1 FINAL CLINICAL STUDY PROTOCOL

Meiji Pharma USA Inc.

Protocol Title: A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase 2a Study to Assess the Efficacy and Safety of ME3183 Administered Orally in Subjects with Moderate to Severe Plaque Psoriasis

Protocol Number: ME3183-3

Investigational New Drug (IND) Number:	IND140688
Name of Investigational Product:	ME3183
Phase of Development:	2a
Indication:	Plaque psoriasis
Sponsor:	Meiji Pharma USA Inc. (herein after collectively referred to as Meiji) 500 Frank W. Burr Boulevard Teaneck, NJ 07666 USA Tel: +1-201-777-7133 Fax: +1-201-777-7134
Protocol Version:	Version 2.0
Protocol Date:	07 Dec 2021

PROTOCOL APPROVAL SIGNATURES

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Protocol Number: ME3183-3

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation guidelines for current Good Clinical Practice, and applicable regulatory requirements.

Sponsor Signatory

PPD

Meiji Pharma USA Inc.

PPD

Signature

Dec 9, 2021

Date (DD-Mmm-YYYY)

PPD

PPD, MD
PPD
PPD

PPD

Signature

Dec 9, 2021

Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

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Confidentiality and Current Clinical Practice (GCP)/E6 Compliance Statement

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Meiji Pharma USA Inc. or Meiji Seika Pharma Co., Ltd. (herein after collectively referred to as Meiji) including, but not limited to, the current investigator's brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Meiji and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Meiji and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Meiji study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and study records that include all pertinent observations on each of the site's subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third-party.
- Information developed in this clinical study may be disclosed by Meiji to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Printed Name	Investigator Signature
Title	Date (DD-Mmm-YYYY)
Institution	

2 SYNOPSIS

Title of Study:	A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase 2a Study to Assess the Efficacy and Safety of ME3183 Administered Orally in Subjects with Moderate to Severe Plaque Psoriasis
Protocol Number:	ME3183-3
Investigators/Study Sites:	Approximately 30 study sites across the United States and Canada will participate in this study.
Phase of Development:	Phase 2a
Objectives:	**Primary Objective** • To evaluate the efficacy of oral ME3183 compared with placebo at Week 16 in subjects with moderate to severe plaque psoriasis as measured by the Psoriasis Area and Severity Index (PASI) score **Secondary Objectives** • To evaluate the safety and tolerability of oral ME3183 in subjects with moderate to severe plaque psoriasis • To evaluate the efficacy of oral ME3183 in subjects with moderate to severe plaque psoriasis at various time points • To evaluate the effect of oral ME3183 on patient-reported outcome (PRO) measures in subjects with moderate to severe plaque psoriasis • To evaluate the pharmacokinetics (PK) of ME3183 and its metabolite (CCI) in subjects with moderate to severe plaque psoriasis who are treated with oral ME3183 **Exploratory Objectives** CCI [redacted]
Study Endpoints:	**Primary Endpoint** The primary efficacy endpoint is the proportion of subjects achieving ≥ 75% reduction from Baseline in the PASI score (PASI-75) at Week 16. **Secondary Endpoints** <u>Safety Endpoints</u> The safety endpoints are as follows: • The incidence, severity, and seriousness of adverse events (AEs) reported over the 16-week Treatment Period and the 4-week Follow-up Period • Changes from Baseline in clinically significant (CS) physical examination findings and vital sign measurements (blood pressure, heart rate, respiratory rate, body temperature, and body weight) over the 16-week Treatment Period and the 4-week Follow-up Period • Changes from Baseline in electrocardiogram (ECG) findings over the 16-week Treatment Period and the 4-week Follow-up Period • Changes from Baseline in safety laboratory values (hematology, coagulation,

	blood chemistry, and urinalysis) over the 16-week Treatment Period and the 4-week Follow-up Period Efficacy Endpoints The secondary efficacy endpoints are as follows: • The percent change from Baseline in PASI score at all visits from Week 1 to Week 16 • The proportion of subjects achieving PASI-50, PASI-75, PASI-90, PASI-100 at all visits from Week 1 to Week 16 • Time to PASI-50 and PASI-75 • The proportion of subjects achieving a Static Physicians Global Assessment (sPGA) score of "0" ("clear") or "1" ("almost clear") combined with 2-point reduction on the 5-point sPGA scale at all visits from Week 1 to Week 16 • The change from Baseline in affected body surface area (BSA) at all visits from Week 1 to Week 16 • The change from Baseline in the itch numerical rating scale (NRS) at all visits from Week 1 to Week 16 • The change from Baseline in the Dermatology Life Quality Index (DLQI) score at all visits from Week 1 to Week 16 • Percentage of subjects with at least a 5-point reduction from Baseline in the DLQI score at all visits from Week 1 to Week 16 **Pharmacokinetic Endpoint** The PK endpoint is the trough plasma concentration of ME3183 and its metabolite (CCI). **Exploratory Endpoints** CCI [redacted]
Study Design:	This multi-center, randomized, double-blind, placebo-controlled, parallel group, Phase 2a study is designed to assess the efficacy and safety of ME3183 administered orally in subjects with moderate to severe plaque psoriasis. The study consists of a 4-week Screening Period (Day -28 to Day -1), a 16-week double-blind Treatment Period (Day 1 to Day 113), and a 4-week Follow-up Period (Day 114 to Day 141). The total duration of study participation for each subject is approximately 24 weeks. Note: The study drug is administered from Day 1 to Day 112 in the Treatment Period and the end of Treatment Period assessments will be performed on Day 113. The duration of the Follow-up Period is from Day 114 to Day 141 and the end of

	Follow-up Period assessments will be performed on Day 141. After the Screening Period, approximately 125 eligible subjects with a confirmed diagnosis of psoriatic plaques, a BSA involvement of ≥ 10% (at Screening and Baseline), a PASI score 12 to 40 (at Screening and Baseline), and an sPGA ≥ 3 (at Screening and Baseline) will be randomly assigned to receive ME3183 ([CCI] mg twice daily [BID], [CCI] mg once daily [QD], [CCI] mg BID, or [CCI] mg QD) or placebo in a 1:1:1:1:1 ratio. To promote balanced allocation, randomization will be stratified by the subject's receipt (yes/no) of previous treatment with a biologic drug for psoriasis. Bio-naïve subjects will be randomized above 50% of the planned total subject randomization. After randomization (Day 1), all subjects will be evaluated at Baseline and at Weeks 1, 2, 4, 8, 12, 16, and 20. Efficacy assessments (ie, PASI, BSA, sPGA, and PRO assessments [DLQI and the itch NRS]), will be assessed at Baseline (Day 1) and at Weeks 1, 2, 4, 8, 12, 16, and 20. Blood samples for PK assessment will be collected predose at Weeks 1, 4, 8 and 16. Blood samples for [CCI] assessments will be collected predose at Baseline (Day 1), Weeks 4 and 16. Safety and tolerability will be assessed by physical exam, monitoring for AEs and serious AE (SAEs), demographics, medical history, vital signs and safety laboratory tests (hematology, coagulation, blood chemistry, and urinalysis) at Baseline (Day 1) and Weeks 1, 2, 4, 8, 12, 16, and 20. ECGs will be assessed at Baseline (Day 1) and Weeks 4, 8, 12, 16, and 20.
Selection of Subjects:	**Inclusion Criteria:** 1. Subject is willing and able to participate in the study and has read, understood, and signed the informed consent form according to national regulations. 2. Subject is a male or female aged 18 to 75 years (inclusive) at the time of consent (ie, Screening). 3. Subject has a body mass index ≥ 18.5 to < 40 kg/m^2 at Screening. 4. Subject has a diagnosis of plaque psoriasis for ≥ 24 weeks prior to Screening. 5. The subject's symptoms of plaque psoriasis are stable in the opinion of the investigator. Stable is defined as no acute deterioration (eg, pustulation or erythroderma) within 12 weeks before Screening and no rebound of plaque psoriasis within 4 weeks before Screening. 6. The subject's severity of disease meets all of the following criteria: • Psoriatic plaques must cover ≥ 10% of BSA at Screening and Baseline • PASI score 12 to 40 at Screening and Baseline • sPGA ≥ 3 at Screening and Baseline 7. Subject is deemed by investigator to be eligible for phototherapy or systemic therapy. 8. Subject agrees to avoid prolonged exposure to sunlight or use of artificial sunbathing (eg, tanning booths) or other ultraviolet light sources during the Treatment Period. 9. Subject, if female and of childbearing potential, must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline. Any women of childbearing potential (WOCBP) must agree to sexual abstinence or to use a highly effective contraceptive measure starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy,

and bilateral oophorectomy).

10. Subject, if a fertile male, agrees to sexual abstinence or to use a condom during sexual activity with their female partner of childbearing potential starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment. A male subject is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Additionally, if their partner is a WOCBP, then their partner should be advised to use a highly effective contraceptive measure during sexual activity starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment.
11. Subject, if female, must agree to not donate, or retrieve for her own use, ova starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment.
12. Subject, if male, must agree to not freeze or donate sperm starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment.

Exclusion Criteria:

1. Subject has a diagnosis of non-plaque psoriasis (predominantly guttate, pustular, inverse, or erythrodermic) or drug-induced psoriasis.
2. Subject has any unstable or CS (as determined by the investigator) cardiac, endocrinologic, gastroenterologic, pulmonary, neurologic, psychiatric (such as major depression), hepatic, renal, hematologic, immunologic disease, or other disease (eg, uncontrolled diabetes) that would place the subject at unacceptable risk if they were to participate in the study.
3. Subject has suicidal ideation or behavior in the past 12 months as indicated by a positive response (yes) to questions 3, 4, or 5 on the Columbia-Suicide Severity Rating Scale completed at Screening and/or at Baseline.
4. Subject has a present recurrent medical condition associated with significant gastrointestinal events (eg, nausea, vomiting, constipation, abdominal pain, diarrhea).
5. Subject has any condition that would confound the ability to interpret data from the study (eg, eczema, atopic dermatitis, lupus, inflammatory bowel disease).
6. Subject has any degree of dysphagia that may interfere with the oral dosing of the study treatment.
7. Subject has a history of allergy or hypersensitivity to any component of the study treatments.
8. Subjects who have had a prior laboratory confirmed COVID-19 test or have been in close physical contact (6 feet or closer for at least 15 minutes) with a person who is known to have laboratory confirmed COVID-19 or with anyone who has any symptoms consistent with COVID-19 within the past 14 days at Screening or Baseline.
9. Subjects experiencing any of the following symptoms at Screening or Baseline:
    - Fever or chills
    - Cough
    - Shortness of breath or difficulty breathing
    - Fatigue
    - Muscle or body aches
    - Headache
    - New loss of taste or smell
    - Sore throat

	• Congestion or runny nose • Nausea or vomiting • Diarrhea 10. Subject has active or chronic hepatitis B virus or hepatitis C virus (HCV) infection as per Screening viral serology tests. Exception: If the subject has received documented treatment which was curative for HCV and tests negative for HCV RNA at Screening, the subject may be considered for randomization. 11. Subject is positive for the HIV antibodies (HIV-1 or HIV-2) at Screening or has a history of congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease). 12. Subject has a recent history of drug, substance, or alcohol abuse/dependence within 1 year prior to Screening as determined by the investigator. 13. Subject has an active infection (bacteria, viral, fungal, etc.) requiring treatment with systemic antibiotics within 4 weeks of Screening. Any treatment for such infections must be completed at least 4 weeks prior to Screening. 14. Subject has active tuberculosis or history of incompletely treated tuberculosis per medical history. 15. Subject has a malignancy or history of malignancy (except for treated [ie, cured] basal cell or squamous cell in situ skin carcinomas and treated [ie, cured] cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence). 16. Subject is pregnant or breastfeeding at Screening or at Baseline. 17. Subject has a history of lack of efficacy (inadequate efficacy when used in adequate dose and duration in accordance with the approved label) to any biological products for psoriasis. 18. Subject has received 2 or more biological products in the past for the treatment of psoriasis. 19. Subject has a history of lack of efficacy to 2 or more non-biologic systemic therapy due to inadequate efficacy when administered in adequate dose and duration in accordance with their label (approved in the subject's country) for psoriasis. 20. Subject has received any prior treatment with apremilast or any other phosphodiesterase 4 inhibitor. 21. Subject has received ustekinumab, secukinumab, brodalumab, ixekizumab, guselkumab, risankizumab, tildrakizumab, or briakinumab (or any other therapeutic agent targeting IL-12, IL-17, or IL-23) within 24 weeks of first administration of study treatment. 22. Subject has received TNF-α inhibitor(s)/blocker(s) within 8 weeks of first administration of study treatment. 23. Subject has received natalizumab (an integrin receptor antagonist), or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, alefacept) within 12 weeks of first administration of study treatment. 24. Subject has received rituximab within 24 weeks of first administration of study treatment. 25. Subject has received any systemic immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus), any protein kinase inhibitor (eg, tofacitinib, baricitinib, peficitinib, upadacitinib), or anakinra within 4 weeks of the first administration of study treatment. 26. Subject has received phototherapy (e g, ultraviolet B including narrow band ultraviolet B, Goeckerman therapy, and excimer laser or psoralen ultraviolet A) or any systemic medications/treatments that could affect psoriasis or sPGA evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues,

	psoralens, sulfasalazine, or fumaric acid derivatives) within 4 weeks of the first administration of study treatment. 27. Subject has had a recent initiation of a drug that is known to potentially cause or exacerbate psoriasis (including, but not limited to, beta-blockers, lithium, and anti-malarials) within the 8 weeks prior to the first administration of study treatment; a subject who has been on a stable dose for at least 8 weeks prior to the first administration of study treatment without exacerbation of psoriasis may be randomized and does not need to discontinue these medications. 28. Subject has used topical medications/treatments that could affect psoriasis or sPGA evaluation (including, but not limited to, certain corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralen, pimecrolimus, tacrolimus, or phosphodiesterase 4 inhibitor) within 2 weeks of the first administration of study treatment. 29. Subject has received an investigational drug for biologic therapy within the previous 24 weeks prior to the first administration of study treatment or received any other non-biologic investigational therapy/drugs or device within 4 weeks or 5 half-lives (whichever is longer) prior to the first administration of study treatment. 30. Subject has received any prior treatment with ME3183. 31. Subject has any of the following abnormal laboratory test findings at Screening. • Abnormal hepatic function o Aspartate aminotransaminase or alanine aminotransaminase $\geq 2 \times$ upper limit of normal or o Total bilirubin $\geq 2 \times$ upper limit of normal, unless the subject has a diagnosis of Gilbert's syndrome • White blood cell count $< 3000/mm^3$ ($< 3.0 \times 10^9/L$) • Neutrophil count $< 1000/mm^3$ ($< 1.0 \times 10^9/L$) • Platelet count $< 100,000/\mu L$ ($< 100 \times 10^9/L$) • Hemoglobin < 8.0 g/dL • Creatinine clearance estimated by Cockcroft-Gault formula < 60 mL/min • Hemoglobin A1c $> 9.0\%$ 32. Subject has a CS abnormality on a 12-lead ECG or corrected QTcF > 450 msec at Screening or Baseline. 33. Subject has a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 100 mmHg (based on at least 2 repeat measurements) at Screening. 34. Prisoners or subjects who are incarcerated for any reason. 35. Subject has any other factor constituting disqualification for study inclusion in the judgement of the investigator.
Planned Sample Size:	Approximately 125 eligible subjects are planned to be randomized (25 subjects per treatment group). Eligible subjects will be centrally randomized in a 1:1:1:1:1 ratio to 1 of the following treatment groups: • Treatment Group 1: ([redacted] mg ME3183 BID administered orally): [redacted] capsule of [redacted] mg ME3183 and [redacted] capsules of matching placebo in the morning and evening • Treatment Group 2: ([redacted] mg ME3183 QD administered orally): [redacted] capsules of [redacted] mg ME3183 and [redacted] capsule of matching placebo in the morning and [redacted] capsules of matching placebo in the evening • Treatment Group 3: ([redacted] mg ME3183 BID administered orally): [redacted] capsule of [redacted] mg ME3183 and [redacted] capsule of [redacted] mg ME3183 and [redacted] capsule

	of matching placebo in the morning and evening • Treatment Group 4: ([redacted] mg ME3183 QD administered orally): [redacted] capsules of [redacted] mg ME3183 in the morning and [redacted] capsules of matching placebo in the evening • Treatment Group 5 (Placebo BID administered orally): [redacted] capsules of matching placebo in the morning and evening To promote balanced allocation, randomization will be stratified by subject's receipt (yes/no) of previous treatment with a biologic drug for psoriasis. Each treatment group will include randomized subjects who 1) are bio-naïve and 2) received previous treatment with a biologic drug for psoriasis. After randomization of subjects has reached the maximum percentage as determined by the sponsor for subjects that have received previous treatment with a biologic drug for psoriasis, randomization in this group will be stopped and the study sites will be informed accordingly.
Study Treatments	ME3183 ([redacted] mg, [redacted] mg, [redacted] mg, and [redacted] mg) and matching placebo will be prepared using the following ME3183 and placebo capsules: • ME3183 Capsule [redacted] mg • ME3183 Capsule [redacted] mg • ME3183 Placebo Capsule
Treatment Duration:	The treatment duration for an individual subject will be 16 weeks. Each subject will receive BID treatment under fed condition (within approximately 30 minutes after a standard meal) from Day 1 to Day 112.
Efficacy:	Efficacy assessments (including PRO assessments) will include: • PASI score • BSA • sPGA • Itch NRS • DLQI

Safety:	Safety assessments will include:
	• AE/ SAEs
	• 12-lead ECGs
	• Physical examinations (complete/targeted) including height and body mass index
	• Vital signs
	  o Blood pressure (systolic and diastolic)
	  o Heart rate
	  o Respiratory rate
	  o Body temperature
	  o Body weight
	• Safety laboratory tests including:
	  o Viral serology (hepatitis B virus, HCV, and HIV)
	  o Hematology and coagulation
	  o Blood chemistry
	  o Urinalysis
	  o Pregnancy tests (WOCBP only; serum or urine β-human chorionic gonadotropin)
	  o Serum follicle-stimulating hormone (postmenopausal women only)

Pharmacokinetics:	Blood samples for the determination of the concentrations of ME3183 and its metabolite ([redacted]) will be collected from each subject in each treatment group. The PK blood samples will be taken predose at scheduled visits until Week 16.
[redacted]	
Other Assessments:	Other assessments will include: • Eligibility assessments: Informed consent • Inclusion/exclusion criteria • Dermatologic and medical history • History of previous treatment with a biologic drug for psoriasis • Columbia-Suicide Severity Rating Scale • Demographics • Prior and concomitant medications/therapies or procedures • Treatment compliance • Medical photography of the target skin lesion (at selected sites in a selected number of subjects for documentation and publication purposes only)
Statistical Methods and Planned Analyses:	**Determination of Sample Size** No formal sample size calculation was performed. For the assessment of efficacy and safety of ME3183 in subjects with moderate to severe plaque psoriasis in this proof-of-concept study, approximately 125 eligible subjects will be enrolled. Twenty-five subjects will be randomized to each of the following treatment groups: ME3183 [redacted] mg BID, ME3183 [redacted] mg QD, ME3183 [redacted] mg BID; ME3183 [redacted] mg QD, and placebo. The number of planned subjects is considered adequate to assess safety and to provide efficacy estimates for in this Phase 2a study. The expected drop-out rate is assumed to be 10%. **Analysis Sets** Full Analysis Set All subjects who have been randomized, received at least 1 dose of study drug, and have at least 1 evaluable post-Baseline time point for primary endpoint will be included in the full analysis set (FAS). Analyses in the FAS will be based on the subject's randomized treatment group. Per Protocol Set The per protocol set (PPS) is a subset of the FAS; the PPS will exclude subjects with protocol deviations that may significantly impact the assessment of the primary objective of the study. Analyses in the PPS will be based on the study treatment actually received by each subject. All decisions to exclude subjects from the PPS will be made prior to the unblinding of the study. Safety Analysis Set All randomized subjects who received at least 1 dose of study drug will be included in the safety analysis set. Analyses in the safety analysis set will be based on the study treatment actually received by each subject. Pharmacokinetic Analysis Set The PK analysis set will consist of all subjects who were correctly administered at

least 1 ME3183 dose and where ME3183 or CCI concentration data is available without any protocol deviation interfering with these results. Analyses in the PK analysis set will be based on the study treatment actually received by each subject.

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Statistical Analyses

Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be performed using the FAS. The analysis of the primary efficacy endpoint will also be performed using the PPS.

Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects achieving ≥ 75% reduction from Baseline in the PASI score at Week 16. For each ME3183 treatment group, the difference in the proportion of subjects achieving the difference in PASI-75 (ME3183 – placebo) and its 95% confidence interval will be estimated and tested for superior treatment effect using the Cochran-Mantel-Haenszel test at a 1-sided significance level of $\alpha = 0.025$. The PASI score will be reported for each treatment group together with the 95% confidence interval for mean.

Analyses of the Secondary Efficacy Endpoints

The proportion of subjects achieving PASI-50, PASI-75, PASI-90, and PASI-100, the proportion of subjects with an sPGA score of "0" or "1" combined with 2-point reduction on the 5-point sPGA scale, and the proportion of subjects with at least a 5-point reduction from Baseline in the DLQI score will be analyzed similar to the primary endpoint analysis.

The proportion of subjects achieving PASI-50, PASI-75, PASI-90, and PASI-100, the proportion of subjects with an sPGA score of "0" or "1" combined with 2-point reduction on the 5-point sPGA scale, and the proportion of subjects with at least a 5-point reduction from Baseline in the DLQI score will be summarized by treatment group and visit. The percent change from Baseline in PASI score and change from Baseline in affected BSA, the itch NRS, and the DLQI score will be summarized by treatment group and visit. The percent change from Baseline in PASI score and the change from Baseline in the affected BSA, the DLQI score, and the itch NRS will be analyzed using a mixed-effect model for repeated measures when applicable.

Kaplan-Meier estimate will be used for summarizing the time to PASI-50 and PASI-75. The log-rank test may be used for comparing the time to PASI-50 and PASI-75 between each ME3183 treatment group and placebo. The Cox proportional hazard model may also be used for analyzing the time to PASI-50

	and PASI-75. The time to PASI-50 and PASI-75 will be summarized by treatment group. Analyses of the Exploratory Efficacy Endpoints CCI [redacted] Safety Analyses All safety analyses will be performed using the safety analysis set. All recorded AE and SAEs will be listed and tabulated by Medical Dictionary for Regulatory Activities (version 24.1 or higher) system organ class, preferred term, and treatment group over the 16-week Treatment Period and the 4-week Follow-up Period. Vital signs and safety laboratory test results will be listed and summarized by treatment group over the 16-week Treatment Period and the 4-week Follow-up Period. Summaries will be provided using descriptive statistics, including mean values and mean change from Baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point. Any CS physical examination findings and safety laboratory results will be summarized. ECG readings will be evaluated by the investigator and abnormalities, if present, will be summarized and listed. The clinically noteworthy QT/QTc interval (> 450, > 480, or > 500 msec) or clinically noteworthy change from Baseline (> 30 or > 60 msec) will also be summarized using descriptive statistics. Summary tables will be provided for concomitant medications initiated during the study period. Pharmacokinetic Analysis The PK analysis set will be used for the PK analysis. Trough plasma concentrations of ME3183 and its metabolite (CCI [redacted]) will be summarized descriptively by treatment group in the tables, figures, and listings (TFL). CCI [redacted]

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AUC	area under plasma concentration-time curve
$AUC_{0\text{-}24hr}$	area under the plasma concentration-time curve from time zero to 24 hours
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time zero to infinity
CCI	[redacted]
BID	twice daily
BMI	body mass index
BSA	body surface area
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	trough plasma concentration
CCI	[redacted]
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IL	interleukin
IRB	institutional review board
IWRS	interactive web response system
MAD	multiple ascending dose
NOAEL	no-observed-adverse-effect-level
NRS	numerical rating scale
CCI	[redacted]
PASI	Psoriasis Area and Severity Index

Abbreviation	Definition
PASI-50	≥ 50% reduction from Baseline in the PASI score
PASI-75	≥ 75% reduction from Baseline in the PASI score
PASI-90	≥ 90% reduction from Baseline in the PASI score
PASI-100	100% reduction from Baseline in the PASI score
CCI [redacted]	
PDE4	phosphodiesterase 4
CCI [redacted]	
PI	principal investigator
PK	pharmacokinetic
PPS	per protocol set
PRO	patient-reported outcome
QD	once daily
QOL	quality of life
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
sPGA	Static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
TFL	Tables figures and listings
WOCBP	women of childbearing potential
UV	ultraviolet
UVB	ultraviolet B

5 INTRODUCTION

5.1 Background on Plaque Psoriasis

Psoriasis is a chronic immune-mediated inflammatory disorder that affects approximately 2% to 3% of the population, which translates to 17 million people in North America and Europe and approximately 170 million people worldwide.(1) It is characterized by disfiguring, scaling, erythematous plaques that may be painful or often severely pruritic and may cause significant quality of life (QOL) issues. The plaques are irregular, round to oval in shape, and most often located on the scalp, trunk, buttocks, and limbs, with a predilection for extensor surfaces such as the elbows and knees.(2)

Nearly one-quarter of people worldwide with psoriasis are considered to have moderate to severe form of the disease.(3) A survey of data from National Health and Nutrition Examination in the United States, concluded that psoriasis is independently associated with an increased risk of mortality, which might be mediated by increased prevalence of comorbidities (cardiovascular, infectious, and neoplastic disorders) in psoriatic patients.(4)

Treatment options for psoriasis include topical treatments for milder disease, and systemic treatments for moderate to severe disease not sufficiently responsive to topical treatments. Topical treatments include corticosteroids, anthralin, synthetic vitamin D3, and vitamin A. Systemic therapies include phototherapy, acitretin, cyclosporine, methotrexate, apremilast, and various systemic biologic products. Acitretin is a potent teratogen that should be avoided in women of childbearing age and potential. Cyclosporine works rapidly and is effective in the majority of patients, however, impaired renal function, hypertension, concerns about lymphoma, and a potential increase in cutaneous malignancies are known adverse effects after long-term treatment with cyclosporine. Methotrexate, although effective in the majority of patients, has the potential for hepatotoxicity.(2) Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor, approved for moderate to severe psoriasis. Despite the advancement in dermatology, and the introduction of newer biological drugs, apremilast is the only novel oral medication that has been introduced to treat psoriasis in the past 2 decades.(5) For its safety profile and easy route of administration, apremilast may offer an oral treatment option for those patients that discontinue treatments because of ineffectiveness, intolerability or ineligibility to the currently available drugs.(6) However, the efficacy of apremilast is not so great compared to other systemic therapies. Therefore, additional oral treatments for psoriasis that can provide high levels of efficacy, safety and tolerability remain an unmet need.

5.2 Background on ME3183

ME3183 (1-{[2-(3,6-Diazabicyclo [3.1.1]heptan-3-yl)-7-(1,3-thiazol-2-yl)-1,3-benzoxazol-4-yl]oxy}-1,1-difluoro-2-methylpropan-2-ol) is a synthesized, small molecule, discovered by Meiji Seika Pharma Co., Ltd., that acts as a PDE4 inhibitor. ME3183 shows a higher potency of inhibitory activity for PDE4 and a higher potency of inhibition against lipopolysaccharide-

induced tumor necrosis factor-α (TNF-α) production in human blood cells than existing PDE4 inhibitors and thus is expected to have a higher clinical efficacy in psoriasis. Also, few ME3183 was detected in the rat brain after single oral administration, indicating low distribution of ME3183 into the brain. Therefore, ME3183 is expected to show less central neurocircuitry associated adverse effect (eg, vomiting) than other PDE4 inhibitors.

5.2.1 Nonclinical Studies

ME3183 is a highly selective PDE4 inhibitor, non-selective among PDE4 subtypes: half maximal inhibitory concentration (IC_{50}) at PDE4 A1A of 1.28 nmol/L, at PDE 4B1 of 2.33 nmol/L, and at PDE4 D2 of 1.63 nmol/L. Inhibition of PDE4 affords ME3183 potent anti-inflammatory activity. The efficacy of ME3183 was assessed in pharmacology studies, which supports the rationale for assessment of ME3183 in clinical studies. ME3183 inhibited vascular permeability in a histamine-induced mouse model. In addition, evaluation of ME3183 in a chronic oxazolone-induced mouse model of dermatitis demonstrated that oral treatment of ME3183 suppressed ear swelling with a drug dose producing median effective dose (ED_{50}) of 1.43 mg/kg.

No effects of ME3183 on central nervous system (CNS) in male mice at dose levels of 3, 10, and 30 mg/kg. An increase in heart rate and a prolongation of corrected QT interval (QTc) duration ([redacted]% longer than the individual time-matched own control value) was observed in [redacted] of 4 monkeys at 10 mg/kg of ME3183. The IC_{50} for the human Ether-à-go-go-Related Gene (hERG) was [redacted] nmol/L ([redacted] ng/mL).

The phototoxic potential of ME3183 was evaluated in the cultured mammalian cells (Balb/c 3T3 cells). The IC_{50} values for cell viability with and without irradiation were determined to be [redacted] µg/mL and [redacted] µg/mL, respectively, and the photo irritation factor was [redacted] and less than 5, that is the positive criteria defined by the International Council for Harmonisation (ICH) S10 guidance. Therefore, ME3183 was categorized as having no phototoxicity.

The plasma pharmacokinetic (PK) profiles of ME3183 were observed in mice, rats, dogs, and monkeys after oral and/or intravenous administration. Oral bioavailability in rats, dogs, and monkeys were approximately [redacted] to [redacted]%, [redacted]%, and [redacted] to [redacted]%, respectively. ME3183 exhibited non-linear absorption and area under the plasma concentration-time curve (AUC) increased greater than dose proportionality in mice, rats, and monkeys. Plasma protein binding of ME3183 ranged from [redacted]% in mouse, rat, dog, monkey and human, and no apparent differences were observed among these species and concentrations. ME3183 was notably stable in human and animal hepatocytes except monkey hepatocytes. The reaction phenotyping studies indicated that the formation of [redacted] was mainly mediated by cytochrome 3A4/5. The excretion of ME3183 into urine and bile was approximately [redacted]% of doses after intravenous administration to rats. ME3183 at the concentration of [redacted] µmol/L showed little to no inhibition for cytochrome 1A, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A enzyme assays. [redacted]

The toxicity of ME3183 was assessed in mice and monkeys with up to [redacted]-week and [redacted]-week of consecutive once daily oral dosing. In mice and monkeys, the toxicity profile of ME3183 was identified as arteritis and deteriorated clinical condition due to the severe gastrointestinal motility inhibition. Arteritis was observed in multiple organs in the moribund animals at high dose in both species. In the [redacted]-week repeated dose toxicity study, there was no difference of toxicity findings between mice and monkeys; however, it was considered that monkeys were more sensitive to toxicity than mice because toxicity findings were observed at lower plasma concentrations in monkeys.

In mice, the mean maximum plasma concentration (C_{max}) on Day 28 at no-observed adverse effect level (NOAEL) (3 mg/kg/day) were [redacted] and [redacted] ng/mL, and $AUC_{0\text{-}24h}$ were [redacted] and [redacted] ng·hr/mL in male and female, respectively.

In monkeys, C_{max} on Day 28 at NOAEL (1 mg/kg/day) were [redacted] and [redacted] ng/mL, and $AUC_{0\text{-}24h}$ were [redacted] and [redacted] ng·hr/mL in male and female, respectively. The toxicity of oral administration of ME3183 was evaluated in mice and monkeys in a 16-week repeated dose toxicity study followed by a 4-week recovery study. The toxicities observed in this study were similar (inflammation including arteritis) to those observed in the 28-day repeated dose toxicity study and the NOAEL was 3 mg/kg/day in both mice and monkeys. In mice, arteritis and periarteritis were noted in a dead mouse at 10 mg/kg/day. The $AUC_{0\text{-}24hr}$ on the last dosing day was [redacted] ng hr/mL in males and [redacted] mg hr/mL in females. In monkeys, no arteritis was observed, and no animal died or sacrificed due to moribundity and the average $AUC_{0\text{-}24hr}$ on the last dosing day was [redacted] ng hr/mL in males and [redacted] ng hr/mL in females.

The effects of oral ME3183 on embryo-fetal development were studied in a preliminary study in pregnant mice. ME3183 was orally administered once daily (QD) to pregnant mice (8 to 10 dams/group) at dose levels of 0 (vehicle), 1, 3, and 10 mg/kg/day during the period from implantation to the closure of the hard palate (from Day 6 to Day 15 of gestation). The NOAEL was considered to be 10 mg/kg/day of ME3183 for general toxicity and reproductive functions in dams and embryo-fetal development. No test article-related changes were noted in the number of live fetuses, fetal viability rate, number of embryo-fetal deaths, post-implantation loss rate, fetal body weight, placental weight, sex ratio, or external, placental, visceral, or skeletal findings at any dose level. At the NOAEL, the C_{max} of drug of ME3183 averaged [redacted] ng/mL and the mean $AUC_{0\text{-}24hr}$ of ME3183 averaged [redacted] ng·hr/mL on Day 15 of gestation.

For complete details on the nonclinical studies of ME3183, refer to the investigator's brochure (IB).

5.2.2 Clinical Studies

Two (2) Phase 1 studies in healthy adult subjects (ME3183-1 and ME3183-2 studies) have been conducted and 126 individuals who received study treatment (96 subjects received ME3183 and 30 subjects received placebo). ME3183 was tolerable and safe in healthy adults up to 25 mg single administration, and 10 mg twice daily (BID) and 15 mg QD for 14 days multiple administrations. Frequently reported treatment-emergent adverse events (TEAEs), the TEAEs reported by more than 2 subjects, in single administration were diarrhea, headache, lipase increased, tachycardia, and nausea. The majority of TEAEs in single ascending dose (SAD) studies were classified as mild. Most of the TEAEs were recovered/resolved within few days without any medication. The serious adverse event (SAE) of severe vasovagal neurocardiac syncope occurred in 12.5 mg subject. When ME3183 were administered repeatedly, the frequently reported TEAEs were; medical device site reaction, headache, diarrhea, abdominal pain, vomiting, nausea, hematochezia, back pain, arthralgia, pain in extremity, myalgia, dermatitis, decreased appetite, and dysmenorrhea. The majority of TEAEs in multiple ascending dose (MAD) study were classified as mild. All TEAEs were temporal and resolved during the dosing period. No SAE was occurred in MAD study.

ME3183 was administered to healthy adult subjects in either in suspension (1 mg to 12.5 mg) or capsule (12.5 mg to 25 mg) in SAD studies. ME3183 was absorbed orally in both form with peak concentration recorded at approximately 3.5 hours to 4 hours postdose and was eliminated slowly with an elimination half-life ($t_{1/2}$) of approximately 16 hours to 24 hours. The means of C_{max} and AUC increased slightly greater than a dose proportionality from 1 mg to 10 mg suspension, while C_{max} and AUC increased almost dose proportionally over the dose range of 12.5 mg to 25 mg of capsule administration. The means of C_{max} and AUC in CCI (metabolite of ME3183) were approximately from CCI% to CCI% compared with those of ME3183 at each dose level. As the dose of ME3183 increases, the ratio of C_{max} and AUC of CCI to ME3183 tended to decrease. The mean of cumulative urinary excretion rate in ME3183 was CC% to CC% which was quite small.

In the MAD study, the means of C_{max} and AUC increased over the dose range of 2.5 mg BID to 10 mg BID. The mean C_{max} increased by 4- to 5-fold with multiple dosing from Day 1 to Day 14, in all the BID dose groups. The mean C_{max} increased by 2-fold with multiple dosing from Day 1 to Day 14, in 15 mg QD dose group. The mean plasma concentration in the steady-state of ME3183 was achieved around Day 3 to Day 4 in all the groups.

PK profiles of ME3183 and CCI were affected slightly by food intake. The food intake decreased the systemic exposures of ME3183 after single dose of ME3183. The time to peak plasma concentration of ME3183 under fed condition was delayed by approximately 2 hours compared with that under fasted condition. The observed geometric means were in the ratio (fed/fasted) of 65% for C_{max} and 82% for area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$). There was no apparent difference of $t_{1/2}$ of ME3183 between fasted and fed conditions.

Refer to the IB for further details on clinical studies with ME3183.

5.3 Clinical Risks/Benefits of ME3183

ME3183 was tolerable and safe in healthy adults up to 25 mg single administration and 10 mg BID and 15 mg QD for 14 days multiple administrations. The frequently reported adverse drug reactions (ADRs), the ADRs reported by more than 2 subjects, in single administration were diarrhea, tachycardia, and lipase increased. Majority of ADRs were classified as mild. All events except for vasovagal neurocardiac syncope were recovered/resolved within few days without any medications. No subjects discontinued the study due to ADRs in SAD studies.

One subject in 12.5 mg suspension group experienced an SAE of severe vasovagal neurocardiac syncope during ME3183-1 SAD study. The subject had a prior history of syncope and dizziness likely due to orthostatic intolerance. The subject was tested with the tilt table test and showed a vasovagal response clearly, suggesting the subject had a risk factor of syncope.

When ME3183 was administered repeatedly, the frequently reported ADRs, the ADRs reported by more than 2 subjects, were headache, diarrhea, abdominal pain, vomiting, nausea, and decreased appetite. The number of ADRs of diarrhea increased with the dose. Nausea and vomiting were noted in higher doses (10 mg BID and 15 mg QD). Diarrhea was noted in the early period of dosing, around Day 1 to Day 2, in all dose groups. Headache began from around Day 7 in lower dose (2.5 mg BID or 5 mg BID) and from Day 1 to Day 2 in higher dose groups (10 mg BID or 15 mg QD). Vomiting was observed from Day 7 sporadically, but resolved during the dosing period. The majority of ADRs were classified as mild. There were 6 moderate ADRs of headache, diarrhea, abdominal pain, vomiting, nausea, and tachycardia in 10 mg BID, and 1 moderate vomiting in 15 mg QD dose group. There was no severe ADR in MAD study. All ADRs were temporal and were resolved during the dosing period. In 10 mg BID dose group, 2 subjects withdrew consent due to adverse events (AEs). The ADRs observed in these 2 subjects were headache, diarrhea, vomiting, feeling hot, nausea, abdominal pain, anxiety, and skin exfoliation. The events such as nausea, vomiting and diarrhea, and headache are known to be side effects of existing PDE4 inhibitors.

The potential risks of ME3183 can be estimated based on the AE profile of apremilast (a PDE4 inhibitor) presented in the commercial labeling. The common AEs include diarrhea, nausea, vomiting, depression, weight decrease, upper respiratory tract infection, nasopharyngitis, abdominal pain upper, and headache (Otezla package insert, USA, revised: 04/2020). Also, the most common side effects of known oral PDE4 inhibitors are gastrointestinal (GI) effects such as nausea, vomiting, and diarrhea.(7) Additionally, GI motility disorder, inflammatory findings including arteritis/vasculitis, and QTc prolongation were reported based on the nonclinical studies.

The potential side effects identified in ME3183 nonclinical studies and also in studies involving other oral PDE4 inhibitors will be carefully monitored in the current study. The GI motility disorder will be identified by monitoring the subjects for any signs of abdominal discomfort,

abdominal distension, abdominal pain, nausea, vomiting, loss of appetite, and constipation. Besides the above, all subjects will be monitored for any cardiovascular manifestations using vital signs and 12-lead electrocardiograms (ECGs). Drug class potential effects such as weight loss and major depression will be monitored during this study. Weight will be measured at scheduled visits throughout the study to check for any potential excessive weight loss. Subjects with major depression or at risk for suicide will be excluded and suicidal ideation will be assessed at Screening and/or Baseline by Columbia-Suicide Severity Rating Scale (C-SSRS).

Considering the above safety profile of ME3183, caution will be exercised (investigator's judgement) before randomizing subjects with any clinically significant (CS) comorbidities (cardiovascular, GI, neurological, etc.). See Section 8 for detailed list of inclusion and exclusion criteria.

5.4 Study Rationale

This study is designed to assess the efficacy, safety, and tolerability of ME3183 administered orally for 16 weeks in subjects with moderate to severe plaque psoriasis as a proof-of-concept study. Phase 1 studies with ME3183 showed it was safe and generally well tolerated in healthy subjects. This is the first study in the target patient population.

Efficacy will be assessed through a set of validated measures for plaque psoriasis. In addition, PK and CCI [redacted] evaluations will be conducted. The results of the study will inform the design and the dosing regimens of the subsequent study.

5.5 Rationale for Dose Selection

Four different dose levels ([redacted] mg BID, [redacted] mg QD, [redacted] mg BID and [redacted] mg QD) were selected as dosing regimens for this study. The dose regimens were selected based on the results of Phase 1 studies which have been concluded that ME3183 was safe and generally well tolerated in healthy subjects.

The following points were considered for dose selection:

- The doses were selected within the range of doses tested in the SAD and MAD cohorts in Phase 1 studies.
- The nonclinical study of ME3183 showed that the inhibitory activity of ME3183 to TNF-α production was stronger at 31 times than that of apremilast. Given that the plasma concentration, that is steady-state trough plasma concentration (C_{trough}) and AUC, of selected doses of ME3183 would be expected to be comparable to therapeutic exposure level anticipated by the result of the nonclinical study.
- High doses were selected within the tolerable dose (20 mg per day for 14 days) in Phase 1 studies, to assess the near maximally therapeutic responses. Exposure level, that is C_{max} and AUC per day, of selected doses were estimated not to exceed the exposure level of 10 mg BID.

- Based on the PK profile of ME3183 in Phase 1 studies, a QD dosing regimen was selected in addition to the BID dosing regimen.

Refer to the IB for complete details for safety and PK.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

- To evaluate the efficacy of oral ME3183 compared with placebo at Week 16 in subjects with moderate to severe plaque psoriasis as measured by the Psoriasis Area and Severity Index (PASI) score

6.1.2 Secondary Objectives

- To evaluate the safety and tolerability of oral ME3183 in subjects with moderate to severe plaque psoriasis
- To evaluate the efficacy of oral ME3183 in subjects with moderate to severe plaque psoriasis at various time points
- To evaluate the effect of oral ME3183 on patient-reported outcome (PRO) measures in subjects with moderate to severe plaque psoriasis
- To evaluate the PK of ME3183 and its metabolite ([redacted]) in subjects with moderate to severe plaque psoriasis who are treated with oral ME3183

6.1.3 Exploratory Objectives

[redacted]

6.2 Study Endpoints

6.2.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects achieving ≥ 75% reduction from Baseline in the PASI score (PASI-75) at Week 16.

6.2.2 Secondary Endpoints

6.2.2.1 Safety Endpoints

The safety endpoints are as follows:

- The incidence, severity, and seriousness of AEs reported over the 16-week Treatment Period and the 4-week Follow-up Period

- Changes from Baseline in CS physical examination findings and vital sign measurements (blood pressure, heart rate, respiratory rate, body temperature, and body weight) over the 16-week Treatment Period and the 4-week Follow-up Period
- Changes from Baseline in ECG findings over the 16-week Treatment Period and the 4-week Follow-up Period
- Changes from Baseline in safety laboratory values (hematology, coagulation, blood chemistry, and urinalysis) over the 16-week Treatment Period and the 4-week Follow-up Period

6.2.2.2 Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- The percent change from Baseline in PASI score at all visits from Week 1 to Week 16
- The proportion of subjects achieving PASI-50, PASI-75, PASI-90, PASI-100 at all visits from Week 1 to Week 16
- Time to PASI-50 and PASI-75
- The proportion of subjects achieving a Static Physicians Global Assessment (sPGA) score of "0" ("clear") or "1" ("almost clear") combined with 2-point reduction on the 5-point sPGA scale at all visits from Week 1 to Week 16
- The change from Baseline in affected body surface area (BSA) at all visits from Week 1 to Week 16
- The change from Baseline in the itch numerical rating scale (NRS) at all visits from Week 1 to Week 16
- The change from Baseline in the Dermatology Life Quality Index (DLQI) score at all visits from Week 1 to Week 16
- Percentage of subjects with at least a 5-point reduction from Baseline in the DLQI score at all visits from Week 1 to Week 16

6.2.3 Pharmacokinetic Endpoint

The PK endpoint is the C_{trough} of ME3183 and its metabolite (CCI).

6.2.4 Exploratory Endpoints

CCI

CCI

[redacted]

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This multi-center, randomized, double-blind, placebo-controlled, parallel group, Phase 2a study is designed to assess the efficacy and safety of ME3183 administered orally in subjects with moderate to severe plaque psoriasis. The study consists of a 4-week Screening Period (Day -28 to Day -1), a 16-week double-blind Treatment Period (Day 1 to Day 113), and a 4-week Follow-up Period (Day 114 to Day 141). The total duration of study participation for each subject is approximately 24 weeks.

Note: The study drug is administered from Day 1 to Day 112 in the Treatment Period and the end of Treatment Period assessments will be performed on Day 113.

The duration of the Follow-up Period is from Day 114 to Day 141 and the end of Follow-up Period assessments will be performed on Day 141.

A suitable number of subjects with moderate to severe plaque psoriasis will be screened to randomize approximately 125 subjects across approximately 30 study sites in the United States and Canada. Subjects will be centrally randomized (25 subjects per treatment group) in a 1:1:1:1:1 ratio to 1 of the following treatment groups to receive oral ME3183 or matching placebo for a duration of 16 weeks.

- Treatment Group 1: [redacted] mg ME3183 BID administered orally: [redacted] capsule of [redacted] mg ME3183 and [redacted] capsules of matching placebo in the morning and evening
- Treatment Group 2: [redacted] mg ME3183 QD administered orally: [redacted] capsules of [redacted] mg ME3183 and [redacted] capsule of matching placebo in the morning and 3 capsules of matching placebo in the evening
- Treatment Group 3: [redacted] mg ME3183 BID administered orally: [redacted] capsule of [redacted] mg ME3183 and [redacted] capsule of [redacted] mg ME3183 and [redacted] capsule of matching placebo in the morning and evening
- Treatment Group 4: [redacted] mg ME3183 QD administered orally: [redacted] capsules of [redacted] mg ME3183 in the morning and [redacted] capsules of matching placebo in the evening
- Treatment Group 5: Matching placebo BID administered orally: [redacted] capsules of matching placebo in the morning and evening

To promote balanced allocation, randomization will be stratified by subject's receipt (yes/no) of previous treatment with biologic drug for psoriasis. Each treatment group will include randomized subjects who 1) are bio-naïve and 2) received previous treatment with a biologic drug for psoriasis. Bio-naïve subjects will be randomized above 50% of the planned total subject randomization. After randomization of subjects has reached the maximum percentage as determined by the sponsor based on enrollment rates for subjects that have received previous treatment with a biologic drug for psoriasis, randomization in this group may be stopped and the study sites will be informed accordingly.

Screening Period (Day -28 to Day -1):

A suitable number of subjects with moderate to severe plaque psoriasis will be screened based on the inclusion and exclusion criteria.

Treatment Period (Day 1 to Day 113):

During the Treatment Period, the first dose of the study drug will be administered in the evening upon the subject returning to their home on Day 1 (Visit 2) and the last dose will be self-administered by the subject on Day 112 (the day before Visit 8). Subjects will self-administer the study drug at home when they are not visiting the study site for clinical visits (see Table 1 for all the scheduled visits). The total number of capsules needed for at home administration will be dispensed during each study site visit. See Section 9.2 for additional details.

All randomized subjects will be evaluated for efficacy, safety and tolerability, PK, and CCI assessments at scheduled visits per Schedule of Assessments (Table 1).

Efficacy assessments (ie, PASI, BSA, sPGA, and PRO assessments [DLQI and the itch NRS]) will be assessed at scheduled visits as indicated in the Schedule of Assessments (see Table 1 for all the scheduled visits). Refer to Section 11 for more details on efficacy assessments.

Safety and tolerability will be assessed by physical exam, monitoring for AEs and SAEs, demographics, medical history, vital signs, ECG, and safety laboratory tests (hematology, coagulation, blood chemistry, and urinalysis) at scheduled visits as indicated in the Schedule of Assessments (see Table 1 for all the scheduled visits). Complete details on the safety and tolerability assessments are provided in Section 12.

Refer to Section 13 and Section 14.1 for PK and CCI assessments, respectively.

Follow-up Period (Day 114 to Day 141):

Subjects will be followed up to 4 weeks after the last dose of the study treatment. Refer to Table 1 for a complete list of assessments to be performed during the follow-up visit.

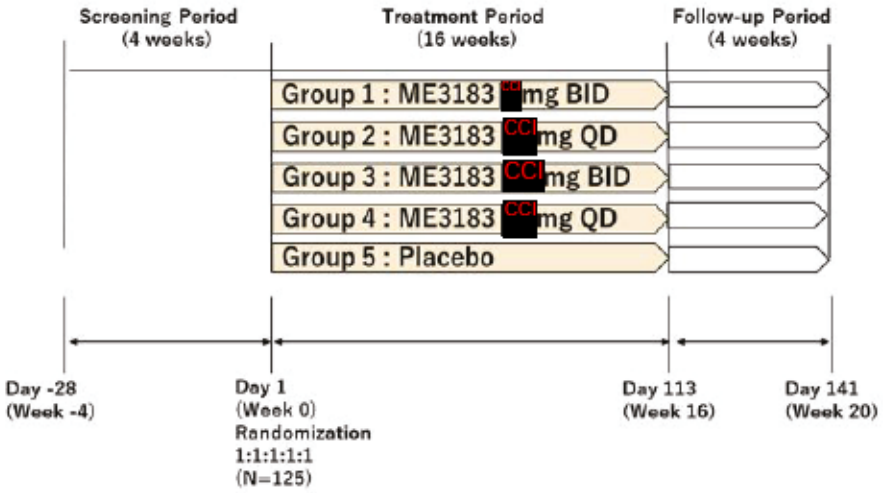
Order of Assessments During Each Study Site Visit:

The following priority order should be considered when more than 1 assessment is required at a particular time point, with PK and CCI blood sampling performed at the specified time:

1. 12-lead ECG
2. Vital signs
3. Blood sampling for safety laboratory tests, PK, and CCI assessments
4. Efficacy assessments

Figure 1 presents the study design.

Figure 1. Study Design



Abbreviations: QD = once daily; BID = twice daily; N = approximate number of subjects to be randomized.

7.2 Discussion of Study Design

A double-blind, randomized, placebo-controlled study is considered a gold-standard for conducting any interventional study. This design will minimize bias and provide reference data (ie, data from placebo treatment group) for comparison of the efficacy and safety parameters of the ME3183.

Psoriasis is a chronic immune-mediated inflammatory disorder, which requires a chronic therapy. Primary efficacy assessments of psoriasis clinical studies are usually performed at 12 or 16 weeks after initiation of study treatment. This is therefore considered an acceptable treatment duration to observe a CS response that allows for discriminating among different tested doses of ME3183. Primary evaluations of apremilast, the only PDE4 inhibitor currently approved for psoriasis treatment, were also conducted at week 16. A 16-week Treatment Period was also deemed acceptable for the placebo arm because psoriasis is not a life-threatening disease; in case of unbearable flares, subjects can discontinue early from the study and receive appropriate treatment.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods (ie, Screening Period, Treatment Period, and Follow-up Period) as indicated in the Schedule of Assessments (Table 1).

The end of the study or study completion will be the last subject's last visit for any protocol-related activity.

7.4 Early Termination

If a subject withdraws or is terminated from study treatment prior to completion of all study periods, all data collected at Visit 8 (Day 113) should be collected at the time of early termination. The subject will be asked to return to the study site 4 weeks after the last dose of study drug to complete the follow-up visit assessments (those performed on Day 141) as indicated in the Schedule of Assessments (Table 1).

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be randomized.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject is willing and able to participate in the study and has read, understood, and signed the informed consent form (ICF) according to national regulations.
2. Subject is a male or female aged 18 to 75 years (inclusive) at the time of consent (ie, Screening).
3. Subject has a body mass index (BMI) $\geq$ 18.5 to < 40 kg/m^2 at Screening.
4. Subject has a diagnosis of plaque psoriasis for $\geq$ 24 weeks prior to Screening.
5. The subject's symptoms of plaque psoriasis are stable in the opinion of the investigator. Stable is defined as no acute deterioration (eg, pustulation or erythroderma) within 12 weeks before Screening and no rebound of plaque psoriasis within 4 weeks before Screening.
6. The subject's severity of disease meets all of the following criteria:
   - Psoriatic plaques must cover $\geq$ 10% of BSA at Screening and Baseline
   - PASI score 12 to 40 at Screening and Baseline
   - sPGA $\geq$ 3 at Screening and Baseline
7. Subject is deemed by investigator to be eligible for phototherapy or systemic therapy.
8. Subject agrees to avoid prolonged exposure to sunlight or use of artificial sunbathing (eg, tanning booths) or other ultraviolet (UV) light sources during the Treatment Period.
9. Subject, if female and of childbearing potential, must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline. Any women of childbearing potential (WOCBP) must agree to sexual abstinence or to use a highly effective contraceptive measure starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). For the definition and a complete list of acceptable contraceptive measures see APPENDIX 1.
10. Subject, if a fertile male, agrees to sexual abstinence or to use a condom during sexual activity with their female partner of childbearing potential starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking

the last dose of study treatment. A male subject is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Additionally, if their partner is a WOCBP, then their partner should be advised to use a highly effective contraceptive measure during sexual activity starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment. For the definition and a complete list of acceptable contraceptive measures see APPENDIX 1.

11. Subject, if female, must agree to not donate, or retrieve for her own use, ova starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment.
12. Subject, if male, must agree to not freeze or donate sperm starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment.

8.2 Exclusion Criteria

Individuals meeting any of the following criteria at Screening or Baseline (as applicable) are ineligible to participate in this study:

1. Subject has a diagnosis of non-plaque psoriasis (predominantly guttate, pustular, inverse, or erythrodermic) or drug-induced psoriasis.
2. Subject has any unstable or CS (as determined by the investigator) cardiac, endocrinologic, gastroenterologic, pulmonary, neurologic, psychiatric (such as major depression), hepatic, renal, hematologic, immunologic disease, or other disease (eg, uncontrolled diabetes) that would place the subject at unacceptable risk if they were to participate in the study.
3. Subject has suicidal ideation or behavior in the past 12 months as indicated by a positive response (yes) to questions 3, 4, or 5 on the C-SSRS completed at Screening and/or at Baseline.
4. Subject has a present recurrent medical condition associated with significant GI events (eg, nausea, vomiting, constipation, abdominal pain, diarrhea).
5. Subject has any condition that would confound the ability to interpret data from the study (eg, eczema, atopic dermatitis, lupus, inflammatory bowel disease).
6. Subject has any degree of dysphagia that may interfere with the oral dosing of the study treatment.
7. Subject has a history of allergy or hypersensitivity to any component of the study treatments.
8. Subjects who have had a prior laboratory confirmed COVID-19 test or have been in close physical contact (6 feet or closer for at least 15 minutes) with a person who is

known to have laboratory confirmed COVID-19 or with anyone who has any symptoms consistent with COVID-19 within the past 14 days at Screening or Baseline.

9. Subjects experiencing any of the following symptoms at Screening or Baseline:
    - Fever or chills
    - Cough
    - Shortness of breath or difficulty breathing
    - Fatigue
    - Muscle or body aches
    - Headache
    - New loss of taste or smell
    - Sore throat
    - Congestion or runny nose
    - Nausea or vomiting
    - Diarrhea
10. Subject has active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as per Screening viral serology tests. Exception: If the subject has received documented treatment which was curative for HCV and tests negative for HCV RNA at Screening, the subject may be considered for randomization.
11. Subject is positive for the HIV antibodies (HIV-1 or HIV-2) at Screening or has a history of congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).
12. Subject has a recent history of drug, substance, or alcohol abuse/dependence within 1 year prior to Screening as determined by the investigator.
13. Subject has an active infection (bacteria, viral, fungal, etc.) requiring treatment with systemic antibiotics within 4 weeks of Screening. Any treatment for such infections must be completed at least 4 weeks prior to Screening.
14. Subject has active tuberculosis or history of incompletely treated tuberculosis per medical history.
15. Subject has a malignancy or history of malignancy (except for treated [ie, cured] basal cell or squamous cell in situ skin carcinomas and treated [ie, cured] cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence).
16. Subject is pregnant or breastfeeding at Screening or at Baseline.
17. Subject has a history of lack of efficacy (inadequate efficacy when used in adequate dose and duration in accordance with the approved label) to any biological products for psoriasis.

18. Subject has received 2 or more biological products in the past for the treatment of psoriasis.
19. Subject has a history of lack of efficacy to 2 or more non-biologic systemic therapy due to inadequate efficacy when administered in adequate dose and duration in accordance with their label (approved in the subject's country) for psoriasis.
20. Subject has received any prior treatment with apremilast or any other PDE4 inhibitor.
21. Subject has received ustekinumab, secukinumab, brodalumab, ixekizumab, guselkumab, risankizumab, tildrakizumab, or briakinumab (or any other therapeutic agent targeting IL-12, IL-17, or IL-23) within 24 weeks of first administration of study treatment.
22. Subject has received TNF-α inhibitor(s)/blocker(s) within 8 weeks of first administration of study treatment.
23. Subject has received natalizumab (an integrin receptor antagonist), or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, alefacept) within 12 weeks of first administration of study treatment.
24. Subject has received rituximab within 24 weeks of first administration of study treatment.
25. Subject has received any systemic immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus), any protein kinase inhibitor (eg, tofacitinib, baricitinib, peficitinib, upadacitinib), or anakinra within 4 weeks of the first administration of study treatment.
26. Subject has received phototherapy (eg, ultraviolet B including narrow band ultraviolet B, Goeckerman therapy, and excimer laser or psoralen ultraviolet A) or any systemic medications/treatments that could affect psoriasis or sPGA evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, or fumaric acid derivatives) within 4 weeks of the first administration of study treatment.
27. Subject has had a recent initiation of a drug that is known to potentially cause or exacerbate psoriasis (including, but not limited to, beta-blockers, lithium, and anti-malarials) within the 8 weeks prior to the first administration of study treatment; a subject who has been on a stable dose for at least 8 weeks prior to the first administration of study treatment without exacerbation of psoriasis may be randomized and does not need to discontinue these medications.
28. Subject has used topical medications/treatments that could affect psoriasis or sPGA evaluation (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralen, pimecrolimus, tacrolimus, or PDE4 inhibitor) within 2 weeks of the first administration of study treatment.

29. Subject has received an investigational drug for biologic therapy within the previous 24 weeks prior to the first administration of study treatment or received any other non-biologic investigational therapy/drugs or device within 4 weeks or 5 half-lives (whichever is longer) prior to the first administration of study treatment.
30. Subject has received any prior treatment with ME3183.
31. Subject has any of the following abnormal laboratory test findings at Screening.
    - Abnormal hepatic function
      - Aspartate aminotransaminase or alanine aminotransaminase $\geq 2 \times$ upper limit of normal or
      - Total bilirubin $\geq 2 \times$ upper limit of normal, unless the subject has a diagnosis of Gilbert's syndrome
    - White blood cell count $< 3000/mm^3$ ($< 3.0 \times 10^9/L$)
    - Neutrophil count $< 1000/mm^3$ ($< 1.0 \times 10^9/L$)
    - Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9/L$)
    - Hemoglobin < 8.0 g/dL
    - Creatinine clearance estimated by Cockcroft-Gault formula < 60 mL/min
    - Hemoglobin A1c $> 9.0\%$
32. Subject has a CS abnormality on a 12-lead ECG or QTcF > 450 msec at Screening or Baseline.
33. Subject has a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 100 mmHg (based on at least 2 repeat measurements) at Screening.
34. Prisoners or subjects who are incarcerated for any reason.
35. Subject has any other factor constituting disqualification for study inclusion in the judgement of the investigator.

See APPENDIX 2 for details on the medications and procedures that are prohibited prior to randomization and during the course of the study unless otherwise specified.

8.3 Rescreening

Individuals who failed the initial Screening may be considered for rescreening up to 1 time, upon approval of Sponsor and/or Medical Monitor on a case-by-case basis. All assessments will be repeated when rescreening. When re-testing within the same 28-day Screening Period, only the exclusionary laboratory tests will be repeated once in case the exclusionary laboratory result was not due to a pathological condition and was occasional (except for individuals who have positive viral serology results).

8.4 Study Withdrawal, Removal, and Replacement of Subjects

Although the importance of completing the entire clinical study will be explained to the subjects, any subject is free to discontinue his/her participation in the study at any time and for whatever

reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated. Investigators or the Sponsor can also withdraw subjects from the clinical study if deemed to be necessary.

If a subject discontinues study treatment and/or is withdrawn from the study for any reason, the study site must immediately notify the Medical Monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who do not complete or discontinue early from the study treatment will be asked to return to the study site to complete assessments as indicated in the Schedule of Assessments (Table 1).

In the event that a subject discontinues prematurely from the study treatment because of a TEAE or serious TEAE, he/she will be followed up until it resolves (returns to normal or Baseline values) or stabilizes, or until it is judged by the investigator to no longer be CS. If a TEAE or SAE is causing a long-term effect and could not be followed until resolution, the reason for not following up any further must be recorded in the source document.

Once a subject is withdrawn from the study, the subject cannot reenter the study.

A subject may voluntarily withdraw or be withdrawn from the study treatment or the study at any time for reasons including, but not limited to, the following:

- progressive disease
- unacceptable toxicity or AE
- QT interval corrected using Fridericia's formula (QTcF) >500 msec
- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgement. The reason for subject withdrawal will be noted in the eCRF
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- subject fails to adhere to the protocol requirements (eg, drug noncompliance, failure to return for defined number of visits, used or require to use any of the prohibited concomitant medication or procedures [see APPENDIX 2])
- lost to follow-up: the subject stopped coming for visits, and study personnel are unable to contact the subject
- subject has any other factor constituting disqualification for study inclusion in the judgement of the investigator

- pregnancy, as indicated in Section 12.6.6.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with Good Clinical Practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low randomization.

Withdrawn subjects may not be replaced once randomized.

8.4.1 Pregnancy

The safety of ME3183 in pregnant or lactating women has not been established.

Subjects will be instructed that a known or suspected pregnancy occurring during the study will be confirmed by serum testing and reported to the investigator. If a subject becomes pregnant, the investigator must withdraw the subject from the study treatment without delay. The subject must not receive any further doses of the study drug and will be asked to return for the follow-up visit 4 weeks after the last dose of study drug. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a female subject or female partner of a male subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor (or designee) after delivery. See Section 12.6.6 for further reporting and monitoring details.

The investigator should notify the Sponsor (or designee) on a Pregnancy Reporting form within 24 hours of knowledge of the pregnancy. Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the eCRF, or an SAE report will be completed if the subject has completed the study. Pregnancy is not to be considered an AE; however, spontaneous miscarriages, congenital abnormalities, and any premature termination of pregnancy will be reported as SAEs as described in Section 12.6.6.

8.4.2 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's source document.

9 TREATMENTS

9.1 Details of Study Treatments

ME3183 ([redacted] mg, [redacted] mg, [redacted] mg, and [redacted] mg) and a matching placebo will be prepared using the following ME3183 and placebo capsules:

- ME3183 Capsule [redacted] mg
- ME3183 Capsule [redacted] mg
- ME3183 Placebo Capsule

Refer to the IB for complete details on the study treatment.

A designated pharmacist will dispense the study drugs at each visit. Additional details on dispensing of the study drugs will be provided in the pharmacy manual.

9.1.1 Description of Active Study Treatment

ME3183 is a white crystalline powder that is formulated as capsules.

9.1.2 Description of Placebo Study Treatment

Placebo will be identical in appearance to active study treatment and contains the same inactive ingredients as the active formulation but without the active ingredient.

9.1.3 Packaging and Labeling

The investigational study drugs will be packaged and labeled according to applicable local and regulatory requirements. Labeling will fulfill the Good Manufacturing Practice requirements and will comply with legal requirements of each country. ME3183/placebo capsules are packaged in press through pack sheet (21 capsules per sheet) and a child-resistant blister pack. Blister packs will be dispensed by a designated pharmacist at each visit for morning and evening doses.

Clinical supplies are to be dispensed only in accordance with the protocol. Study drug labels will not bear any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated. Labels on the blister packs will contain the following open-label information:

- Protocol number
- Medication number
- Expiration date
- Identical batch number
- Content: 21 capsules/ sheet, 2 sheets/ child-resistant blister pack
- Storage condition: [redacted]°C to [redacted]°C ([redacted]°F to [redacted]°F)
- Directions: For oral use
- Caution: New Drug – Investigational Use Only
- Sponsor name and address

9.1.4 Study Drug Storage

All study drug supplies must be stored at ambient temperature ([redacted]°C to [redacted]°C [[redacted]°F to [redacted]°F]). Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location in accordance with the labeled storage conditions.

9.1.5 Study Drug Retention

Study drug must be retained until completion or termination of the study, and written authorization from the Sponsor has been received. The details regarding the study drug retention will be detailed in the Pharmacy Manual. All unused and used study drug should be returned to the distributor, if specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused study drug may be disposed until fully accounted for by the study monitor.

9.2 Dosage Schedule

The first dose of the study drug will be administered in the evening (upon returning to their home after the Day 1 [Visit 2] assessments are completed) within approximately 30 minutes after a standard meal and the last dose will be self-administered by the subject at home on Day 112 (the day before Visit 8) within approximately 30 minutes after a standard meal. On Day 1, all subjects will receive the study drugs in the evening. From Day 2 to Day 112, all subjects will receive the study drugs in the morning and evening.

At Home Dosing:

The study drug must be taken in the mornings and evenings approximately 12 hours apart with water within approximately 30 minutes after a standard meal. Subjects will be advised to take the study drug at approximately the same time each day without fail.

At Study Site:

For all the study site visits, subjects will arrive at the study site after fasting overnight (except water) for at least 10 hours. All the safety laboratory tests, efficacy assessments, and PK and [redacted] assessments (per Schedule of Assessments; Table 1) will be performed upon arrival at the study site. Refer to Section 7.1 for the order in which the assessments should be performed. Subjects will be released after all the scheduled assessments are performed and will be advised to take the morning dose of the study drug upon returning to their home and within approximately 30 minutes after a standard meal.

For the purposes of PK analysis, the actual date and time of the administrations (both morning and evening in the previous day) and each blood sample collection will be recorded on the subject's eCRF at all visits where PK blood samples are to be collected.

Subjects will be advised to return the unused study drug during each study site visit for compliance check.

Subjects must stop using any permitted topical preparations 24 hours prior to scheduled study site visit starting from Visit 2 (Day 1). See Section 9.6 for additional details.

9.3 Measures to Minimize Bias

9.3.1 Method of Study Treatment Assignment

Prior to dosing on Day 1, all the eligible subjects will be randomly assigned to 1 of the 5 treatment groups in a 1:1:1:1:1 ratio. Subjects will be assigned a randomization number through interactive web response system (IWRS), in accordance with the randomization code generated by the authorized personnel at PPD. An unblinded, independent study statistician will be assigned to produce the randomization schedule. At study site, the randomization schedule will only be accessible to authorized pharmacy personnel. Once a randomization number is allocated to 1 subject, it may not be assigned to another subject even if the former discontinued the study.

To promote balanced allocation, randomization will be stratified by the subject's receipt (yes/no) of previous treatment with a biologic drug for psoriasis. Bio-naïve subjects will be randomized above 50% of the planned total subject randomization.

9.3.2 Blinding

This is a double-blind study.

An IWRS will be used for subject randomization and a unique subject identification number will be assigned automatically. According to the randomization schedule as indicated in the Schedule of Assessments (Table 1), the investigator or designee will obtain the study drug kit number from the IWRS for the subject, and the number will be provided to the pharmacist or designee at the study center who is responsible for handling the study drugs. This pharmacist or designee will dispense the study drug to the subject based on the study drug kit number generated from the IWRS. An unblinded, independent study statistician will be assigned to produce the randomization schedule. No other study site personnel, subjects, Sponsor personnel, or Sponsor designees will be unblinded to treatment assignment throughout the duration of the study unless unblinding is required. If an investigator becomes unblinded to a given subject's study treatment, that subject will be discontinued from the study unless there are ethical reasons for that subject not to be discontinued; approval from the Medical Monitor must be obtained in such instances. In the event that emergency unblinding is required for a given subject because of AEs or concerns for the subject's safety or wellbeing, the investigator may break the randomization code for the subject via the IWRS, by which system the unblinding will be captured. The investigator is responsible for notifying the Medical Monitor and/or Sponsor of such an event as soon as possible. The unblinding and its cause will also be documented in the eCRF.

The bioanalytical laboratory will receive a copy of the randomization schedule for PK analysis, as the Sponsor does not intend to analyze the samples from the placebo group. The blinding procedure will be documented in a separate document.

9.4 Dosage Modification

Dose modifications are not permissible in this study.

9.5 Treatment Accountability and Compliance

All the study drugs will be stored at a central drug distribution center maintained by PPD and will be distributed to individual study sites as needed.

The pharmacist or designee will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study subjects.

At each visit after initiation of treatment, study site personnel will record compliance of the subject with the subject's assigned regimen. Subjects will be instructed to bring their unused/partially used/empty study drug blister packs back for inspection at each study visit. Subjects are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug on schedule, maintaining the prescribed interval between doses, and documenting the dose each day in the subject's diary.

The investigators or designated study personnel will maintain records that adequately document that the subjects were provided with the correct study treatment blister packs and reconcile the products received from the central drug distributing center. Investigational product will not be returned to the Sponsor until accountability has been fully monitored.

Study drug blister packs must be returned at each visit, as compliance will be assessed by capsule counts. Noncompliance is defined as taking less than 70% or greater than the protocol-specified number of doses (ie, 2 doses per day) of study drug during any outpatient evaluation period (visit to visit). Discontinuation for noncompliance is at the investigator's discretion and is to be noted in the eCRF.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Restricted prior therapies are provided in Section 8.2 and a complete list of prohibited concomitant medications and procedures prior to randomization and during the course of the study is provided in APPENDIX 2.

All medications and other treatments (including supplements) taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded in the eCRF.

Medications taken by or administered to the subject for the time period before Screening will be recorded in the eCRF. After the Baseline visit, any concomitant medication that is not restricted

by the protocol is acceptable. The dosage regimen of any chronic medication should remain unchanged as much as possible during the study. Any medication or therapy that is taken by or administered to the subject prior to start of the study or during the course of the study must be recorded on appropriate pages of the eCRF. The entry must include the dose, unit, regimen, route, indication, and dates of use. For any permitted topical medications taken for psoriasis, the area of the body to which they are applied should also be recorded.

The following topical therapy will be permitted:

1. Low-potency or weak corticosteroids (Class 6 [eg, betamethasone valerate lotion, desonide cream, and fluocinolone acetonide solution] or Class 7 [eg, dexamethasone sodium phosphate cream, hydrocortisone acetate cream, or methylprednisolone acetate cream] in the United States) will be allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study.
2. Coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions will be permitted to use by subjects with scalp psoriasis.
3. An unmedicated skin moisturizer (eg, Eucerin) will be permitted for body lesions only.

Subjects will be advised not to use the above topical preparations within 24 hours prior to any study site visit.

Subjects will also be advised to protect against sun exposure through avoidance of prolonged exposure to sun, use of protective clothing (long sleeves, pants, hats, etc.), and use of sunscreen from at least 1 week prior to the first administration of study treatment until the follow-up visit at Week 20.

Subjects must avoid the use of artificial sunbathing (eg, tanning booths) or other UV light sources during the Treatment Period.

CCI

[redacted]

10 STUDY PROCEDURES

Table 1 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.5 specifies safety laboratory assessment samples to be obtained. See Sections 11, 12, and 13 for additional details regarding efficacy assessments, safety assessments, and PK assessments, respectively. Details of other assessments such as CCI are provided in Section 14.

In case a randomized subject is not able to attend scheduled study visit on-site due to restrictions related to SARS-CoV-2, a remote visit may be conducted instead (a phone call or a televisit).

It is strongly recommended to conduct the study assessments for the applicable visit as per protocol Schedule of Assessments (see Table 1) as much as possible. If possible and if local regulations allow and the subject agrees, trained and authorized members of the site staff are encouraged to collect study assessments, including samples for scheduled laboratory tests at subject's home or at a local facility. Alternatively, the subject could have the hematology, coagulation, chemistry, urinalysis, and pregnancy testing at a local laboratory and the laboratory reports will be provided to the investigator. The local laboratory results should be entered in the eCRF.

Subjects with signs and symptoms of infection, including SARS-CoV-2 infection should immediately contact the investigator, who should inform the Medical Monitor or designee as soon as possible to discuss subject's continuation of study treatment. In case of suspicions for SARS-CoV-2 infection, relevant testing should be performed local site procedures. In case study visits or assessments are not performed for reasons related to SARS-CoV-2 restrictions, this should be documented in the source documents and eCRF.

Table 1. Schedule of Assessments

	Screening Period	Treatment Period							Follow-up Period[b]
	Screening (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8[a]	Follow-up Visit (Visit 9)
	Week -4	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20
Study Procedures	Days -28 to -1	Day 1 (Baseline)	Day 8 (±1 day)	Day 15 (±1 day)	Day 29 (±3 days)	Day 57 (±3 days)	Day 85 (±3 days)	Day 113* (±3 days)	Day 141** (±3 days)
Eligibility Assessments									
Informed consent	X	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-
Dermatologic and medical history[c]	X	-	-	-	-	-	-	-	-
Prior and concomitant medications/therapies and procedures	X	X	X	X	X	X	X	X	X
History of previous treatment with a biologic drug for psoriasis	-	X	-	-	-	-	-	-	-
C-SSRS	X	X	-	-	-	-	-	-	-
Safety Assessments									
Physical examination (complete)	X	-	-	-	-	-	-	-	-
Physical examination (targeted)	-	X	X	X	X	X	X	X	X
Height and weight[d]	X	-	-	-	-	-	-	-	-

	Screening Period	Treatment Period							Follow-up Period[b]
	Screening (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8[a]	Follow-up Visit (Visit 9)
	Week -4	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20
Study Procedures	Days -28 to -1	Day 1 (Baseline)	Day 8 (±1 day)	Day 15 (±1 day)	Day 29 (±3 days)	Day 57 (±3 days)	Day 85 (±3 days)	Day 113* (±3 days)	Day 141** (±3 days)
Vital signs: blood pressure (systolic and diastolic), heart rate, respiratory rate, body temperature, and body weight	X	X	X	X	X	X	X	X	X
12-lead ECGs[e]	X	X	-	-	X	X	X	X	X
Safety Laboratory Tests									
Viral serology[g]	X	-	-	-	-	-	-	-	-
Hematology and Coagulation[h]	X	X[i]	X	X	X	X	X	X	X
Blood chemistry[j]	X	X[i]	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Pregnancy test (serum β-hCG) (WOCBP only)	X[k]	-	-	-	-	-	-	-	-
Pregnancy test (urine β-hCG) (WOCBP only)	-	X[l, m]	-	-	X[m]	X[m]	X[m]	X[m]	X[m]
Serum FSH (postmenopausal women only)	X	-	-	-	-	-	-	-	-
AE Monitoring									
Monitor for AEs and SAEs	X	X	X	X	X	X	X	X	X

Study Procedures		Screening Period	Treatment Period							Follow-up Period[b]
		Screening (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8[a]	Follow-up Visit (Visit 9)
		Week -4	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20
		Days -28 to -1	Day 1 (Baseline)	Day 8 (±1 day)	Day 15 (±1 day)	Day 29 (±3 days)	Day 57 (±3 days)	Day 85 (±3 days)	Day 113* (±3 days)	Day 141** (±3 days)
Pharmacokinetic Assessments										
PK sample (blood)[n]		-	-	X	-	X	X	-	X	-
Efficacy Assessments										
PASI score		X	X[o]	X	X	X	X	X	X	X
BSA		X	X[o]	X	X	X	X	X	X	X
sPGA		X	X[o]	X	X	X	X	X	X	X
PRO assessments	Itch NRS	-	X	X	X	X	X	X	X	X
	DLQI	-	X	X	X	X	X	X	X	X
CCI										
Other Assessments										
Medical photography (target skin lesion)[p]		-	X	-	X	X	-	-	X	-
Clinical Drug Supplies										
Subject randomization		-	X	-	-	-	-	-	-	-
Dispense study drug		-	X	X	X	X	X	X	-	-
Administration of study drug[q]		-	X	X	X	X	X	X	-	-

Study Procedures	Screening Period	Treatment Period							Follow-up Period[b]
	Screening (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8[a]	Follow-up Visit (Visit 9)
	Week -4	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20
	Days -28 to -1	Day 1 (Baseline)	Day 8 (±1 day)	Day 15 (±1 day)	Day 29 (±3 days)	Day 57 (±3 days)	Day 85 (±3 days)	Day 113* (±3 days)	Day 141** (±3 days)
Subject to return back unused study treatment for compliance check	-	-	X	X	X	X	X	X	-
Schedule the date/time for the next visit	X	X	X	X	X	X	X	X	-
Discharge the subject from the study site[r]	X	X	X	X	X	X	X	X	X

Abbreviations: β-hCG = β-human chorionic gonadotropin; AE = adverse event; BMI = body mass index; BSA = body surface area; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; PASI = Psoriasis Area and Severity Index; CCI [redacted]; PK = pharmacokinetic; PRO = patient-reported outcome; QTcF = QT interval corrected using Fridericia's formula; SAE = serious adverse event; sPGA = Static Physicians Global Assessment; WOCBP = women of childbearing potential; NRS = numerical rating scale.

* The duration of the Treatment Period is from Day 1 to Day 112 and the end of Treatment Period assessments will be performed on Day 113.

** The duration of the Follow-up Period is from Day 114 to Day 141 and the end of Follow-up Period assessments will be performed on Day 141.

[a] or Early Termination Visit.

[b] Subjects who discontinued or withdrew early from study treatment should return after 4 weeks of last dose of study treatment for follow-up safety assessments.

[c] Must include history of drug, substance, or alcohol abuse/dependence within 1 year prior to Screening as determined by the investigator.

[d] Record height at Screening only.

[e] 12-lead ECG must include QTcF measurement.

[g] All subjects must have the following viral serology tests completed at Screening: anti-HCV antibody, HBV surface antigen, HBV core antibody, HIV-1 antibody, and HIV-2 antibody. If the subject tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection. If the subject has received documented treatment which was curative for HCV and tests negative for HCV ribonucleic acid (RNA) at Screening, the subject may be considered for enrollment.

[h] Includes complete full and differential blood count, platelet count, hemoglobin, hemoglobin A1c (only at Screening), fibrinogen and prothrombin time. See Section 12.5 for a complete list of tests to be performed.

[i] To be obtained predose (subjects are required to fast for at least 10 hours prior to the collection of specimens for safety laboratory tests).

[j] See Section 12.5 for a list of tests to be performed.

[k] All WOCBP must have a negative serum pregnancy test at Screening to be eligible for the study.

[l] All WOCBP must have a negative urine pregnancy test prior to randomization and dosing on Day 1.
[m] A serum pregnancy test should be performed for confirmation of any positive urine pregnancy test. The subject will be withdrawn from the study treatment if the confirmatory serum pregnancy test is positive. The subject must not receive any further doses of the study drug and will be asked to return for the follow-up visit 4 weeks after the last dose of study drug.
[n] The PK and CCI blood samples will be collected predose at all scheduled visits as per Schedule of Assessments.
[o] To be performed prior to randomization.
[p] Medical photography of the target skin lesion will be obtained at selected sites in a selected number of subjects for documentation and publication purposes only.
[q] Subjects will take the first dose of the study drug upon returning to their home after all Day 1 (Visit 2) assessments are completed.
[r] Subjects will be discharged from the study site after all the postdose study procedures are completed.

10.1 Informed Consent

ICFs must be approved for use by the reviewing institutional review board/independent ethics committee (IRB/IEC). Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the subject.

In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new subject identification number.

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 1). Section 12.5 specifies safety laboratory assessment samples to be obtained.

Assessments and procedures scheduled should be performed before administration of treatment unless otherwise indicated in the Schedule of Assessments (Table 1).

Efficacy assessments are described in Section 11 and include PASI, sPGA, BSA, itch NRS, and DLQI scoring.

Safety assessments are described in Section 12 and include demographics, medical history, vital signs (including body temperature, body weight, respiratory rate, heart rate, and systolic and diastolic blood pressure measurements), complete/targeted physical examinations, ECGs, safety laboratory assessments (hematology, coagulation, chemistry, urinalysis, viral serology, pregnancy tests, and serum follicle-stimulating hormone tests), and AEs.

PK and CCI sampling is described in Section 13 and Section 14.1, respectively.

Other assessments such as medical photography of affected skin area and C-SSRS are described in Section 14.2 and Section 14.3, respectively.

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures are described in Section 8.4.

The procedures to be performed during each study visit are provided in Schedule of Assessments (Table 1).

A follow-up visit is performed at the clinical study site 4 weeks after the last dose of study drug.

11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 1) outlines the efficacy assessments to be performed throughout the study and their timing.

Only trained assessor qualified personnel at site will conduct efficacy assessments. The same assessor should perform all assessments throughout the study at least within the same subject when possible.

11.1 Psoriasis Area Severity Index

PASI will be determined for all subjects throughout the study. The PASI scoring tool is shown in APPENDIX 3.

The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, induration, and desquamation) and percentage of affected skin surface area on defined anatomical regions. The PASI is a validated instrument that is most widely used for measurement of severity of psoriasis.

PASI scores range from 0 to 72, with higher scores reflecting greater disease severity.(5) Erythema, induration/thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. The scores for each anatomic region are combined to yield the final PASI score (see Table 1).

11.2 Static Physician's Global Assessment

The investigator will rate the severity of subject's psoriasis on the 5-point scale ranging from 0 (clear) to 4 (severe).

The sPGA is used to determine the subject's psoriasis state overall at a given time point.

See APPENDIX 4 for grading criteria (see Table 1).

11.3 Body Surface Area

BSA is a measurement of the affected skin area. The overall BSA affected by psoriasis plaques is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint" including the fingers), which equates to approximately 1% of total BSA (see Table 1).

11.4 PRO Assessment: Itch Numerical Rating Scale

Each subject will be asked to complete the itch NRS assessment: maximal intensity of itch during the previous 24 hours, rated on an integer scale ranging from 0 (no itch at all) to 10 (worst itch imaginable) during the scheduled study site visit (see Table 1).

11.5 PRO Assessment: Dermatology Life Quality Index

The DLQI is a simple, self-administered questionnaire designed to measure the health-related QOL of an adult suffering from a skin disease. It consists of 10 questions (each scored from 0 to 3) concerning subjects' perception of the impact of skin disease on different aspects of their health-related QOL over the last week. Nine of the 10 questions have 4 response options: "Not at all", "A little", "A lot", and "Very much" with corresponding scores of 0, 1, 2,3 and 3, respectively. Question 7 is a multipart item, the first part ascertains whether the skin condition prevented them from either working or studying ("Yes" or "No"), and the second part determines to what degree the skin condition has been a problem for working or studying ("A lot", "A little", "Not at all"). Eight items also have a "Not relevant" option scored "0," which indicates no problem. Individual item scores are combined to give a total score that ranges between 0 and 30. The higher the score, the more QOL is impaired. See APPENDIX 5 for the DLQI questionnaire.

12 SAFETY ASSESSMENTS

Safety assessments (demographics, medical history, vital signs, completed/targeted physical examinations, ECGs, safety laboratory results [routine hematology, coagulation, chemistry, and urinalysis, viral serology, pregnancy tests, and serum follicle-stimulating hormone tests], and AEs [including SAEs]) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 1).

12.1 Demographics and Medical and Dermatological History

Demographic data will be collected for all subjects at Screening and recorded in the eCRF.

Medical history will be recorded at Screening. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses, from birth until Screening. Additional preexisting conditions present at the time when informed consent is given and up to the time of first dosing (Visit 2) are to be regarded as concomitant. Medical history will also include any toxicities or allergies to previous treatments, alcohol consumption, and smoking history.

Medical history will also include history of drug, substance, or alcohol abuse/dependence within 1 year prior to Screening as determined by the investigator.

Dermatological history collected will also include date and/or age of diagnosis of psoriasis, and all prior treatments for plaque psoriasis. All the prior psoriasis treatments should be included under prior and concomitant medications page in the eCRF.

The degree of skin surface involvement, severity, and lesion characteristics (erythema, scaling, and thickness) are to be documented at Screening.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs in the eCRF in accordance with Section 12.6. All changes not present at Baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

12.2 Vital Signs

Vital signs (body temperature, body weight, respiratory rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 1). All vital signs will be measured after the subject has been resting in a sitting position for at least 10 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated if CS or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, body temperature, body weight or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, CS vital sign measurements must be recorded as AEs.

12.3 Complete/Targeted Physical Examination

A complete physical examination including height and weight will be performed at Screening (Visit 1). The complete physical examination should include the following systems: head, eyes, ears, nose and throat; respiratory; cardiovascular; musculoskeletal; neurological; metabolic/endocrine/nutritional; hematopoietic; allergies; abdominal; and general appearance. Physical examinations will be performed by a physician.

A targeted physical examination to verify continued subject eligibility and to follow-up regarding any change in medical history will be performed at the visits indicated in the Schedule of Assessments (Table 1).

Symptom-driven, targeted physical examinations will be performed as clinically indicated at any study visit.

Height will be recorded at Screening only.

Any CS physical examination finding should be reported as an AE.

12.4 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 1). During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements will be obtained.

All the ECGs obtained will be interpreted by an experienced single independent blinded reader at the central laboratory.

At Screening, the investigator will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study (QTcF >450 msec). An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented in the eCRF. ECGs will be repeated if CS abnormalities are observed, or artifacts are present. The date and time of each ECG and its results will be documented in the source documents and eCRF.

Any CS ECG abnormalities must be recorded as AEs.

12.5 Safety Laboratory Assessments

Safety laboratory assessment samples (Table 2) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 1).

Table 2. Safety Laboratory Assessments

Hematology	Blood Chemistry	Urinalysis (Dipstick)
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential HbA1c*	Albumin ALT ALP AST BUN or urea Creatinine Creatinine clearance** Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin LDL HDL Total cholesterol Triglycerides Amylase Lipase C-reactive protein	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen
	Viral Serology*** HBV HCV HIV	
Coagulation Fibrinogen PT		
Pregnancy test: A serum β-hCG pregnancy test (premenopausal women only) will be performed on all WOCBP at Screening. A urine β-hCG will be performed at later time points as indication in the Schedule of Assessments. A serum pregnancy test should be performed for confirmation of any positive urine pregnancy test. Serum FSH levels will be tested for all postmenopausal women at Screening.		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; β-HCG = β-human chorionic gonadotropin; HDL = high-density lipoproteins; Hb = hemoglobin; Hct = hematocrit; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

* At Screening only.

** Estimated by Cockcroft-Gault formula < 60 mL/min

***All subjects must have the following viral serology tests completed at Screening: anti-HCV antibody, HBV surface antigen, HBV core antibody, HIV-1 antibody, and HIV-2 antibody. If the subject tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out

active infection. If the subject has received documented treatment which was curative for HCV and tests negative for HCV ribonucleic acid (RNA) at Screening, the subject may be considered for enrollment.

Blood for laboratory assessments will be collected under fasting conditions from each subject before the study drug dosing. The investigator or qualified study personnel will collect the samples as required.

Blood and urine samples will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. Full details of equipment and procedures for laboratory testing will be listed in the laboratory manual.

All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all the signed laboratory reports must be filed with both the subject's eCRF and medical record (source document) for that visit. The investigator must categorize all abnormal urine, hematology, coagulation, and chemistry laboratory values as either CS or not CS. Any laboratory test result considered by the investigator to be CS abnormal should be considered and reported as an AE (CS AEs include those that require an intervention). CS abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer abnormal CS.

12.6 Adverse Events

AEs will be collected from the time the subject signs the ICF through 4 weeks after the last dose of study drug. All AEs must be recorded in the subject's eCRF. The Sponsor and investigator or qualified study personnel will review and evaluate AEs on an ongoing basis.

12.6.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at Screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at Screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. CS laboratory abnormalities (eg, safety laboratory assessments or ECGs) should also be recorded as AEs. Surgical procedures that were planned before the subject randomized in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

Subjects will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented in the eCRF with reference to date of onset, date of outcome, severity, relationship to study drug, action taken with study drug, treatment of event, and

outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented in the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject gives informed consent until the follow-up visit. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the event should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Any AEs of moderate or severe in severity should be notified to the Sponsor or designee immediately.

Specific guidelines for classifying AEs by severity and relationship to study drug are given in Table 3 and Table 4.

Table 3. Classification of Adverse Events by Severity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 4. Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with reexposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Abbreviation: AE = adverse event.

For the purposes of this study, any AEs classified as 'Unrelated' or 'Unlikely' will be considered as 'Not Related' and 'Possibly', 'Probably', or 'Definitely' as 'Related' to the study treatment.

12.6.2 Treatment-Emergent Adverse Events

A TEAE will be an AE that occurred during the study after the first dose of study drug or that was present prior to dosing and exacerbates after the first dose of study drug.

12.6.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or

- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgement, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

The management of subject's COVID-19 data will be detailed in a COVID-19 guidance document.

12.6.4 Serious Adverse Event Reporting

An SAE occurring from the time informed consent is obtained, during the study, or within 4 weeks of stopping the treatment must be reported to PPD and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within **24 hours of occurrence or when the investigator becomes aware of the event**. Notification can be made using the dedicated fax line or email for PPD by fax or email:

PPD

If the investigator contacts PPD by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the study drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to PPD within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to Baseline values (if a Baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.6.5 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the current version of the IB)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or PPD) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or PPD) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or PPD) first has knowledge of them.

The Sponsor (or PPD) is responsible for reporting SUSARs, and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

12.6.6 Pregnancy

WOCBP must have a negative pregnancy test at Screening. After administration of study drug, any known cases of pregnancy in female subjects will be reported until the subject completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow-up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal

death, or congenital anomaly, the investigator will report the event as an SAE by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event.

If the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, the pregnancy should be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. Details of the pregnancy must only be collected after obtaining written consent from the pregnant partner. A separate pregnant partner consent form will be used to obtain the consent from pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The pregnant partner will be followed to term and the outcome of the pregnancy will be reported to the Sponsor (or designee).

Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor (or designee) after delivery as described in Section 12.6.4.

12.6.7 Overdose

For the purposes of this study, overdose is defined as an accidental or intentional use of a dose higher than the protocol recommended dose. In case of overdose, subjects will be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

The investigator must immediately notify the Sponsor (or designee) of any occurrence of overdose with study drug.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 Blood Samples

Blood samples for PK analysis of ME3183 and its metabolite (CCI) levels will be collected predose at the time points indicated in the Schedule of Assessments (Table 1). The actual date and time of the study drug administrations (both morning and evening in the previous day) and each blood sample collection will be recorded on the subject's eCRF.

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in the laboratory manual.

13.2 Pharmacokinetic Analytical Methodology

The C_{trough} of study drug and its metabolite (CCI) will be determined from the plasma samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

Additional parameters may be estimated and reported, as appropriate.

14 OTHER ASSESSMENTS

CCI

14.2 Medical Photography of Affected Skin Area

Photographs of the affected skin area (target skin lesion) will be taken at selected sites in a selected number of subjects for documentation and/or publication purposes only. The subject must sign a separate ICF for photographs to be taken. A third-party vendor (designated by the Sponsor) will supply the photography equipment to the selected sites along with the user manual containing contact information, quick reference guide, and supply request forms. Sites will transmit digital images to the third-party vendor.

14.3 Columbia-Suicide Severity Rating Scale

The C-SSRS is a suicidal ideation and behavior rating scale created by researchers at Columbia University, University of Pennsylvania, University of Pittsburgh, and New York University to evaluate suicide risk. It is administered as a clinical interview.

Subjects will be asked to self-report using the C-SSRS. Subjects with active suicidal ideation or behavior within the past 12 months based on "yes" response to question 3, 4, or 5 at Screening or Baseline will be excluded from the study.

See APPENDIX 6 for the detailed questionnaire to be administered to each subject.

15 STATISTICAL ANALYSIS

A SAP will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS® Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and percentage of subjects for each category by treatment group.

15.1 Determination of Sample Size

No formal sample size calculation was performed.

For the assessment of efficacy and safety of ME3183 in subjects with moderate to severe plaque psoriasis in this proof-of-concept study, approximately 125 eligible subjects will be enrolled. Twenty-five subjects will be randomized to each of the following treatment groups: ME3183 [redacted] mg BID, ME3183 [redacted] mg QD, ME3183 [redacted] mg BID; ME3183 [redacted] mg QD, and placebo. The number of planned subjects is considered adequate to assess safety and to provide efficacy estimates for in this Phase 2a study. The expected drop-out rate is assumed to be 10%.

15.2 Analysis Sets

Full Analysis Set

All subjects who have been randomized, received at least 1 dose of study drug, and have at least 1 evaluable post-Baseline time point for primary endpoint will be included in the full analysis set (FAS). Analyses in the FAS will be based on the subject's randomized treatment group.

Per Protocol Set

The per protocol set (PPS) is a subset of the FAS; the PPS will exclude subjects with protocol deviations that may significantly impact the assessment of the primary objective of the study. Analyses in the PPS will be based on the study treatment actually received by each subject. All decisions to exclude subjects from the PPS will be made prior to the unblinding of the study.

Safety Analysis Set

All randomized subjects who received at least 1 dose of study drug will be included in the safety analysis set. Analyses in the safety analysis set will be based on the study treatment actually received by each subject.

Pharmacokinetic Analysis Set

The PK analysis set will consist of all subjects who were correctly administered at least 1 ME3183 dose and where ME3183 or CCI concentration data is available without any protocol deviation interfering with these results. Analyses in the PK analysis set will be based on the study treatment actually received by each subject.

CCI

[redacted]

15.3 Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be performed using the FAS. The analysis of the primary efficacy endpoint will also be performed using the PPS.

15.3.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects achieving ≥ 75% reduction from Baseline in the PASI score at Week 16. For each ME3183 treatment group, the difference in the proportion of subjects achieving the difference in PASI-75 (ME3183 – placebo) and its 95% confidence interval will be estimated and tested for superior treatment effect using the Cochran-Mantel-Haenszel test at a 1-sided significance level of $\alpha = 0.025$. The PASI score will be reported for each treatment group together with the 95% confidence interval for mean.

15.3.2 Analyses of the Secondary Efficacy Endpoints

The proportion of subjects achieving PASI-50, PASI-75, PASI-90, and PASI-100, the proportion of subjects with an sPGA score of "0" or "1" combined with 2-point reduction on the 5-point sPGA scale, and the proportion of subjects with at least a 5-point reduction from Baseline in the DLQI score will be analyzed similar to as the primary endpoint analysis.

The proportion of subjects achieving PASI-50, PASI-75, PASI-90, and PASI-100, the proportion of subjects with an sPGA score of "0" or "1" combined with 2-point reduction on the 5-point sPGA scale, and the proportion of subjects with at least a 5-point reduction from Baseline in the DLQI score will be summarized by treatment group and visit. The percent change from Baseline in PASI score and change from Baseline in affected BSA, the itch NRS, and the DLQI score will be summarized by treatment group and visit. The percent change from Baseline in PASI score

and the change from Baseline in the affected BSA, the DLQI score, and the itch NRS will be analyzed using a mixed-effect model for repeated measures when applicable.

Kaplan-Meier estimate will be used for summarizing the time to PASI-50 and PASI-75. The log-rank test may be used for comparing the time to PASI-50 and PASI-75 between each ME3183 treatment group and placebo. The Cox proportional hazard model may also be used for analyzing the time to PASI-50 and PASI-75. The time to PASI-50 and PASI-75 will be summarized by treatment group.

15.3.3 Analyses of the Exploratory Efficacy Endpoints

CCI [redacted]

15.4 Safety Analyses

All safety analyses will be performed using the safety analysis set. All recorded AE and SAEs will be listed and tabulated by Medical Dictionary for Regulatory Activities (version 24.1 or higher) system organ class, preferred term, and treatment group over the 16-week Treatment Period and the 4-week Follow-up Period.

The incidence of TEAEs (events with onset dates on or after the first dose of the study drug or that was present prior to dosing and exacerbates after the first dose of study drug) will be included in incidence tables. Events with missing onset dates will be included as TEAEs. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. SAEs and AEs causing study discontinuation will be tabulated. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, seriousness, action taken with study drug, treatment of event, and outcome.

Vital signs and safety laboratory results will be listed and summarized by treatment group over the 16-week Treatment Period and the 4-week Follow-up Period. Summaries will be provided using descriptive statistics, including mean values and mean change from Baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point.

Any CS physical examination findings and safety laboratory results will be summarized. ECG readings will be evaluated by the investigator and abnormalities, if present, will be summarized and listed. The clinically noteworthy QT/QTc interval (> 450, > 480, or > 500 msec) or clinically noteworthy change from Baseline (> 30 or >60 msec) will also be summarized using descriptive statistics.

Summary tables will be provided for concomitant medications initiated during the study period.

15.5 Pharmacokinetic Analysis

The PK analysis set will be used for the PK analysis. The C_{trough} of ME3183 and its metabolite (CCI [redacted]) will be summarized descriptively by treatment group in the TFL.

CCI

[redacted]

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with ICH and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets, and other subject-facing material. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will promptly report to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the principal investigator (PI) or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

The ICF should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised forms, the subjects must be re-consented for continued participation in the study.

A pregnant partner consent form should be obtained before collecting any data from a female pregnant partner of a male subject, if becomes pregnant during the course of the study or within 4 weeks of the last dose of study drug.

16.2 Data Handling

Any data to be recorded directly in the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported in the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by PPD. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of study-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The investigator should immediately notify the Sponsor of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the study may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/IEC. Such audits/inspections may take place at the Sponsor's

site(s), PPD , or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study. The investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the EDC system.

16.4 Record Retention

Study records and source documents must be preserved for at least 25 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Health Insurance Portability Accountability Act Privacy Regulation and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to PPD monitoring plan approved by the Sponsor to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits, on-site and remote and contacts will be made at appropriate times during the study. The PI will assure him/her and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor or its designee will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard

operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The Sponsor will ensure that acknowledgment is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable regulatory authority mandates is a site responsibility.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; and in compliance with ICH GCP E6 guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. To facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

17 REFERENCES

1. Gulliver WP, Randell S, Gulliver S, et al. Do Biologics Protect Patients With Psoriasis From Myocardial Infarction? A Retrospective Cohort. J Cutan Med Surg 2016 Nov;20(6):536-541. doi: 10.1177/1203475416650430. Epub 2016 May 10.
2. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008 May;58(5):826-50. doi: 10.1016/j.jaad.2008.02.039.
3. National Psoriasis Foundation. https://www.psoriasis.org/content/statistics. Last updated 08 Oct 2020. Accessed 05 Oct 2021.
4. Semenov YR, Herbosa CM, Rogers AT, et al. Psoriasis and mortality in the United States: Data from the National Health and Nutrition Examination Survey J Am Acad Dermatol. 2021 Aug;85(2):396-403. doi: 10.1016/j.jaad.2019.08.011. Epub 2019 Aug 12.
5. Shavit E, Shear NH. An update on the safety of apremilast for the treatment of plaque psoriasis. Expert Opin Drug Saf. 2020 Apr;19(4):403-408. doi: 10.1080/14740338.2020.1744562. Epub 2020 Mar 21.
6. Dattola A, Del Duca E, Saraceno R, et al. Safety evaluation of apremilast for the treatment of psoriasis. Expert Opin Drug Saf. 2017 Mar;16(3):381-385. doi: 10.1080/14740338.2017.1288714. Epub 2017 Feb 7.
7. Fredriksson T, Pettersson U. Severe psoriasis -- oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-244. doi:10.1159/000250839.

18 APPENDICES

APPENDIX 1. CONTRACEPTION GUIDELINES

Women of childbearing potential (WOCBP) must use at least 1 highly effective method of contraception during the starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment.

Fertile men whose sexual partners are WOCBP must practice sexual abstinence or to use a condom during sexual activity with their female partner of childbearing potential starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment. Additionally, if their partner is a WOCBP, then their partner should be advised to use a highly effective contraceptive measure during sexual activity starting at Screening, continuing throughout the entire Treatment Period, and for at least 4 weeks after taking the last dose of study treatment.

A woman is considered to be a WOCBP (fertile) after menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal 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 insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical study, in line with the preferred and usual lifestyle of the subject)

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant while on-study treatment or for 4 weeks after the last dose. A female

subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference

1. [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf. 15 Sep 2014. Accessed 04 Oct 2021.

APPENDIX 2. PROHIBITED CONCOMITANT MEDICATIONS AND PROCEDURES

The following concomitant medications and procedures are prohibited prior to randomization and during the course of the study unless otherwise specified.

1. Topical therapy:

   Topical therapy unless otherwise specified (including but not limited to topical corticosteroids, topical retinoid [tazorotene] or vitamin D analogue preparations [calcipotriene and calcitriol], tacrolimus, pimecrolimus, methoxsalen, trimethylpsoralen, pimecrolimus or anthralin/dithranol). Topical therapy is prohibited from 2 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment unless otherwise specified in Section 9.6.1.

2. Systemic therapy:

   Systemic therapy including but not limited to oral or injectable retinoids, apremilast (or any other PDE4 inhibitors), acitretin, methotrexate, cyclosporine, corticosteroids, mycophenolate mofetil, 6-thioguanine, hydroxyurea, thioguanine, sirolimus, isotretinoin, sulfasalazine, azathioprine, or fumaric acid esters are be prohibited from 4 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.

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3. Biologic Agents:

   - Tumor necrosis factor (TNF)-α inhibitors (certolizumab pegol, etanercept, adalimumab, infliximab, and golimumab) are prohibited from 8 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.
   - TNF-α inhibitor, rituximab, is prohibited from 24 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.
   - Interleukin (IL)-12/23 inhibitors (ustekinumab or any other therapeutic agent targeting IL-12 or IL-23) is prohibited from 24 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.
   - IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, or any other therapeutic agent targeting IL-17) are prohibited from 24 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.

- IL-23 inhibitors (tildrakizumab, risankizumab, guselkumab, or any other therapeutic agent targeting IL-23) are prohibited from 24 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.
- IL-12 inhibitors (briakinumab or any other therapeutic agent targeting IL-12) are prohibited from 24 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.
- T-cell inhibitors: alemtuzumab, abatacept, alefacept - from 12 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.
- Integrin receptor antagonist: natalizumab - from 12 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.

4. Phototherapy:

   Prolonged exposure to ultraviolet B (including narrow band ultraviolet B, Goeckerman therapy and excimer laser) or psoralen ultraviolet A unless otherwise specified in Section 8.2 and Section 9.6.1. Phototherapy is prohibited from 4 weeks prior to the first administration of study treatment until 4 weeks after the last dose of study treatment.

5. Use of any investigational drug:

   Investigational drugs for biologic therapy are prohibited from 24 weeks prior to Day 1 until 4 weeks after the last dose of study treatment. All non-biologic investigational drugs/therapy/devices are prohibited from 4 weeks (or 5 half-lives whichever is longer) prior to Day 1 until after the last dose of study treatment.

6. Prolonged sun exposure or use of artificial sunbathing (eg, tanning booths) or other UV light sources from Day 1 until after the last dose of study treatment (ie, Treatment Period).

7. Subject has had a recent initiation of a drug that is known to potentially cause or exacerbate psoriasis (including, but not limited to, beta blockers, lithium, and anti-malarials), within the 8 weeks prior to the first administration of study treatment; a those subject who have has been on a stable dose for at least 8 weeks prior to the first administration of study treatment without exacerbation of psoriasis may be enrolled randomized and does not need to discontinue these medications.

APPENDIX 3. PSORIASIS AREA SEVERITY INDEX - WORKSHEET

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		**x 0.1**	**x 0.2**	**x 0.3**	**x 0.4**
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score = ☐

Reference

1. British Association of Dermatologists. Accessed at http://www.bad.org.uk/shared/get-file.ashx?id=1654&itemtype=document. Accessed on 05 Oct 2021.

APPENDIX 4. 5-POINT STATIC PHYSICIAN'S GLOBAL ASSESSMENT

For the determination of Static Physician's Global Assessment (sPGA), the degree of overall lesion severity will be evaluated using the categories below:

0 = Clear: No signs of psoriasis. Post-inflammatory hyperpigmentation may be present

1 = Almost clear: Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.

2 = Mild: Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling

3= Moderate: Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling

4 = Severe: Bright to deep dark red coloration; severe thickening with hard edges; severe/coarse scaling covering almost all or all lesions

Reference

1. Langley RG, Feldman SR, Nyirady J, et al. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat 2015 Feb;26(1):23-31. doi: 10.3109/09546634.2013.865009.

APPENDIX 5. DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (√) 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**?	Yes ☐ No ☐ Not Relevant ☐
If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot ☐ A little ☐ Not at all ☐
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	□ □ □ □ □

Please check you have answered EVERY question. Thank you.

Reference

1. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994 May; 19(3):210-216. doi: 10.1111/j.1365-2230.1994.tb01167.x.

APPENDIX 6. COLUMBIA-SUICIDE SEVERITY RATING SCALE

(Screening Version)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Past X Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

 C-SSRS—Screening (Version 1/14/09)

SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events; must ask about all types)*	Past X Years or Lifetime
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Reference

1. Posner K, Brent D, Lucas C, et al. Columbia-Suicide Severity Rating Scale (C-SSRS). 2008 The Research Foundation for Mental Hygiene, Inc. Version 14 Jan 2009. Accessed date 27 Sep 2021 at https://cssrs.columbia.edu/wp-content/uploads/C-SSRS1-14-09-Screening.pdf