be summarized using the MedDRA dictionary by System Organ Class and Preferred Term, by treatment group, severity, and relationship to study drug.

An AE is considered treatment emergent if it was not present prior to the first dose of treatment or, if it was present, it worsened in severity or treatment attribution.

Safety analyses will be performed on the Safety Population. All safety data will be listed by treatment and subject in data listings. AEs will also be summarized by actual dose at time of onset of the AE to account for possible dose reductions over the course of the study.

9.8 Efficacy Assessment

Primary endpoint:

- Proportion of subjects with at least 75% improvement in PASI (PASI75) at Week 16

Key Secondary endpoint:

- Proportion of subjects achieving IGA of “clear” (0) or “almost clear” (1) with at least two-grade reduction from Baseline to Week 16

Other Secondary endpoints:

- Percent change from Baseline in mean PASI score at Weeks 12, 16, 20, 28 and 52
- PASI75 response rate at Weeks 12, 20, 28, and 52

- PASI50, PASI90, and PASI100 response rate at Weeks 12, 16, 20, 28, and 52
- Change from Baseline in PSSD score at Weeks 16, 20, 28, and 52
- Change from Baseline in DLQI score at Weeks 16, 20, 28, and 52
- Proportion of subjects with IGA score of "clear" or "almost clear" with at least two-grade reduction from baseline to Weeks 12, 20, 28, and 52
- Time to achieve PASI75 response
- Time to achieve IGA response of "clear" or "almost clear" with at least two-grade reduction from baseline
- Change from baseline in BSA involvement at Weeks 12, 16, 20, 28, and 52
- Change from baseline in PGIS at Weeks 16, 20, 28, and 52
- Proportion of subjects with improvement in PGIC at Weeks 16, 20, 28, and 52
- [redacted]
- [redacted]
- Steady state C_{trough} concentrations of SCD-044 at the dose levels evaluated in the study population
- Frequency, type, and severity of adverse events (AEs)

Tertiary endpoints

- Proportion of subjects with Scalp IGA "clear" or "almost clear" with at least two-grade reduction from baseline at Weeks 16, 20, 28, 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 16, 20, 28, and 52
- Proportion of psoriatic arthritis subjects who achieve ACR20 response at Weeks 16, 28, and 52.
- Proportion of subjects with PPPGA score of 0 or 1 at Weeks 16, 20, 28, and 52 among subjects with a baseline PPPGA score of ≥3.

Exploratory endpoints

- [redacted]
- Proportion of subjects achieving ≥ 4-point improvement in NRS from baseline at Weeks 16, 20, 28, 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 16, 20, 28 and 52 among subjects with a baseline Scalp Itch NRS of ≥4
- Change from baseline in subject global assessment of PtA-P at Weeks 16, 28, and 52 among subjects with PsA at baseline
- Level of lymphocyte sub-types and cytokines in blood/plasma/serum.

Other exploratory analyses may be performed based on available data. The Intent-to-Treat Population (ITT) will be used for all efficacy analyses.

Efficacy Analysis

The primary and key secondary efficacy variables will be analyzed using a Cochran-Mantel-Haenszel (CMH) test, stratified by gender and prior biologic therapy (Yes/No), and using the Intent-to-Treat (ITT) Population. Additional details will be included in the SAP

Tests for superiority over placebo for the primary and the key secondary endpoint will be conducted using a hierarchical closed testing step-down approach to preserve the overall Type I error rate of 0.05.

[redacted]

[redacted]

Sensitivity Analyses

For sensitivity testing, the primary and key secondary endpoints analyses will also be performed using the per protocol (PP) population.

Additional sensitivity analyses will be performed for the primary efficacy variable using the following populations:

- The Intent-to-Treat (ITT) Population using Last-Observation-Carried-Forward imputation (LOCF)
- The Per Protocol (PP) Population, using Observed Cases (OC)
- The Intent-to-Treat (ITT) Population, active treatment worst case (ATWC), defined as all missing assessments in the placebo group defaulted to responder but missing assessments in active treatment arm defaulted to nonresponder. Full tipping point analysis methods will be discussed in the SAP.

Subgroup analysis on the stratification factors gender and prior biologic therapy (yes/no) may be performed for the primary and key secondary endpoints.

Tests for superiority over placebo for the primary and the key secondary endpoint will be conducted using a hierarchical closed testing step-down approach to preserve the overall Type I error rate of 0.05.

[redacted]

Continuous secondary efficacy endpoints will be analyzed using a mixed model repeated measures procedure (MMRM) based on the ITT Population. The MMRM will include fixed effects for treatment, visit, treatment by visit interaction, gender, prior biologic therapy (yes/no), and Baseline value as a covariate. This MMRM approach will also be applied at the single time point of Week 16. All such analyses are considered supportive. Additional details of the statistical approach will be provided in the statistical analysis plan.

[redacted]

Further details will be provided in the Statistical Analysis Plan (SAP). [redacted]

[redacted]

[redacted]

[redacted]

Blood samples collected from subjects treated with SCD-044 will be assayed and the samples collected from placebo treated subjects will not be assayed. The bio-analyst will receive the subject IDs of the samples that needs to be analyzed.

[redacted]

9.9 Concomitant Medication

The start and stop date of concomitant medication use during the study will be provided in the data listings in addition to the reason for the medication use.

9.10 Summary of Subjects who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

9.11 Pharmacokinetic parameters

Concentrations of SCD-044 in plasma will be measured by the central laboratory using a fully validated analytical method. In addition, remnant plasma PK samples from the study may be used for exploratory metabolite profiling or to assess PK of metabolites. The approach to steady-state concentrations will be evaluated from the measurable pre-dose concentrations on the study weeks 16, 20, 28, and 52.

Graphical presentations of mean results will use the scheduled times of sample collections. A complete listing of the scheduled and actual times of sample collections for each patient and the concentration reported for each collected sample will be provided. The PK data related to metabolites would be reported separately.

Additional details of PK analysis will be included in the SAP.

Analyses will be performed to evaluate relationship between SCD-044 plasma concentrations and PASI response, [redacted] and change in lymphocyte counts.

Plasma concentrations from samples collected due to adverse events related to bradycardia will be tabulated. Other exploratory analyses may be performed based on available data.

9.12 Pharmacodynamic parameters

Change from baseline and during the course of the study treatment will be evaluated for levels of ALC, lymphocyte sub-types and cytokines in blood/plasma.

10. ADVERSE EVENTS

10.1 Reporting of Adverse Events

Any untoward medical occurrence in a subject or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can

therefore be any unfavorable and unintended sign, symptom, clinically significant abnormal laboratory finding or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any AE associated with the use of a drug in humans, whether or not considered product-related, including the following: An AE occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an AE occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. Reporting an adverse event does not necessarily reflect a conclusion that the product caused or contributed to the adverse event.

All AEs, whether observed by an Investigator or Study coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented in the Subject records, together with details, i.e., date of onset, description of the AE, the duration and intensity of each episode, the action taken, the relationship to the Investigational Product and the degree of severity, the seriousness, date of resolution, and the outcome.

[redacted]. SCD-044 also resulted in gastrointestinal adverse events like diarrhea, abdominal pain, flatulence, constipation and frequent bowel movements that did not need any corrective treatment or discontinuation of SCD-044 and resolved with continued administration of SCD-044.

The Principal Investigator must strive to follow the subject until the AE has resolved, becomes clinically insignificant, is stabilized or the subject is lost to follow-up. The Principal Investigator must immediately report to the Contract Research Organization, by telephone and follow-up in writing, all study drug discontinuations due to adverse events.

Assessment of Severity

The intensity or severity of an AE is characterized as:

- Mild: an AE that is easily tolerated
- Moderate: an AE sufficiently discomforting to interfere with daily activity
- Severe: an AE that prevents normal daily activities

Relationship to Study Medication

The relationship is characterized as:

- Not Related: This applies to any AE that is clearly not related to use of the study drug.
- Possible: This means the association of the AE with the study drug is unknown; however, a relationship between drug and event cannot be ruled out.
- Probable: There is a reasonable temporal relationship between the use of the study drug and the AE. Based upon the Principal Investigator's clinical experience, the association of the event with the study drug seems likely.
- Definite: The AE occurs following the application of the study drug and it cannot be reasonably explained by any known characteristics of the Subject's clinical state, environmental or toxic factors or other modes of therapy administered to the Subject. It disappears or decreases upon discontinuation of the study drug and reappears on a re-challenge of the investigational product.

10.2 Pregnancy

Female Subjects of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study.

For the purpose of this study, a female is considered of childbearing potential i.e. fertile following menarche and until becoming post-menopausal unless permanently sterile. The methods of permanent sterilization are hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without any other medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is in-sufficient [Per CTFG guidelines (Clinical Trials Facilitation and Coordination Group CTFG 21/09/2020 Version 1.1)]

Women of childbearing potential, in addition to having a negative pregnancy test, must be willing to use a highly effective form (failure rate of less than 1% per year when used consistently and correctly) of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug (refer to section 5.4).

A negative result of a pregnancy test having a minimum sensitivity of at least 50mIU/ml for hCG should be obtained from each applicable visit. Pregnancy testing will be performed at applicable study visits and the results of all pregnancy tests (positive or negative) will be documented.

If following initiation of study treatment, it is subsequently discovered that a study Subject is pregnant or may have been pregnant at the time of Investigational Product exposure, the Investigational Product will be permanently discontinued. The Principal Investigator must immediately notify the CRO of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the Subject. Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Principal Investigator must report to the sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks after birth.

10.3 Serious Adverse Events

An **Adverse Event or Suspected Adverse Reaction** is considered ‘‘serious’’ if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death
- A life threatening adverse event; (Note: the term “life-threatening” as used here refers to an event in which the Subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- In-Subject hospitalization or prolongation of existing hospitalization

  (A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health or if the hospitalization is clearly not associated with an AE (e.g., hospitalization due to social / logistic reason) are not to be considered as SAEs)
- A persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any “other” important medical event

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered Serious Adverse Events when, based on appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Regardless of the above, any additional adverse events, which the Principal Investigator considers significant, should be immediately reported to the Contract Research Organization.

SAE reporting by the Investigator:

Any Serious Adverse Event (SAE), whether deemed drug-related or not, must be reported by the Investigator to the Contract Research Organization (CRO) within 24 hours after the Principal Investigator or Study Coordinator becomes aware of its occurrence. The Principal Investigator or the Principal Investigator's Designee must complete an SAE Form and email it to the CRO, along with the subject's AEs, Medical History, and Concomitant Medications Log within 24 hours of notification of the event.

The Principal Investigator or the Principal Investigator's Designee must be prepared to supply the following information:

a. Principal Investigator Name and Site Number

b. Subject I.D. Number

c. Subject initials and date of birth

d. Subject Demographics

e. Clinical Event

   1) Diagnoses and Description

   2) Date of onset

   3) Severity

   4) Treatment

   5) Medical records, hospitalization/discharge records

   6) Relationship to study drug

   7) Action taken regarding study drug

f. **If the AE was Fatal or Life-threatening**

   1) Cause of death (whether or not the death was related to study drug)

   2) Autopsy findings (if available)

   3) Death Certificate

The Principal Investigator must provide a follow-up written report within **5 calendar days** of reporting the event to the CRO. The written report must contain a full description of the event and any sequelae. Subjects who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized. The Investigator must also report follow-up information if it becomes known to the Investigator.

SAE reporting by the CRO:

The CRO must notify the Taro Pharmaceuticals U.S.A, Inc.'s Study Manager and Sponsor Drug Safety Department **within 24 hours** of the initial notification of the event. Documentation should be sent to Taro's SAE Coordinator and Sponsor Drug Safety listed below:

[redacted]

Taro Pharmaceuticals U.S.A, Inc.'s Study Manager and/or Sponsor Drug Safety Department must receive any follow-up **within 24 hours** of receipt by CRO.

10.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

An **AE or Suspected Adverse Reaction** is considered a SUSAR if it is serious, unexpected, and suspected. Prior to reporting to the applicable Regulatory Authorities, the Sponsor will evaluate the available evidence and to judge the likelihood that the drug actually caused the adverse event. The SUSAR must be reported to FDA within 15 days, or if fatal or life threatening, within 7 days, by the Sponsor. The Sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. Additionally, potential Hy's law cases will be reported as SUSARs.

The Sponsor is responsible for reporting of suspected unexpected serious adverse reactions and notifying the relevant regulators (including the authorities in the EEA via EudraVigilance and the IRBs/IECs) and the Investigator sites within the specified timeframes of all SUSARs, as applicable per local requirements.

The applicable Regulatory Authorities shall be notified by Sponsor Safety Physician of any SUSAR, as per local Regulatory Authorities guidelines and timeframe specified as per local regulation.

All participating Investigators, EC/IRB and other stakeholders shall be notified of any SUSAR by CRO's Medical Monitor as per local regulatory requirement.

10.5 Adverse Events of Special Interest

Adverse events of special interest (AESI) should be reported by a site to the CRO using an SAE form within 24 hours of awareness. The CRO must notify the Taro Pharmaceuticals U.S.A, Inc.'s Study Manager and Sponsor Drug Safety within 24 hours of the initial notification of the event.

10.6 Post-study Events

Any AE/SAE that occurs up until the follow-up visit, or if the follow-up visit does not occur within the defined time window, then 4 weeks post the end of treatment visit or 4 weeks post the last dose of study drug for subjects with early discontinuation, should be reported and included in the safety analysis of the study.

Any AE/SAE which occurs past this date will be reported if it is considered related to study drug by the Investigator.

11. ETHICS

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements (including EU CT Regulation 536/2014). The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study Subjects are the most important considerations and should prevail over interests of society and science.

The Sponsor ensures that local regulatory requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any RA approvals required prior to release of IP for shipment to the site.

11.1 Informed Consent

The Principal Investigator must ensure that subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent, according to applicable Regulations and ICH GCP will be followed. Whenever applicable copy of the proposed consent form must be submitted to the IRB, together with the protocol, for approval. Before study initiation, and wherever applicable, the Principal Investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials and any other written information to be provided to Subjects.

In the EU region, the Sponsor will submit the required study documents, including the informed consent

form, for Member State authorization through the Clinical Trials Information System (CTIS).

The Principal Investigator will use the informed consent approved under Regulation (EU) No 536/2014 of the European Parliament. The Principal Investigator must obtain fully informed consent per Chapter V (Protection of subjects and informed consent) defined in the European Union Regulation No. 536/2014 on clinical trials on medicinal products for human use.

Informed consent will be obtained from all subjects using the following procedure: Subjects must have provided IRB/Member State approved written informed consent. Prior to initiating screening for the study, Subjects will be given the approved ICF describing the study and any risks associated with participation. The subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. The ICF must be signed by the Subject before any protocol assessments can be undertaken. Each Subject's signed informed consent must be kept on file by the Principal Investigator.

11.2 Institutional Review Board

Before study initiation, the Principal Investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials and any other written information to be provided to Subjects.

Any changes to the protocol as well as a change of the Principal Investigator, which is approved by the Sponsor, must also be approved by the site's IRB and documentation of this approval provided to the Sponsor/designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the Principal Investigator and are subject to inspection during or after completion of the study. All SAEs must also be reported to the IRB.

Periodic status reports must be submitted to the IRB at least annually, as well as notification of completion of the study and a final report within one (1) month of study completion or discontinuation or per the local ethics committee requirements. A copy of all reports submitted to the IRB must be sent to the Sponsor/designee.

The Principal Investigator will ensure that an IRB that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.

11.3 Subject Confidentiality

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including, but not limited to, HIPAA and GDPR). Appropriate consent for collection, use, and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the study database; if the participant's name appears on any other document (eg laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

The monitor(s), the auditor(s), IRB/IEC, and the regulatory authority (ies), will be granted direct access to the Subject's original medical records for verification of the clinical trial procedures and/or data, without violating the confidentiality, to the extent permitted by the applicable laws and regulations and that by signing a written informed consent form, the Subject or the Subject's legally acceptable representative is authorizing such access.

The identifying the Subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the trial are published, the Subject's identity will remain confidential.

11.4 Indemnity/Liability and Insurance

The Sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO/Investigator as necessary.

12. DOCUMENTATION

12.1 Site Regulatory Documents Required for Initiation

The following documents will be received by the CRO prior to the initiation of the study:

1. Completed and signed FDA Form 1572
2. Current curricula vitae, signed and dated for the Principal Investigator and each Sub-Investigator named in the FDA Form 1572 (current within 2 years)
3. Current medical licenses of the Principal Investigator and Sub-Investigators named in FDA Form 1572
4. Documentation of IRB approval of this study protocol, Principal Investigator and informed consent form
5. Current IRB membership list or roster
6. A copy of the protocol agreement page signed by the Principal Investigator
7. Non-disclosure Agreements for the Principal Investigator and Sub-Investigators named in FDA Form 1572
8. Financial Disclosure Statement for the Principal Investigator and each Sub-Investigator named in FDA Form 1572.
9. Statement of Non-Debarment

12.2 Maintenance and Retention of Records

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Copies of all pertinent records will be retained by the Principal Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IRB, informed consent, source documents. No documents shall be transferred from the site or destroyed without first notifying the Sponsor. If the Principal Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to the Sponsor.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories designed to document all observations and other data pertinent to the investigation on each individual treated with the Investigational Product or entered as a control in the investigation.

12.3 Data Collection and Reporting

Data for individual Subjects will be collected on source documents. The data management system will be Electronic Data Capture (EDC). The Investigator and his/her study site personnel will be responsible for transferring data to the electronic Case Report Forms (eCRFs). The Investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

Source documents such as the clinic chart are to be maintained separately from the eCRF in order to allow data verification. Because of the potential for errors, inaccuracies and illegibility in transcribing data into eCRFs, originals of laboratory and other test results must be kept on file. Source documents and copies of test results must be available at all times for inspection by the study monitor. The following should also be available for review:

1. Subject Screening Log – reflecting the reason any Subject screened for the study was found to be ineligible
2. Delegation of Authority / Study Personnel Signature Log – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. Monitoring Log – the date and purpose of all monitoring visits by the Sponsor/Designee will be documented
4. Enrollment Log – documenting Subject initials and start and end dates for all Subjects enrolled
5. Drug Inventory/Packing Slip – reflecting the total amount of drug shipped to the site and received and signed for by the Principal Investigator
6. Drug Accountability Log – reflecting the total amount of Investigational Product dispensed to and returned by each Subject
7. Informed Consent Form and Assent Form – which must be available for each Subject and be verified for proper documentation

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. All queries issued by the data management personnel will be answered by site personnel and verified by the monitor.

Electronically generated data like laboratory results, ECG results etc. could be directly integrated with or transferred to the clinical database.

[redacted]

12.4 Primary Source Documents

The Principal Investigator must maintain primary source documents supporting significant data for each Subject's medical notes. These documents, which are considered "source data", should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the Subject is being studied
- General information supporting the Subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any evaluations, relevant findings/notes by the Principal Investigator(s), occurrence (or lack) of adverse events and changes in medication usage, including the date the study drug commenced and completed.
- Any additional visits during the study
- Any relevant telephone conversations with the Subject regarding the study or possible adverse events
- An original, signed informed consent form or assent form for study participation

The Principal Investigator must also retain all Subject specific printouts/reports of tests/procedures performed as a requirement of the study.

12.5 Study Monitoring

The study will be monitored by a representative of the Contract Research Organization to assess compliance with ICH-GCP and applicable regulations. The Principal Investigator will be visited by a

monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol. The investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, including provision of direct access to source data and documents.

The study monitor will review the informed consent/assent forms and verify eCRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The monitor will review the maintenance of regulatory documentation and drug accountability. The monitor will review on a regular basis the progress of the study with the Principal Investigator and other site personnel.

eCRF sections may be monitored during these visits. At the end of the study, a closeout monitoring visit will be performed. Monitoring visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The Study Coordinator and/or Principal Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Principal Investigator.

12.6 Data and Safety Monitoring Board

An independent DSMB has been established for periodic review of safety data for this study. The composition and responsibilities of the DSMB are described in the DSMB Charter. The DSMB has access to study un-blinded data. In order not to disseminate the data, only the members of the DSMB and the un-blinded study statistician have access to these data. The results are sent confidentially to the DSMB by the statistician. Based on the accumulating data review the DSMB may recommend to the study team to modify or stop the trial early due to safety concerns. .

Adverse event of special interest will be adjudicated by the DSMB periodically throughout the study.

[redacted]

12.7 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the course of the study and/or after it has been completed.

The investigators and institutions involved in the clinical trial are to permit clinical trial-related audits and regulatory inspections, including provision of direct access to source data and documents.

THE INVESTIGATOR MUST NOTIFY THE CONTRACT RESEARCH ORGANIZATION and SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

12.8 Modifications to the Protocol

The procedures defined in the protocol will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no violations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB/regulatory agency, as applicable, prior to implementation.

The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a Subject or Subjects. However, the Principal Investigator must notify the Sponsor immediately and the IRB within 5 working days after implementation.

All protocol violations will be reported on the protocol violation log and included in the study reports. A protocol violation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations.

The sponsor will notify the authorities as applicable (in line with country/region requirements) about a serious breach of the regulations or of the version of the protocol applicable at the time of the breach. A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

12.9 Completion of Study

The Principal Investigator is required to sign the eCRFs and all other relevant data and records to the Contract Research Organization.

The Principal Investigator is expected to submit a final report to the IRB and the Sponsor within one (1) month of study completion or discontinuation.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements.

Study results reporting:

The Sponsor will provide Clinical Study Report (or its summary) to the regulatory agencies, as applicable, in timeframe in line with country requirements.

For the EU countries: irrespective of the outcome of the clinical trial, the Sponsor will submit a summary of the intermediate results, as well final results of the clinical study to the relevant EU clinical study database (the Clinical Trials Information System [CTIS] database at https://euclinicaltrials.eu/home) in a timely manner. As appropriate, the final study results posting this will be accompanied by a summary written in a manner that is understandable to laypersons.

12.10 Data Protection in the European Economic Area

The Sponsor, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations, and guidelines as applicable

The Sponsor will take adequate measures to comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorised access, disclosure, dissemination, alteration, or loss of information and processed personal data. Similarly, measures will be taken to implement and for ensuring confidentiality of records and personal data of subjects.

In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data of subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery etc. Any data breach presenting risks to the rights and freedoms of data of subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach.

13. REFERENCES

1. Johnson-Huang LM, Lowes MA, Krueger JG. Putting together the psoriasis puzzle: an update on developing targeted therapies. Dis Model Mech. 2012 ;5:423-33.
2. National Clinical Guideline Centre, U. Assessment and management of psoriasis. NCGC Guideline 2012.
3. Jacob SE, Butler D, Herro E. Corticosteroid and fragrance allergy exacerbating scalp psoriasis. J Clin Aesthet Dermatol. 2014 ;7:54-5.
4. Augustin M, Mrowietz U, Bonnekoh B, Rosenbach T, Thaçi D, Reusch M, Ardabili M, Reich K. Topical long-term therapy of psoriasis with vitamin D_3 analogues, corticosteroids and their two compound formulations: position paper on evidence and use in daily practice. J Dtsch Dermatol Ges. 2014 ;12:667-82.
5. Martin G, Young M, Aldredge L. Recommendations for Initiating Systemic Therapy in Patients with Psoriasis. J Clin Aesthet Dermatol. 2019;12:13-26.
6. Samarasekera EJ, Sawyer L, Wonderling D, Tucker R, Smith CH. Topical therapies for the treatment of plaque psoriasis: systematic review and network meta-analyses. Br J Dermatol. 2013 ;168:954-67.
7. Papp K et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73:37-49.
8. Paul C et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol. 2015;173:1387-99.
9. Bristol-Myers Squibb Company. SOTYKTU™ (deucravacitinib) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214958s000lbl.pdf. Initial U.S. Approval 2022.
10. Mease PJ et al. Efficacy and safety of selective TYK2 inhibitor, deucravacitinib, in a phase II trial in psoriatic arthritis. Ann Rheum Dis. 2022;81:815-822
11. Vaclavkova A, et al. Oral ponesimod in patients with chronic plaque psoriasis: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet 2014; 384 (9959): 2036-2045
12. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54(8):2665-73
13. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement, PubMed: 31613151
14. Richard Francis for the GLI Consortium. Gli Lung Function Calculator, http://gli-calculator.ersnet.org/index.html (URL:http://gligastransfer.org.au/calcs/spiro.html; Accession date: December 19th 2022).
15. Quanjer PH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40: 1324–1343.
16. Culver BH, et al. Recommendations for a Standardized Pulmonary Function Report: An Official American Thoracic Society Technical Statement. Am J Respir Crit Care Med 2017; 196(11):1463–1472.
17. Jabs DA, Nussenblatt RB, Rosembaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140(3):509-16.

18. https://www.ahrq.gov/professionals/systems/hospital/fallpxtoolkit/fallpxtk-tool3f.html
19. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clinical and Experimental Dermatology. 1994; 19: 210-216.
20. ePROVIDE. Psoriasis Signs and Symptoms Diary (PSSD). https://eprovide.mapi-trust.org/instruments/psoriasis-signs-and-symptoms-diary.
21. FDA. Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. https://www.fda.gov/media/116281/download.
22. Bissonnette R, Pariser DM, Wasel NR, et al. Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis. J Am Acad Dermatol. 2016 Jul;75(1):99-105.
23. Cassell SE. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. J Rheumatol. 2007;34:123-129
24. [redacted]
25. Pirro F et al. Impact of Body Mass Index on the Efficacy of Biological Therapies in Patients with Psoriasis: A Real-World Study. Clin Drug Investig. 2021;41:917-925
26. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-indicated-treatment-psoriasis_en.pdf
27. Ohtsuki M, et al.Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial. J Dermatol. 2017;44:873-884. doi: 10.1111/1346-8138.13829. Epub 2017 Apr 9.
28. Papp KA et al.. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol. 2016;174:1266-76.
29. Armstrong AW et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J Am Acad Dermatol. 2022 9:S0190-9622(22)02256-3
30. [redacted]
31. Cheng S et al. Long-term outcomes in individuals with prolonged PR interval or first-degree Atrioventricular block. JAMA. 2009;301(24):2571-2577.

APPENDIX I: REVISION HISTORY

Version #	Affected Sections
Final 1.0 (September 23, 2020)	N/A (new not implemented)

Final 2.0 (February 9, 2021)

1. [redacted]
2. "List of Tables" was added after Table of Contents.
3. Section 2 was updated to include "intermediate dose" in the secondary endpoint to evaluate the [redacted] response in non-responders at low dose and intermediate dose when switched to high dose of SCD-044
4. Section 3 (Page 20) is revised to describe the scheme for re-randomization at Week 16 (i.e. at start of Part II). Briefly, subjects will be re-randomized based on PASI response as following:

   [redacted]

5. Section 3 (Study Overview Page 21): The flow diagram of study design in Section 3 is updated to illustrate the scheme of re-randomization
6. Section 3 (Study Overview Page 22): In order to manage the challenges regarding study visits caused due to COVID-19 pandemic, study visits 15, 17 and 18 may be performed [redacted].

[redacted]

8. Section 3.1 (Page 24):Schedule of Assessment is edited and updated for consistency and concurrence with the edits made in the text

[redacted]

11. In Section 4.4, (Page 31), NSAIDS were added to prohibited medications within 24 hours before scheduled study visit.
12. In Section 4.5 (Page 32), permitted medications #3 is added to provide clarification regarding provision for vaccination during participation in the study. [redacted]

[redacted]

15. [redacted]

18. In Section 5.7 (Page 38), text is added to explicitly clarify that an ophthalmologist will perform comprehensive eye examination when any subject report visual disturbance during participation in the study
19. Section 5.9 (Page 38) is revised and updated to clarify definition of an adverse event also include clinically significant abnormal lab values

[redacted]

24. Sections 6.1.13, 6.1.15, and 6.1.16: Table numbers 4, 5, 6, were added, respectively.

[redacted]

26. Sections 7.3, 7.4, 7.5, 7.6, 7.11, 7.12, 7.13, and 7.14 were updated to include the pre-dose pharmacokinetic sample and safety events that are to be reviewed [redacted]
27. In Sections 7.2, 7.7, 7.8, 7.9, 7.10, 7.15, 7.16, 7.17, 7.18, 7.19, 7.23 following information is added: [redacted] will review the reports related to lab results and exam results, if available

[redacted]

[redacted]

36. The scales of assessments in Appendices VIII, X, XI, and XIII were updated.
37. References were rearranged and renumbered in order of appearance, and references #12 and #20 were added.

In addition, administrative and editorial changes have been made throughout the version 2 protocol to improvise readability and syntax.

Final Version 3.0 (March 10, 2023)

1. Title page: To enable CTR filing in the EU region EU CT number and UTN number are added on title page
2. Contact list updated to reflect change in the team.
3. List of abbreviation updated
4. Details of "Start of the study" and definition of "End-of-study" are added in the synopsis and in Section 3.

[redacted]

6. In section 1, added a foot-note to provide update regarding International Non-proprietary Name (INN) published in WHO's INN Recommended list
7. In Section 1, a brief summary is added to describe the un-met medical need

[redacted]

10. The inclusion criterion #6 is updated to clarify subjects should not be hypersensitive to drug product or excipients
11. In section 4.2, inclusion criteria #8 and section 5.4, are updated to align with the Protocol Clarification Letter [redacted]
12. In section 4.2, inclusion criteria #8 and #9, are updated to clarify the male subjects must use acceptable contraceptive methods from the day of 1st dose administration to at least 30 days after last administration. [redacted]

[redacted]

21. The section 6.1.15 is updated to correct the typo in Table 5, score and description for pitting
22. The Section 6.2 is updated to clarify pre-dose (trough) blood samples will be collected only at week 16, 20, 28 and 52.

[redacted]

24. In Section 8.3 a statement is added to clarify the IMP packaging and labelling for the EU region will be described in the IMP manual

[redacted]

30. The Section 11.4 is added and Section 10.4, Section 11, Section 11.2, Section 12.8 and Section 12.9 are updated for compliance with the CTR requirements

[redacted]

32. The Section 12.10 is added for compliance with the EU General Data Protection Regulation requirements

[redacted]

Final Version 4.0 (April 10, 2023)

1. [redacted]
2. Section 3: Covid-19 related information added to address possible deviations
3. Editorial changes for consistency between Sections 3.1 and 7
4. [redacted]
5. Other editorial changes through the document to maintain consistency between sections.

Final Version 4.1 (July 28, 2023)

1. Protocol version 4.1, dated July 28, 2023, for study number SCD-044-19-14, is the region-specific version of protocol version 4.0, dated April 10, 2023. [redacted]
2. The title page is updated to include [redacted] the EU CT number (2023-506477-35-00) is corrected on the title page of the protocol to fulfill the requirements of the Clinical Trial Regulation (Regulation (EU) No 536/2014)
3. In the title page, the contact details of the Sponsor and the [redacted] are updated on the title page.

Final Version 4.2 (Dec 20, 2023)

1. The study overview (Section 3.0) is updated to clarify [redacted]
2. A paragraph is added [redacted] to clarify the definitions of women of childbearing potential (WOCBP), fertile men, and post-menopausal state.
3. The exclusion criterion #3 in the synopsis and section 4.3 is edited to provide further clarification.
4. Section 9.1.1. is updated to clarify [redacted].
5. Section 11.1 is updated to clarify the process of obtaining approval [redacted]

In addition, to maintain internal consistency, a few administrative and editorial changes have been made to sections 3.1, 3.2, 7.1 and 7.2 of version 4.2 protocol

APPENDIX II: BODY SURFACE AREA (BSA)

To estimate the % BSA Affected, the Investigator should use the method of approximation: the patient's palm surface of the hand (including fingers) represents approximately one percent of his/her BSA. Measurement of psoriasis body surface area involvement is estimated using the handprint method with the size of a subject's handprint representing ~1% of body surface area involved. The total BSA = 100% with breakdown by body region as follows: head and neck = 10% (10 handprints), upper extremities = 20% (20 handprints), trunk including axillae and groin = 30% (30 handprints), lower extremities including buttocks = 40% (40 handprints). BSA assessments should be performed by the Investigator or a designee who is appropriately trained and experienced in the assessment of psoriasis patients.

APPENDIX III: PSORIASIS AREA SEVERITY INDEX (PASI) SOURCE DOCUMENT EXAMPLE

Areas	PASI Clinical Signs Severity Score (*select one for each area*)			% affected (*select one for each area*)
	Redness (Erythema)	Thickness (Induration)	Scaliness (scaling)	
Head and neck	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (non involvement) ☐ < 10% ☐ 10 – 29% ☐ 30 – 49% ☐ 50 – 69% ☐ 70 – 89% 90 – 100%
Arms	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (non involvement) ☐ < 10% ☐ 10 – 29% ☐ 30 – 49% ☐ 50 – 69% ☐ 70 – 89% 90 – 100%
Trunk	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (non involvement) ☐ < 10% ☐ 10 – 29% ☐ 30 – 49% ☐ 50 – 69% ☐ 70 – 89% 90 – 100%
Legs	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (None) ☐ 1 (Mild) ☐ 2 (Moderate ☐ 3 (Severe) ☐ 4 (Very Severe)	☐ 0 (non involvement) ☐ < 10% ☐ 10 – 29% ☐ 30 – 49% ☐ 50 – 69% ☐ 70 – 89% 90 – 100%

APPENDIX IV: DERMATOLOGY LIFE QUALITY INDEX (DLQI) EXAMPLE

The aim of this questionnaire is to measure how much your skin problem has affected your life over the **past week.** Please check ☑ one box for each question.

1	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
2	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
3	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
4	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
5	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
6	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
7	Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes No A lot A little Not at all	☐ ☐ ☐ ☐ ☐	Not relevant	☐
8	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
9	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐

APPENDIX V: PSORIASIS SYMPTOM AND SIGN DIARY (PSSD) EXAMPLE

Please indicate how severe each of the following skin symptoms was in the **past week**. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

1. Rate the severity of itch in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2. Rate the severity of dryness in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3. Rate the severity of cracking in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4. Rate the severity of skin tightness in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5. Rate the severity of scaling (built-up of skin in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6. Rate the severity of shedding or flaking in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7. Rate the severity of redness in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8. Rate the severity of bleeding in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9. Rate the severity of burning in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10. Rate the severity of stinging in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11. Rate the severity of pain from your psoriasis lesion in the past 7 days	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

To be completed by the clinic staff:

PSSD Score: _____

[redacted]

APPENDIX VI: PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS) EXAMPLE

Please choose the response below that best describes the severity of your Psoriasis SYMPTOM / OVERALL STATUS over the [redacted]

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

APPENDIX VII: PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) EXAMPLE

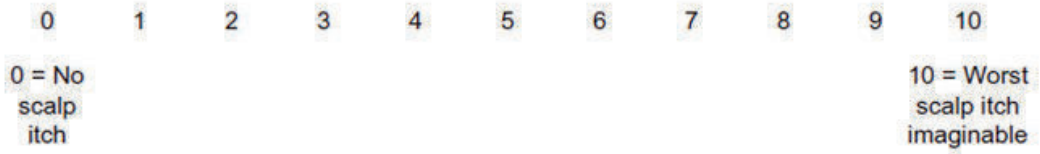
Please choose the response below that best describes the overall change in your psoriasis since you started taking the study medication: Please check ☑ one box only	
☐	Much better
☐	A little better
☐	No Change
☐	A little worse
☐	Much Worse

APPENDIX VIII: ITCH NUMERIC RATING SCALE (ITCH NRS) EXAMPLE

Please rate the itching severity due to your psoriasis by circling the number that best describes your **worst** level of itching in the [redacted].

For subjects with scalp psoriasis:

Please rate the itching severity of your **scalp** due to your psoriasis by circling the number that best describes your **worst** level of itching in the [redacted].



APPENDIX IX: HEALTH ASSESSMENT QUESTIONNAIRE OF DISABILITY (HAQ-DI) EXAMPLE

Please check ☑ the box which best describes your abilities over the **past week:**

DRESSING & GROOMING *Are you able to:*	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐

Check ☐ if you usually need help from another person

Check ☐ if you usually use button hook, zipper pull, shoe horn, etc.

ARISING ***Are you able to:***	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐

Check ☐ if you usually need help from another person

Check ☐ if you usually use special or built up chair

EATING ***Are you able to:***	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐

Check ☐ if you usually need help from another person

Check ☐ if you usually use built up or special utensils

WALKING **Are you able to:**	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Check ☐ if you usually need help from another person

Check ☐ if you usually use cane, walker, crutches, wheelchair

HYGIENE **Are you able to:**	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐

Check ☐ if you usually need help from another person

Check ☐ if you usually use bathtub bar, long-handled appliances in bathroom, raised toilet seat

REACH **Are you able to:**	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐

Check ☐ if you usually need help from another person

Check ☐ if you usually use long-handled appliances for reach

GRIP **Are you able to:**	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐

Check ☐ if you usually need help from another person

Check ☐ if you usually use jar opener for jars previously opened

ACTIVITIES **Are you able to:**	Without ANY difficulty	With SOME difficulty	with MUCH difficulty	UNABLE to do
Run errands and shop?	☐	☐	☐	☐

Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Check ☐ if you usually need help from another person to do errands and chores

To be completed by the clinic staff:

HAQ-DI Score: _____

HAQ-DI Scoring

There are four possible responses for the Disability Index questions:

If more than 2 of the categories, or 25%, are missing, the scale is not scored.

There are 3 steps to scoring the HAQ:

1. For each section the score given to that section is the worst score within the section, i.e. if one question is scored 1 and another 2, then the score for the section is 2.
   - Without ANY difficulty = 0
   - With SOME difficulty = 1
   - With MUCH difficulty = 2
   - UNABLE to do =3
2. In addition, if an aide or device is used or if help is required from another individual, then the minimum score for that section is 2. If the section score is already 2 or more then no modification is made.
   - No assistance is needed, add '0'
   - A special device is used by the patient in his/her usual activities, minimum score is '2'
   - The patient usually needs help from another person, minimum score is '2'
   - The patient usually needs BOTH a special device AND help from another person, the section score is '3'
3. Divide the final sum by the number of categories answered. The score for the disability index is the mean of the 8 category scores rounded to the nearest value. If 1 or 2 of the categories are missing, the sum of the categories is divided by the number of answered categories.

Some patients may question whether their response should reflect a particularly good or bad time, which is out of the time frame requested, because they feel that their response may be missing those times when their functional ability changes. The study requires repeating the HAQ at specific and regular time intervals to examine patterns of function. Inquiring about these activities only when patients are feeling particularly good or bad would result in inaccurate and biased data. The score is not modified if they have difficulties sometimes or required help only occasionally.

Addressing some scenarios which occasionally arise:

• If an item does not apply to an individual, e.g., they do not shampoo their hair, take tub baths, or reach for a heavy object above their heads, then they should leave the item(s) blank since the purpose is to obtain data about what they can do.

•If a patient uses adapted or modified aids or devices (e.g., clothing, faucets, cars), then they should answer the questions based on their usual equipment. If they have no difficulty using the adapted equipment, then they would mark the “no difficulty” column. The adapted equipment (aids and devices) will be taken into account in the assistance variables (see below).

• If an individual can open their own door but not for others, then they should respond in consideration of their own requirements.

APPENDIX X: PATIENT GLOBAL ASSESSMENT OF DISEASE ACTIVITY (PtGA) EXAMPLE

Note: please ensure that the line is 100 mm in length after printing the source document and measuring the distance

Considering all the ways your arthritis affects you, how are you feeling TODAY?" Please answer by placing a mark on the line below:

To be completed by the clinic staff:

VAS Score: _____ / 100

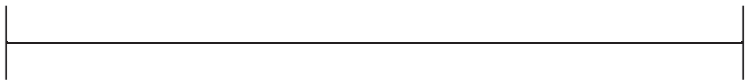
APPENDIX XI: PATIENT ASSESSMENT OF PAIN (PtA-P) EXAMPLE

Note: please ensure that the line is 100 mm in length after printing the source document and measuring the distance

How much pain due to your arthritis are you currently experiencing?

Please rate you pain by placing a mark on the line corresponding to your CURRENT level of pain.

No Pain Worst pain imaginable



0 100

To be completed by the clinic staff:

VAS Pain: _____ / 100

APPENDIX XII: TENDER AND SWOLLEN JOINT COUNT EXAMPLE

To allow for sufficient joint inspection, the physician should ask the patient to wear a standard gown and sit on the front end of the examination table.

In PsA, joint swelling and tenderness are caused by inflammation of the joint synovium, increased synovial fluid production, and periarticular swelling in the joint capsule and surrounding tissues. Visual clues of joint swelling include enlargement of the joint soft tissue, skin stretching with loss of folds and furrows, and red or blue skin color changes around the joint.

After inspection, each joint is examined by palpation using the thumbs and index fingers. Joint swelling may be detected by finding tissue sponginess and ballotting the joint for increased synovial fluid. Identifying anatomical landmarks of specific joints and comparing joints on one side of the body with those on the other side are helpful in assessment of joint swelling.

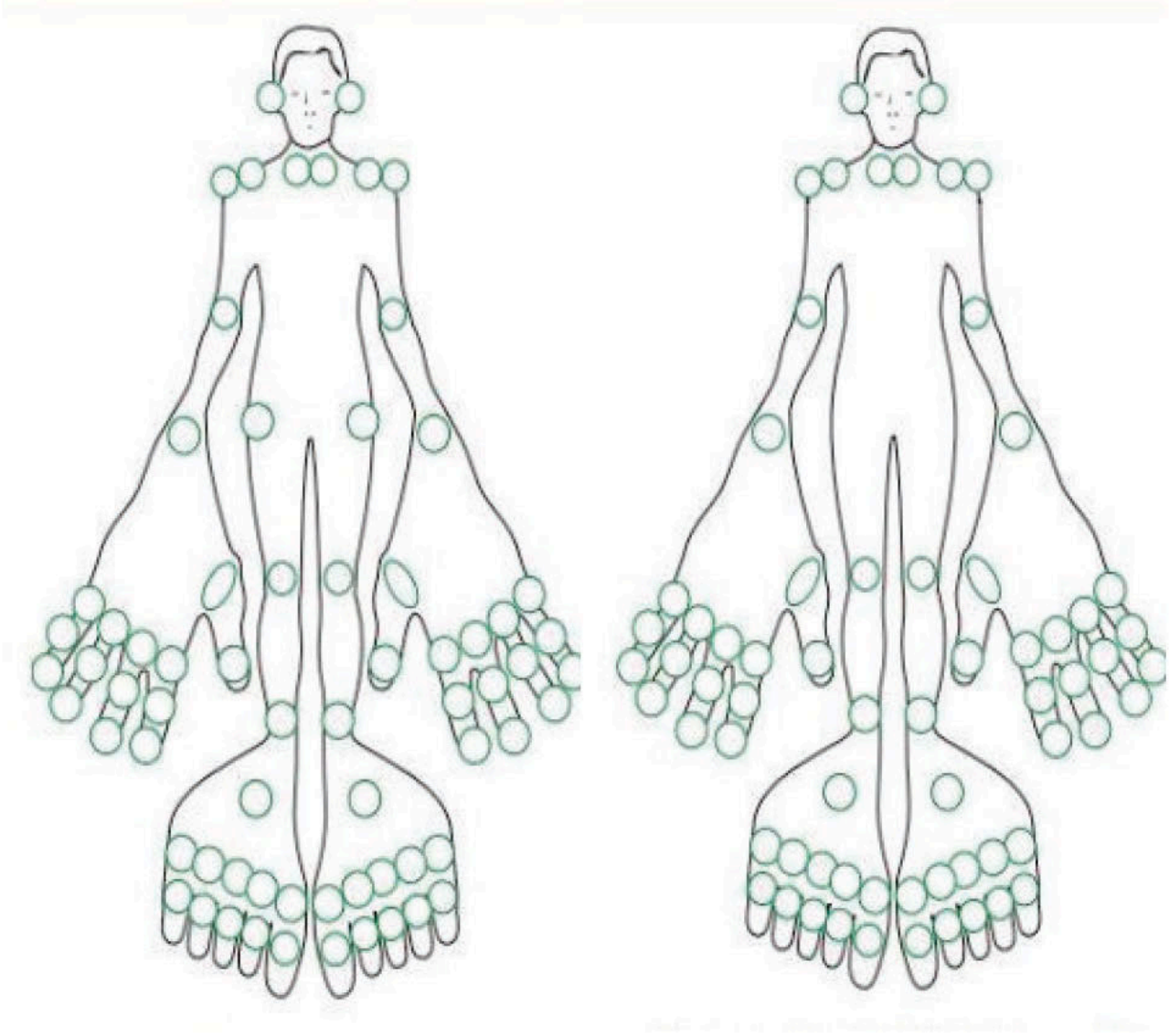
Note that PsA joint and soft tissue structural abnormalities may cause joint malalignment, which may influence the assessment for swelling. Muscles and subcutaneous tissue can atrophy, making the joints appear more prominent. Adipose tissue may be present near joints and is related, in part, to body size; it should not be confused with inflammation. Joints that have severe deformity or are fused should be noted and should not be included in the scoring for swelling.

During joint palpation, tenderness is determined primarily by applying sufficient pressure to the joint line to cause blanching of the examiner's fingernail bed. The patient is asked, “Is that tender?”

Joint tenderness also is assessed by moving joints through their respective ranges of motion. Limited range of motion may be a sign of joint inflammation; this should be interpreted in the context of simultaneous assessment of a patient's pain reaction to joint movement, such as facial grimacing or joint withdrawal.

Joint Count Scoring Sheet

Tender and swollen measurements



Tender Joints: Number _____/68

Swollen Joints: Number _____/66

APPENDIX XIII: PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (PGA) EXAMPLE

Note: please ensure that the line is 100 mm in length after printing the source document and measuring the distance

How do you assess your patient's current arthritis?

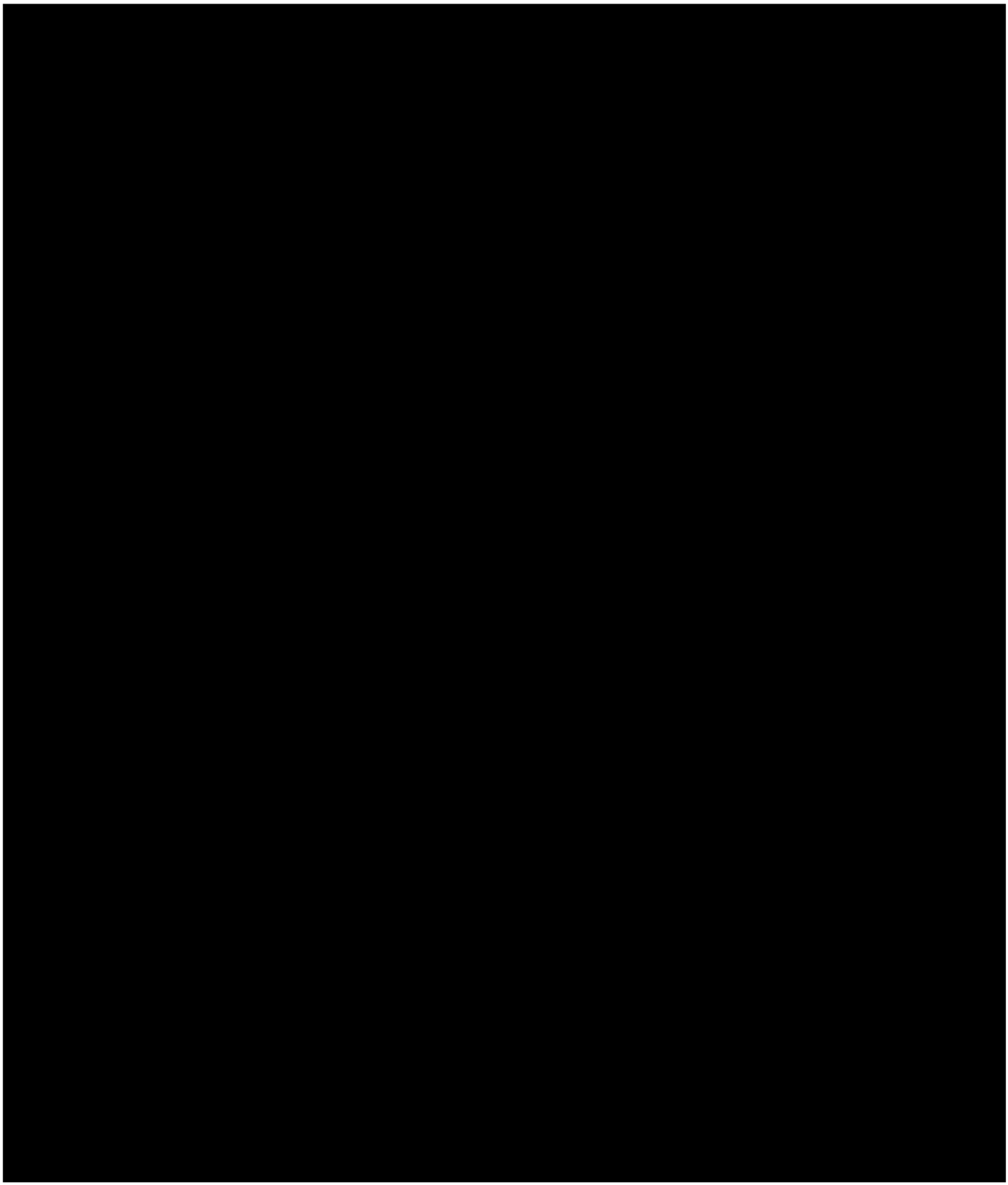
---

0 — No Disease Activity

100 — Maximum Disease Activity

To be completed by the clinic staff:

VAS Score: _____ / 100



[redacted]

[redacted]

[redacted]

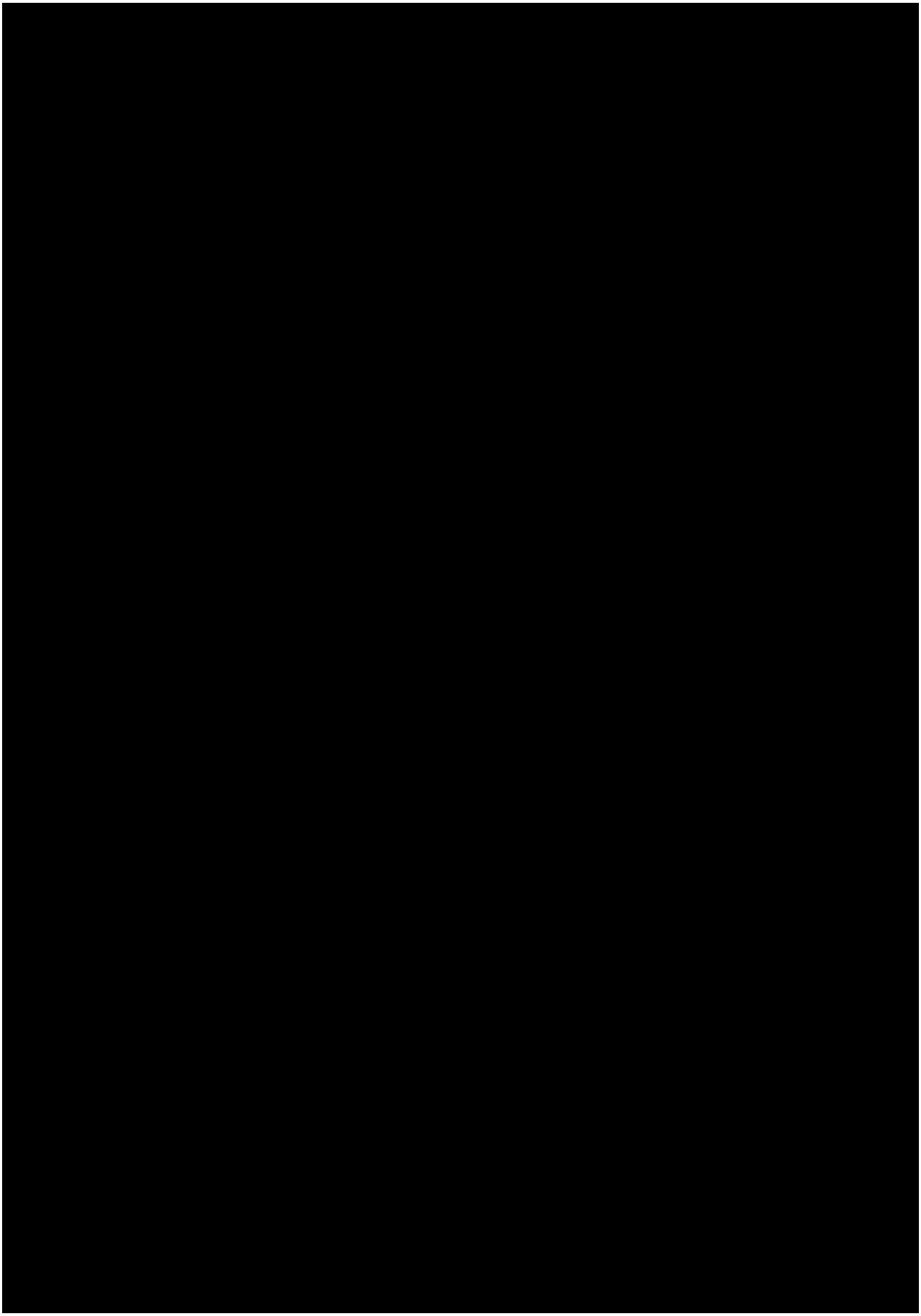
[redacted]

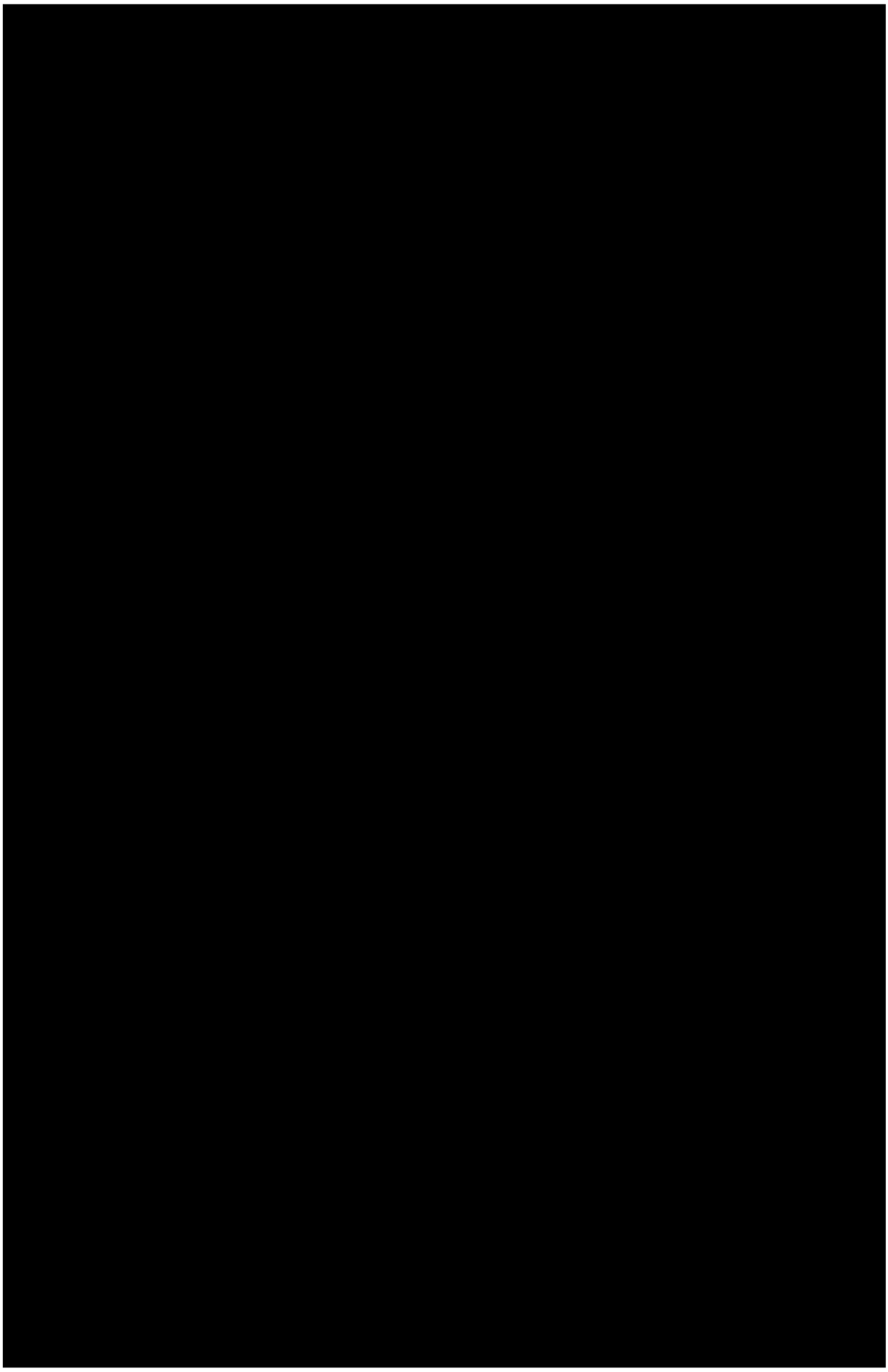
[redacted]

[redacted]

[redacted] [redacted]

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





[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]