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A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study to Evaluate the Efficacy and Safety of DC-806 in Participants With Moderate to Severe Plaque Psoriasis

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PROTOCOL

Protocol Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study to Evaluate the Efficacy and Safety of DC-806 in Participants with Moderate to Severe Plaque Psoriasis
Short Title of Protocol:	Dose-ranging study to evaluate the efficacy, safety of DC-806 in moderate to severe plaque psoriasis
Protocol Number:	DCE806201
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Test Product:	DC-806
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Sponsor Signatory:	DocuSigned by: PPD Signing Reason: I approve this document Signing Time: 01-Nov-2023 | 8:13:39 AM PDT 62770CB90B4B4B829234526E99A07A33 01-Nov-2023 PPD DICE Therapeutics, Inc. **Date**

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Study Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study to Evaluate the Efficacy and Safety of DC-806 in Participants with Moderate to Severe Plaque Psoriasis (Amendment 3.0, Version 4.0) (United States and Canada only)

Signature of Principal Investigator	***Date***
Printed Name of Principal Investigator	
I, the Principal Investigator, submit with the above signature, this statement of commitment as evidence that I have read this protocol and agree to conduct the study as outlined and in accordance with all applicable laws, regulations, and guidelines. I agree to maintain the confidentiality of all information received and developed in connection with this protocol.	

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol (Version 1.0)	04JAN2023	Not applicable
Amendment 1.0 (Version 2.0)	07MAR2023	Not applicable
Amendment 2.0 (Version 3.0) (Czechia, Germany, Hungary, Poland, and Spain only)	19JUL2023	Not applicable
Amendment 2.0 (Version 3.0) (United States and Canada only)	20SEP2023	Not applicable
Amendment 3.0 (Version 4.0) (United States and Canada only)	01NOV2023	Refer to Appendix (Section 12.0)

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1.0 PROTOCOL SYNOPSIS

1.1 Protocol Synopsis

Sponsor: DICE Therapeutics, Inc.

Test Product: DC-806

Active Ingredients: DC-806

Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study to Evaluate the Efficacy and Safety of DC-806 in Participants with Moderate to Severe Plaque Psoriasis

Study Sites: 60 to 65

Phase of Development: 2

Objectives

The primary objectives of this study are:

- To compare the efficacy of multiple doses of DC-806 versus placebo in adult participants with moderate to severe plaque psoriasis
- To compare the safety and tolerability of multiple doses of DC-806 versus placebo in adult participants with moderate to severe plaque psoriasis

The secondary objectives of this study are:

- To compare the efficacy of various DC-806 dose regimens in adult participants with moderate to severe plaque psoriasis
- To compare the efficacy of multiple doses of DC-806 versus placebo on additional efficacy endpoints in adult participants with moderate to severe plaque psoriasis
- To assess the pharmacokinetics (PK) of DC-806 in adult participants with moderate to severe plaque psoriasis

Endpoints

The primary endpoints of this study are:

- Proportion of participants achieving ≥75% reduction in Psoriasis Area of Severity Index score (PASI-75) at Week 12
- Incidence proportion of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to discontinuation

The secondary endpoints of this study are:

- Proportion of participants in each DC-806 treatment group achieving PASI-75 at Week 12
- Proportion of participants achieving a static Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at Week 12
- Proportion of participants achieving ≥50%, ≥75%, ≥90%, and 100% reduction in PASI score (PASI-50, PASI-75, PASI-90, and PASI-100, respectively) at all scheduled timepoints
- Proportion of participants achieving a sPGA score of 0 or 1 at all scheduled timepoints
- Change and percent change from Baseline in PASI score at all scheduled timepoints
- Change and percent change from Baseline in the percentage of body surface area (BSA) affected at all scheduled timepoints
- Measurement of plasma concentration of DC-806 at scheduled timepoints

Study Design:

This is a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy and safety of DC-806 in participants with moderate to severe plaque psoriasis. This study will evaluate the efficacy, safety, tolerability, and PK of multiple oral doses of DC-806 in participants with moderate to severe plaque psoriasis.

Participants who meet eligibility criteria will be randomly allocated in a 1:1:1:1:1 ratio to 1 of 5 treatment groups. CCI

Participants will complete visits for efficacy, safety, PK, and/or pharmacodynamic (PD) evaluations on Days 1, 8, 15, 29, 57, and 85, and at Follow-up (Day 115). Participants may also be required to return to the clinic for additional (unscheduled) safety follow-up visits as deemed necessary by the Investigator. Participants will be closely monitored for AEs throughout the study.

Since DC-806 is a novel investigational agent with immunomodulatory effects, systemic immunosuppressant agents will be discontinued before dosing in order to maximize participant safety. Further, in order to determine whether DC-806 exerts a potent anti-psoriatic effect in the absence of background therapy, participation requires that participants discontinue therapy (with the exception of topical bland moisturizers or emollients, or bland shampoos during the study, as needed) before dosing.

Study Design

Treatment Group	Dose (mg)	Dose Regimen	Approximate Number of Participants	
			DC-806	Placebo
1	CCI	Twice daily	45	0
2		Twice daily	45	0
3		Once daily [a]	45	0
4		Twice daily	45	0
5	Placebo	Twice daily	0	45
Total Approximate Number of Participants			**180**	**45**
			225	

a. Matching placebo administered in the evening

Number of Participants

This study will enroll approximately 225 participants with moderate to severe plaque psoriasis. Participants will be randomly allocated to 1 of 4 DC-806 dose regimens or matching placebo in a 1:1:1:1:1 ratio (ie, approximately 45 participants per treatment group). Participants who withdraw or are withdrawn for reasons not related to study drug may be replaced at the discretion of the Sponsor.

Key Inclusion Criteria

Participants are eligible to be included in this study only if all of the following criteria apply:

- Male or female, 18 to 70 years of age, inclusive
- Body mass index (BMI) of 18 to 40 kg/m^2
- All of the following psoriasis criteria:
  - Clinical diagnosis of plaque psoriasis for ≥6 months before the Baseline visit
  - Stable moderate to severe chronic plaque psoriasis, defined as ≥10% BSA psoriasis involvement, sPGA score of ≥3, and PASI score ≥12 at the Screening and Baseline visits
  - Candidate for phototherapy or systemic therapy, as assessed by the Investigator
- Women of childbearing potential (WOCBP) must be willing to use a highly effective method of contraception during the study and for ≥30 days after the last dose of study drug
- Willing to discontinue topical and/or systemic therapies for psoriasis before the first dose of study drug

Key Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

- Have had a clinically significant flare of psoriasis during the 12 weeks before the Baseline visit, as assessed by the Investigator
- History of erythrodermic psoriasis, generalized or localized pustular psoriasis, predominantly guttate psoriasis, medication-induced or medication-exacerbated psoriasis
- History of chronic infections including human immunodeficiency virus (HIV) or viral hepatitis (hepatitis B virus [HBV], hepatitis C virus [HCV])
- History of active tuberculosis (TB)
- History or evidence of active infection (including but not limited to coronavirus disease 2019 [COVID-19] infection) and/or febrile illness within 7 days, serious infections leading to hospitalization and intravenous antibiotic treatment within 90 days, or serious infection requiring antibiotic treatment within 30 days before the first dose of study drug
- History of malignancy or lymphoproliferative disease except resected cutaneous squamous cell or basal cell carcinoma that has been treated without recurrence
- Presence of active suicidal ideation, or positive suicide behavior using the "Baseline/Screening" version of the Columbia Suicide Severity Rating Scale (C-SSRS) and with either of the following criteria:
  - History of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) within 5 years before the Screening visit
  - Suicidal ideation in the past month before the Screening visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Baseline/Screening" version of the C-SSRS
- Participant has experienced primary failure (no response at approved doses after ≥3 months of therapy) to one or more therapeutic agents targeted to IL-17 (including but not limited to secukinumab, ixekizumab, brodalumab, bimekizumab)
- Systemic use of known strong and moderate cytochrome P450 (CYP)3A4 inhibitors or strong CYP3A4 inducers from Screening through the end of the study
- A 12-lead electrocardiogram (ECG) at Screening that demonstrates clinically significant abnormalities or criteria associated with QT interval abnormalities including prolongation of QT interval corrected for heart rate using Fridericia's formula (QTcF) (>500 msec)
- Laboratory values meeting the following criteria within the screening period before the first dose of study drug:
  - Serum aspartate transaminase ≥2× upper limit of normal (ULN)
  - Serum alanine transaminase ≥2×ULN
  - Serum total, direct, or indirect bilirubin ≥2.0 mg/dL; except for participants with isolated elevation of indirect bilirubin relating to a confirmed diagnosis of Gilbert syndrome
  - Serum albumin ≤3.5 g/dL
  - Prothrombin time ≥4 seconds or International Normalized Ratio ≥1.7
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula <45 mL/min/1.73m^2
  - Total white blood cell count <3000/µL
  - Absolute neutrophil count <1500/µL
  - Platelet count <100,000/µL
  - Hemoglobin <9 g/dL
- In the opinion of the Investigator or Sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's enrollment in the study

Test Product, Dose and Mode of Administration

Participants will receive study drug (DC-806 or placebo) tablets to be taken at home. On Days 1, 15, 29, and 57 during the Treatment Period, the participant will receive a kit (or kits) containing a bottle of 64 tablets for morning administration and another bottle of 64 tablets for evening administration (ie, approximately 2 weeks of treatment per kit) containing the appropriate combination of active and matching placebo study drug to provide their randomized dose regimen. Participants will take 4 tablets each morning and 4 tablets each evening, approximately 12 hours after the morning dose. Participants will be asked to take study drug at approximately the same time each day as it was administered the previous day (±2 hours). Study drug can be taken with or without food except on study Day 1 when fasting is required before the morning dose (Schedule of Assessments, Section 1.3).

Test product: DC-806

DC-806 is a small molecule inhibitor of the cytokine IL-17A in development for the treatment of patients with psoriasis. DC-806 and matching placebo tablets will be supplied by the Sponsor. Tablets are packaged in high-density polyethylene bottles and closed with child-resistant caps.

Comparator

Placebo tablets will be the same size, shape, and color as the active tablets and will consist of the compendial excipients present in the active tablets. Placebo tablets are supplied in the same packaging configuration as the active tablets.

Duration of Treatment

The approximate duration of the study is 20 weeks (142 days), which includes a 4-week Screening Period (28 days), a 12-week Treatment Period (84 days), and a 4-week Follow-up Period (30 days).

The first act of recruitment is the first screening activity (ie, signing of the first informed consent) and will be considered the start of the study. Investigators will be solely responsible for recruitment of participants at their sites (eg, there will not be a centralized recruitment vendor involved in this study).

Participants will receive the first dose of study drug on Day 1 and the last dose on Day 84. Participants will complete study visits on Days 1, 8, 15, 29, 57, and 85, and a Follow-up Visit on Day 115.

End of Study is defined as the date when all participants have had a Follow-up Visit (Day 115), Early Termination Visit, or have otherwise been discontinued from the study. Primary completion is defined as the last date on which data for the primary endpoints are collected.

At the end of the study, the Sponsor will NOT continue to provide study drug to participants /Investigators unless the Sponsor chooses to extend the study.

Criteria for Evaluation

Efficacy

Efficacy will be assessed through PASI, sPGA, BSA, Itch NRS, Skin Pain NRS, and participant-reported DLQI.

Safety

Safety will be assessed through the medical review of AEs, vital signs, 12-lead ECGs, clinical laboratory data (hematology, clinical chemistry, urinalysis), and physical examination findings.

Pharmacokinetics

Pharmacokinetics will be determined by analyzing plasma samples for concentration of DC-806 obtained from participants who receive DC-806 at various time points after the first administration of study drug. Blood (plasma) samples will be analyzed for the concentration of DC-806 by a validated method. Standard PK parameters will be derived by noncompartmental analysis if sufficient data are available, including trough concentration (C_{trough}).

Pharmacodynamics

Exploratory PD assessments may include serum biomarkers (eg, IL-17, IL-19, and potentially other IL-17 pathway and psoriasis biomarkers); immunohistochemistry assessment of biopsy tissues; biopsy mRNA levels that are relevant to the IL-17 pathway and psoriasis.

Safety and Tolerability of Study Drug

Safety and tolerability of study drug will be determined by the Independent Data Monitoring Committee (IDMC).

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of participants enrolled in this study, to ensure the integrity of the blinded nature of the study, and to oversee the planned interim analyses. An IDMC charter will be developed that will specify the roles and responsibilities of the members and interim decision rules. The Sponsor Steering Committee will receive and act on the recommendations from the IDMC. A firewall will be established to ensure the maintenance of the study blind for the Sponsor, the investigational site staff, and study participants and their study partners.

Data summaries and listings will be provided to the IDMC to facilitate their safety assessment at the regularly scheduled times and on an ad hoc basis if needed. The safety review includes SAEs and adverse events of special interest (AESIs), focusing on early signal detection. Further details on the frequency, content, and methods of data reports to the IDMC will be outlined in the charter of that committee along with the processes and procedures the committee will follow.

Statistical Methods

A Statistical Analysis Plan (SAP) will be prepared and finalized before database lock and analysis of data. Any deviations from the final SAP will be described and justified in the study report.

Continuous data will be summarized using the number of participants, mean, standard deviation, median, minimum and maximum values, while categorical data will present the number and percentage of participants within each category. Summaries will be provided by DC-806 dose regimen and placebo. Listings of individual participant data will also be produced.

Sample Size: This study will randomize approximately 225 participants with moderate to severe plaque psoriasis with approximately 45 participants each to 1 of 4 DC-806 dose regimens and approximately 45 participants to placebo.

Analysis Sets

- Enrolled Set: All participants who sign an informed consent form (ICF)
- Full Analysis Set: All participants who are randomized and received at least 1 dose of study drug (DC-806 or placebo); participants will be analyzed as per randomized treatment and all efficacy analyses will be performed using this population
- Safety Analysis Set: All participants who received ≥1 dose of study drug (DC-806 or placebo); this population will be used for safety analyses and will be analyzed as per actual treatment received
- Pharmacokinetics Set: All participants who received any study drug (DC-806 or placebo) and have any available concentration-time data
- Biomarker Set: All participants who received any study drug (DC-806 or placebo) and have both Baseline and ≥1 post-treatment biomarker measurements

Demographics and Baseline Characteristics

Demographics and Baseline characteristics, including baseline disease activity, will be tabulated by DC-806 dose regimen and placebo using descriptive statistics.

Primary Efficacy Analyses

PASI-75 score after 12 weeks of treatment will be analyzed using 2-sample Fisher's exact test or Chi-squared test based on observed count to compare response rates in DC-806 dose regimens and placebo. CCI [redacted] CCI [redacted] The odds ratio (odds in a treatment group /odds in placebo group) in the response rates and its corresponding 2-sided 95% confidence interval (CI) will be provided.

In addition, a logistic regression model may be performed to incorporate some of the covariates if they are assumed to impact the response rates. Details of the tests and models will be provided in the SAP.

Secondary Efficacy Analyses

Similar analyses as in primary efficacy analyses will be performed to compare any 2 DC-806 dose regimens.

A Cochran-Armitage trend test will be conducted to assess a positive trend between DC-806 dose regimens and PASI-75 at Week 12.

The response rate in PASI-50, PASI-75, PASI-90, and PASI-100 will be summarized by treatment group and visit and will be analyzed using a repeated measure model when applicable. CCI [redacted] CCI [redacted] The proportion of participants with an sPGA score of "0" or "1" will be analyzed similarly to the primary analyses. sPGA and DLQI score will be tabulated by treatment group and visit; the corresponding changes from Baseline and percent change from Baseline will be calculated and summarized.

For continuous secondary endpoints (eg, change from Baseline to Week 12 in PASI scores), point estimates and 2-sided 95% CIs for mean change from Baseline within each treatment group will be provided. For binary endpoints (eg, response rate in PASI and sPGA), point estimates of the response rate and 2-sided 95% CIs will be provided using normal approximation within each treatment group.

There will be no adjustment for multiplicity. All comparisons will be performed in a prespecified hierarchical procedure starting from the highest dose regimen to the lowest dose regimen.

Safety Analyses

Safety will be evaluated by presenting summaries of AEs, vital signs, physical examination findings, ECGs, and clinical laboratory evaluations. Safety variables will be tabulated by DC-806 dose regimen and placebo.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The incidence proportion of TEAEs will be presented by system organ class and preferred term, by relationship to study drug, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study drug. A TEAE is defined as an AE that occurs during or after the first study drug administration and up to and including the Follow-up Visit. In addition, the incidence proportion of serious TEAEs and TEAEs leading to discontinuation of study drug will be presented by system organ class, preferred term, and relationship to study drug.

Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed.

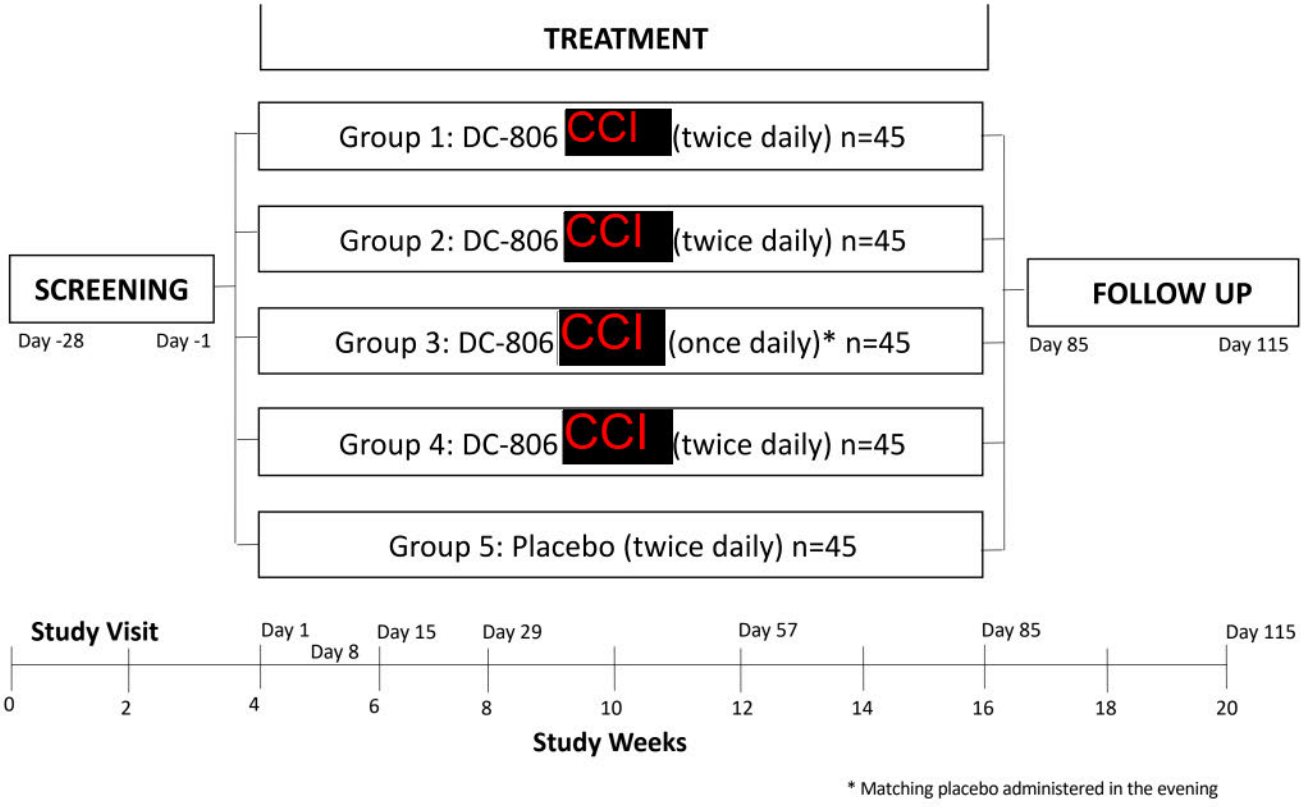
Pharmacokinetic Analyses

Summary statistics will be tabulated for maximum observed concentration (C_{max}) or C_{trough} levels at different planned time points. Additional details will be provided in the SAP as necessary.

Pharmacodynamic Analyses

Serum concentrations of inflammatory cytokines (eg, IL-17 and IL-19 and potentially other IL-17 pathway and psoriasis biomarkers) and gene expression levels of multiple IL-17 pathway related markers in skin before and after DC-806 treatment will be analyzed as exploratory assessments. These analyses are outside the scope of the study SAP.

1.2 Study Schema



1.3 Schedule of Assessments

Procedure	Screening D-28 to D-1	D1[a]	D8 ±2 days	D15 ±2 days	D29 ±2days	D57 ±3 days	D85[b] ±3 days or ET	Follow-up Visit D115 ±7 days
Informed consent [c]	X							
Inclusion /exclusion criteria	X	X						
Pregnancy test [d]	X	X			X	X	X	X
Medical history and demographics [e]	X							
Columbia-Suicide Severity Rating Scale (C-SSRS) [f,g]	X	X	X	X	X	X	X	X
Dermatology Life Quality Index (DLQI) [g]		X			X	X	X	X
Itch NRS [g]		X	X	X	X	X	X	X
Skin Pain NRS [g]		X	X	X	X	X	X	X
Concomitant medications [h]	X	X	X	X	X	X	X	X
Monitor adverse events [i]	X	X	X	X	X	X	X	X
Review daily dosing diary for compliance [j]			X	X	X	X	X	
Vital signs [k]	X	X	X	X	X	X	X	X
Height, weight, body mass index	X							
Weight only		X			X	X		X
Electrocardiogram (12-lead) [l]	X						X	X
Triplicate electrocardiogram (12-lead) [l,m]		X		X		X		
Full physical examination	X	X			X		X	
Targeted physical examination			X	X		X		X
Psoriasis Area and Severity Index score assessment	X	X	X	X	X	X	X	X
Body surface area assessment	X	X	X	X	X	X	X	X
Static Physician's Global Assessment	X	X	X	X	X	X	X	X
Medical skin photography [n] (selected sites only)		X			X		X	
Skin biopsy [n] (selected sites only)		X					X[o]	
Urinalysis	X	X	X	X	X	X	X	X
Hematology including CBC with differential	X	X	X	X	X	X	X	X
Chemistry panel	X	X	X	X	X	X	X	X

Procedure	Screening D-28 to D-1	D1[a]	D8 ±2 days	D15 ±2 days	D29 ±2days	D57 ±3 days	D85[b] ±3 days or ET	Follow-up Visit D115 ±7 days
High sensitivity C-reactive protein		X			X	X	X	
Fasting lipid panel [p]		X					X	
Fasting plasma glucose [p]		X					X	
Serology [q]	X							
TB test [r]	X							
COVID-19 antigen test (nasal swab)	X	X						
Follicle stimulating hormone (postmenopausal women only)	X							
Blood pharmacokinetic sampling [s]		X	X	X	X	X	X	
Serum pharmacodynamic sampling [t]		X	X	X	X	X	X	
RNA Seq analysis (a subset of skin biopsy samples)		X					X	
Immunohistochemistry assessment on biopsy samples		X					X	
mRNA assessment on biopsy samples		X					X	
Assign screening, participant, and IMP kit numbers in IRT [u]	X	X		X	X	X		
Administer morning dose of study drug in clinic		X	X	X	X	X		
Dispense study drug		X		X	X	X		

CBC = complete blood count; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ET = early termination; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; IMP = investigational medicinal product; IRT = interactive response technology; NRS = numerical rating scale; QFT-G = QuantiFERON®-TB Gold Plus panel; PROs = participant-reported outcomes; TB = tuberculosis; WOCBP = women of childbearing potential

a. All Day 1 study procedures must be performed before dosing on Day 1. Please refer to pharmacokinetic sampling schedule (Section 1.4) for predose and postdose timing.
b. Day 85 evaluations are performed in participants who have completed study treatment or are prematurely discontinued from study.
c. A participant is considered enrolled only when the protocol-specific informed consent form is signed. Informed consent must be collected before completing any study procedures.
d. A urine pregnancy test should be collected only for women considered by the Investigator to be of childbearing potential and before completing other screening procedures, see exclusion criteria in Section 5.2. Serum human chorionic gonadotropin testing will be performed centrally to verify urine test results. All WOCBP must have a negative serum pregnancy test prior to dosing on Day 1. Urine pregnancy testing will occur on Days 1, 29, 57, 85, and 115.
e. Medical history includes any clinically significant diseases or procedures, and toxicities or allergies related to previous treatment.
f. The C-SSRS 'Baseline/Screening' version is to be used at Screening and 'Since Last Visit' version is to be used for all other study visits.
g. Participant-reported outcome assessments must be completed before all other clinical assessments (except at Screening). Refer to the Study Reference Manual.
h. All medications used in the 28 days before screening through the end of study/early discontinuation visit must be recorded. In addition, all biologic treatments for psoriasis since diagnosis and all non-biological psoriasis medications /treatments used in the previous 5 years must be recorded (Section 6.7).

i. After informed consent has been obtained, but before initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be collected and reported to the Sponsor. After initiation of study drug, all adverse events will be collected and reported to the Sponsor until the last follow-up visit. In addition, the Sponsor must be notified of any serious adverse events the Investigator becomes aware of that has occurred after the last follow-up visit and that is believed to be related to study drug.
j. Please refer to the Study Reference Manual for compliance thresholds.
k. Vital signs include body temperature (ear or oral), respiratory rate, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for ≥5 minutes. Temperature should be measured using the same methodology throughout the study. Participants must refrain from using tobacco, caffeine or xanthine-containing for 30 minutes before vital signs being recorded.
l. 12-lead ECGs should be recorded after the participant has been supine for ≥5 minutes. Safety ECGs will be read by the Investigator to determine any clinically significant abnormalities that would exclude the participant from further study participation (Section 5.2).
m. 12-lead ECGs will be performed in triplicate, after the participant has been supine for ≥5 minutes, approximately 1 minute apart at predose and at 1 hour after dosing on Days 1, 15, and 57.
n. Please refer to the Study Reference Manual.
o. Skin biopsies are to be performed on Day 85 and are not required at the ET visit but may be collected at Investigator's discretion.
p. Participants are required to fast for ≥8 hours before the collection of specimens.
q. Serology includes HCV Ab, HBsAg, HBsAb, HBcAb, and HIV-1 and HIV-2 antibodies. Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Participants who are HCV Ab positive will have reflex testing for HCV RNA.
r. Perform TB test procedure using the QFT-G. The QFT-G may be repeated once if the Investigator deems this to be necessary. A purified protein derivative test may be performed if central laboratory is unable to determine results of QFT-G. Should the purified protein derivative test be required, the test must be administered and evaluated by a health care professional 48 to 72 hours later. The test should be performed according to local standards with induration of <5 mm required for inclusion. If a negative purified protein derivative test has been documented in the 3 months before Screening, it does not need to be repeated.
s. Pharmacokinetic samples are collected before the morning dose on Days 1, 8, 15, 29, and 57. Pharmacokinetic samples are collected postdose on Day 1 (at 0.5 and 1 hour after morning dose), Day 15 (at 0.5, 1, and 4 hours after morning dose), Day 57 (at 0.5, 1 and 4 hours after morning dose), and Day 85 (approximately 12 hours post Day 84 evening dose)
t. All pharmacodynamic serum samples must be collected before the morning dose
u. At Screening, obtain screening number through IRT. At Day 1, obtain participant number and IMP kit number through IRT. At Days 15, 29, and 57 obtain IMP kit numbers through IRT.

1.4 Pharmacokinetic Sampling Schedule

Study Day	Event	Sample Time (relative to dose) Hour: Minute (window)
1	Predose [a]	Within 2 hours before dosing
	Postdose	00:30 (±10 minutes)
		01:00 (±15 minutes)
8	Predose [a]	Within 2 hours before dosing
15	Predose [a]	Within 2 hours before dosing
	Postdose [b]	00:30 (±10 minutes)
		01:00 (±15 minutes)
		04:00 (±2 hours)
29	Predose [a]	Within 2 hours before dosing
57	Predose [a]	Within 2 hours before dosing
	Postdose [b]	00:30 (±10 minutes)
		01:00 (±15 minutes)
		04:00 (±2 hours)
85	Postdose	Morning on Day 85, approximately 12 hours after Day 84 evening dose

a. Predose samples must be drawn before the morning dose of study drug
b. Postdose samples (0.5, 1, and 4 hours after morning dose) on Day 15 and Day 57.

2.0 INTRODUCTION

2.1 Study Rationale

DC-806 is an orally administered small-molecule inhibitor of the cytokine IL-17 being developed as a potential oral therapy for the treatment of psoriasis and other IL-17 driven inflammatory diseases such as psoriatic arthritis, ankylosing spondylitis, and nonradiographic axial spondylarthritis.

While antibodies that target the IL-17 pathway are efficacious in the treatment of psoriasis, their route of administration by injection make them less ideal for patients requiring long-term treatment. There are few oral therapeutic options for patients who require systemic therapy. Each of these current oral treatment options have reported safety and tolerability concerns or are less efficacious than antibodies that target the IL-17 pathway. Due to these limitations, the need for a safe and efficacious oral therapeutic for psoriasis still exists.

DC-806 demonstrated acceptable PK, PD, and toxicology properties in nonclinical studies that support development of the compound (Section 2.3.2). DC-806 has also demonstrated a favorable tolerability, safety, PK, and PD profile when ascending doses were administered to healthy participants for up to 7 days and to participants with psoriasis for up to 28 days in a Phase 1 study (Section 2.3.3), thus supporting this Phase 2 study in participants with moderate to severe psoriasis.

This Phase 2 study in participants with psoriasis will provide evidence of clinical activity of DC-806 in a relevant disease population and will facilitate dose ranging for future studies in psoriasis and other immune-mediated conditions. Psoriasis is an ideal condition to evaluate the efficacy of the oral small molecule IL-17 inhibitor. Biologic agents targeting the IL-17 signaling pathway are currently available and highly efficacious in the treatment of psoriasis. Thus, it is feasible that psoriasis participants treated with DC-806 may derive therapeutic benefit.

2.2 Background

2.2.1 Psoriasis

Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives. Psoriasis is a chronic, relapsing, inflammatory disease of the skin with a reported prevalence across countries of 0.09% to 11.4% and affecting approximately 1% to 3% of the world's population (World Health Organisation Global Report on Psoriasis 2016; Michalek 2017). In the United States (US), psoriasis remains one of the most common immune-mediated diseases, affecting approximately 7.55 million adults ≥20 years of age (Armstrong 2021). While psoriasis can manifest at any age, there is a bimodal age distribution during the second to fourth, and sixth to seventh, decades of life.

The most common form of the disease is plaque psoriasis representing 80% to 90% of all cases. Plaque psoriasis is defined by well-defined/demarcated red, scaly plaques or patches on skin. It can occur anywhere on the body, but most commonly affects extensor surfaces such as elbows and knees, gluteal folds, scalp, and trunk. Psoriasis can also affect other areas of the body such as the face, nails, hands, and feet. Patients who experience thick painful plaques in the palms and soles have limited function of hands and feet (Armstrong 2020; Griffiths 2021).

Despite psoriasis being a disease of the skin, substantial progress in the field has elucidated comorbidities associated with psoriasis. Psoriasis has been associated with joint disease, as psoriasis either preceded or occurred concurrently in approximately 85% of patients with psoriatic arthritis. Cardiometabolic disease has been reported as a comorbidity associated with psoriasis. Psoriasis is associated with vascular inflammation and high-risk coronary atherosclerotic plaques. The proportion of psoriasis patients with moderate to severe coronary artery calcification is comparable to those with type 2 diabetes. Gastrointestinal disease has been reported as a comorbidity associated with psoriasis, and psoriasis patients have a 4-times greater prevalence of IBD. Psoriasis has a disproportionate effect on the quality of life for those impacted, owing to the clinical presentation of psoriasis in areas such as the face and exposed areas of the skin. Patients with psoriasis have reported increased risk of mental health disorders such as depression, anxiety, and suicidal ideation (Armstrong 2020).

The precise etiology of psoriasis is unclear. However, genetic factors and environmental stimuli are believed to drive the initiation of psoriasis. Tissue-resident dendritic cells activated by genetic or environmental triggers produce IL-23 that drives recruitment and proliferation of T helper 17 (Th17) cells. Activated Th17 cells produce an array of proinflammatory cytokines such as IL-17, IL-26, and TNFα. Either independently or together with TNFα, IL-17 acts on epidermal keratinocytes to drive feed-forward inflammation of the skin. IL-17-stimulated keratinocytes produce antimicrobial peptides such as beta-defensins and proinflammatory chemokines such as CCR20. The cumulation of keratinocyte products drives epidermal hyperplasia and further recruitment of innate and adaptive immune cells that chronically amplify and exacerbate skin inflammation (Hawkes 2018; Blauvelt 2018).

The importance of IL-17 in the pathogenesis of psoriasis was first demonstrated by preclinical models of the disease and has been confirmed by the profound efficacy of inhibiting the IL-17 signaling pathway via α-IL-17A or α-IL-17R antibodies (Langley 2014; Lebwohl 2015; Gordon 2016). The IL-17 cytokine family comprises 6 related proteins, IL-17A through F, where IL-17A has been the most strongly implicated in human health and disease (McGeachy 2019; Amatya 2017). The host protective or detrimental outcome of IL-17A signaling is based on the quantity of the cytokine produced and is context- and tissue-dependent. In protective roles, IL-17A regulates the microbiota, provides anti-fungal protection, and promotes tissue repair and wound healing. In pathologic roles, unregulated IL-17A signaling intensifies local tissue inflammation and tissue damage that leads to autoimmune disease (McGeachy 2019; Mills 2022). IL-17A is produced by many cell types, notably γδ T cells, αβ T cells, Th17 cells, and innate lymphoid cells are primary contributors to psoriasis (Hawkes 2018). The IL-17A monomer forms a homodimer (IL-17A/A) and a heterodimer with IL-17F (IL-17A/F) and signals through a heterodimeric receptor complex of IL-17RA and IL-17RC expressed on a range of cell types (McGeachy 2019; Amatya 2017). Major targets of IL-17 in psoriasis are epithelial cells, endothelial cells, and immune cells (Hawkes 2018).

2.2.2 Current Treatments for Psoriasis

Current treatment guidelines for psoriasis vary depending on the severity of disease. Mild disease is diagnosed when <3% to 5% of BSA is affected and moderate to severe disease is diagnosed when >5% of BSA is affected. In both diagnoses, patients are first evaluated for psoriatic arthritis, as that would favor treatment options that are effective for both psoriasis and psoriatic arthritis. In the absence of psoriatic arthritis, mild psoriasis is treated with topical treatments and targeted phototherapy. Treatment for moderate to severe psoriasis includes phototherapy and systemic treatments such as biologics and oral treatments (Armstrong 2020; Griffiths 2021).

Current biologics used for the treatment of psoriasis are IL-17, IL-12/23, and TNFα antagonists. Of the IL-17 inhibitors, secukinumab and ixekizumab target IL-17A while brodalumab targets the IL-17 receptor (Ixekizumab [TALTZ™] Prescribing Information 2022; Secukinumab [COSENTYX®] Prescribing Information 2021; brodalumab [SILIQ®] Prescribing Information 2020). Head-to-head clinical trials of IL-17A/IL-17RA antibodies versus IL-12/23 antibodies demonstrated superior efficacy of IL-17 antagonists (Hawkes 2018). A fourth biologic, bimekizumab, that targets both IL-17A and IL-17F is approved in the European Union and is currently under development in the US (Glatt 2018). Current oral treatments for psoriasis include methotrexate, cyclosporine, apremilast, and the recently approved deucravacitinib (Armstrong 2020; Griffiths 2021; Armstrong 2022). The current oral treatments for psoriasis are less efficacious than IL-17A/IL-17RA antibody treatments and most of these have been associated with toxicity, limiting their potential for long term use.

2.3 DC-806

DC-806 is an orally administered small-molecule inhibitor of the cytokine IL-17. Detailed information on the mechanism of action, nonclinical studies, and a completed Phase 1 study is provided in the DC-806 Investigator's Brochure (IB).

2.3.1 Mechanism of Action

DC-806 specifically binds to IL-17A and prevents the IL-17A/A homodimer and IL-17A/F heterodimer from binding to the IL-17RA/IL-RC receptor complex. In a rat model of rheumatoid arthritis mediated by IL-17A, DC-806 ameliorated disease to a similar degree as an anti-IL-17A antibody (Details are provided in the DC-806 IB, Section 4.2).

2.3.2 Nonclinical Data

The safety of DC-806 was evaluated in single-dose and repeat-dose toxicity studies of 7 days, 28 days, and 13 weeks in duration. As part of the general studies, and/or as stand-alone studies, DC-806 was evaluated for its potential to impact cardiovascular, respiratory, and nervous system parameters. Additionally, DC-806 has been evaluated in a full genotoxicity battery and in embryo-fetal development studies in rats and rabbits.

In single-dose, maximum tolerated dose studies, DC-806 was tolerated at the highest doses tested, 1000 mg/kg in rats, and 300 mg/kg in dogs.

CCI

CCI All human-relevant findings were monitorable and demonstrated reversibility.

Key findings from repeat-dose toxicity studies were:

CCI

CCI

CCI All human-relevant findings are monitorable and demonstrated reversibility.

Details of the nonclinical program, including nonclinical PK and metabolism, are provided in the DC-806 IB.

2.3.3 Clinical Data

One clinical study of DC-806 has been completed. Study DCE806101 was a Phase 1, randomized, double-blind, placebo-controlled, 3-part study to evaluate the safety, tolerability, PK, and PD of single-ascending and multiple-ascending doses of DC-806 in healthy adult participants and multiple ascending doses of DC-806 in participants with mild to moderate plaque psoriasis. An exploratory assessment of clinical activity in participants with psoriasis was also conducted.

Details of Study DCE806101 are provided in the DC-806 IB.

2.3.3.1 Clinical Pharmacokinetics

Study DCE806101 evaluated the PK of DC-806 following single and multiple ascending dose administration in adult healthy participants and multiple dose administration in participants with psoriasis.

2.3.3.2 Clinical Pharmacodynamics

Serum levels of IL-17A, the target of DC-806, were evaluated following treatment with DC-806 for 28 days. In addition, serum levels of β-defensin 2 (BD-2), a biomarker downstream of IL-17A pathway, were also evaluated. Both biomarkers are assessed using commercially available enzyme-linked immunosorbent assay kits that were validated before using.

BD-2 is a biomarker of IL-17A–driven pathology (Kolbinger 2017). A higher level of BD-2 is detected in serum and skin tissues of psoriasis patients, and secukinumab treatment significantly reduced the level of BD-2 both in serum and skin biopsy tissue. CCI

2.4 Benefit/Risk Assessment

It is likely that participants in this study will benefit from the treatment with DC-806 as it has the potential to be highly efficacious with an acceptable safety profile for the treatment of moderate-to-severe plaque psoriasis. DC-806 is as an inhibitor of IL-17AA and IL-17AF and is being developed as an oral treatment for moderate-to-severe psoriasis. The IL-17/IL-17 receptor signaling pathways are well-characterized pharmaceutical targets for the treatment of psoriasis. DC-806 demonstrated acceptable PK, PD, and preclinical toxicology properties that support development of the compound. In the Phase 1 study DCE806101, DC-806 demonstrated a favorable tolerability, safety, PK, and PD profile when ascending doses were administered to healthy participants for up to 7 days and to participants with psoriasis for up to 28 days. An exploratory analysis of efficacy showed clinically relevant improvement in psoriasis disease activity after administration of DC-806 for up to 28 days, thus supporting this study in participants with moderate to severe psoriasis.

IL-17 inhibitors have been associated with risk of serious infections and opportunistic infections. In addition, participants receiving IL-17 inhibitors may develop or experience worsening of Crohn's disease or ulcerative colitis (Ixekizumab [TALTZ™] Prescribing Information 2022; Secukinumab [COSENTYX®] Prescribing Information 2021; brodalumab [SILIQ®] Prescribing Information 2020). Brodalumab has been associated with increased risk of suicidal ideation and behavior and there are also theoretical considerations linking immunomodulation with the development of malignant tumors. To minimize these potential risks, participants with the following medical conditions will be excluded: chronic infections including HIV or viral hepatitis (HBV, HCV), active TB, acute infections; and active suicidal ideation or suicide behavior. In addition, a history of malignancy or lymphoproliferative disease except resected cutaneous squamous cell or treated basal cell carcinoma will also be exclusionary.

As IL-17 inhibition has the potential to result in infection, participants will be carefully monitored throughout the course of treatment. IL-17 inhibition has not been shown to increase the risk of TB infection or reactivation (Elewski 2021; Fowler 2020; Nogueira 2021). Thus, participants with positive IGRA testing are not required to be treated with prophylactic anti-TB therapy before or during the study if the participant is considered low risk for reactivation per Investigator judgment but will be carefully monitored for any sign of TB reactivation. A participant who develops active TB or pulmonary nontuberculous mycobacterial infection will be discontinued from study treatment. Absence of TB reactivation, despite not receiving anti-TB prophylaxis, will provide important information as to whether TB testing is required before treatment with DC-806.

Participants with newly diagnosed IBD (Crohn's disease or ulcerative colitis) during the study will be discontinued from study drug and referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist.

To evaluate the potential for suicidal ideation, a standard, validated questionnaire (the C-SSRS) will be administered to participants at Screening and at each subsequent study visit. Participants with active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS will be discontinued from study treatment and referred immediately to a mental health professional and may be withdrawn from the study based upon the Investigator's judgment.

Although rare, potential for drug-induced hepatotoxicity is under constant surveillance by sponsors and regulators. A panel of standard clinical tests to evaluate liver function will be carefully monitored specifically to mitigate the risk of potential drug-induced liver injury. This study will ensure timely detection, evaluation, and follow-up of laboratory abnormalities in selected liver laboratory parameters to ensure the safety of participants.

Participants with mild to moderate renal impairment will be allowed to participate in the study, as data from Study DCE-806101 demonstrated that <3% of the dose was eliminated by the renal pathway. In addition, data from the radiolabeled mass-balance study in rats demonstrated that 4.27% of the dose was excreted by renal pathways, while 90% of the dose was excreted by feces. It is anticipated that renal impairment will have minimal effect on DC-806 exposure since the fraction of DC-806 eliminated unchanged in urine (F_e) is below the 0.3 limit set by FDA guidance (US Food and Drug Administration 2020).

Safety in this study will be assessed through the medical review of AEs, vital signs, 12-lead ECGs, clinical laboratory data (hematology, clinical chemistry, urinalysis), and physical examination findings. Nonclinical data have identified small ECG elevations at high doses that have not been observed in clinical studies; nevertheless, ECGs will be monitored during the study. An external IDMC will review unblinded safety data on a periodic basis during the study.

3.0 STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary		
To compare the efficacy of multiple doses of DC-806 versus placebo in adult participants with moderate to severe plaque psoriasis	Proportion of participants achieving PASI-75 at Week 12	**Estimand 1a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of DC-806 versus placebo on a binary composite responder endpoint (PASI-75) at Week 12 without the benefit of other background anti-psoriasis therapy, regardless of the use of topical bland moisturizers, emollients, or bland shampoos as needed, and regardless of treatment interruption **Target Population:** Participants with moderate to severe plaque psoriasis • **Treatment Conditions:** Each of 4 dosing regimens of DC-806 ([redacted] compared to placebo administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks irrespective of interruptions and on top of use of topical bland moisturizers, emollients, or bland shampoos as needed • **Variable:** Responder is defined as achieving ≥75% reduction in PASI-75 at Week 12 without the use of other background anti-psoriasis therapy. Non-responder is defined as not achieving PASI-75 at Week 12 or receiving any prohibited medication[a] (including an alternative therapy for psoriasis and interacting drugs), or discontinuing the treatment due to related AE or requirement for prohibited medication[a] (Composite strategy). • **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to any other reasons occur (Hypothetical strategy) • **Population-Level Summary:** Difference in the response rates at Week 12 **Estimand 1b:** As above but with odds ratio as population-level summary
To compare the safety and tolerability of multiple doses of DC-806 versus placebo in adult participants with moderate to severe plaque psoriasis	Incidence proportion of TEAEs, SAEs, and TEAEs leading to discontinuation	**Estimand 2a:** This estimand is intended to provide a population-level estimate of the incidence proportion of TEAEs • **Target Population:** Same as in E1a • **Treatment Conditions:** Same as in E1a • **Variable:** TEAEs. • **Strategies for Intercurrent Events:** While at-risk strategy will be used where the period considered is defined up to the end of the follow up • **Population-Level Summary:** AE incidence proportion (proportion of participants with TEAE) **Estimand 2b:** As above but with SAE as variable. **Estimand 2c:** As above but with TEAEs leading to permanent treatment discontinuation as variable

Objectives	Endpoints	Estimands
Secondary		
To compare the efficacy of various DC-806 dose regimens in adult participants with moderate to severe plaque psoriasis	Proportion of participants in each DC-806 treatment group achieving PASI-75 at Week 12	**Estimand 3a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of DC-806 (comparison of each dose) on a binary composite responder endpoint (PASI-75) at Week 12 without the benefit of other background anti-psoriasis therapy regardless of the use of topical bland moisturizers or emollients, or bland shampoos, as needed and regardless of treatment interruption • **Target Population:** Same as in E1a • **Treatment Conditions:** Same as in E1a • **Variable:** Same as in E1a • **Strategies for Intercurrent Events:** Same as in E1a • **Population-Level Summary:** Difference in the response rates at Week 12 **Estimand 3b:** As above but with odds ratio as population-level summary.
To compare the efficacy of multiple doses of DC-806 versus placebo on additional efficacy endpoints in adult participants with moderate to severe plaque psoriasis	Proportion of participants achieving an sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at Week 12	**Estimand 4a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of DC-806 versus Placebo on a binary composite responder endpoint (sPGA score of 0 [clear] or 1 [almost clear]) with ≥2 grade improvement from Baseline) at Week 12 without the benefit of other background anti-psoriasis therapy regardless of the use of topical bland moisturizers, or emollients, or bland shampoos as needed and regardless of treatment interruption • **Target Population:** Same as in E1a • **Treatment Conditions:** Same as in E1a • **Variable:** Same as in E1a, but for sPGA score of 0 or 1 with ≥2 grade improvement from Baseline at Week 12 • **Strategies for Intercurrent Events:** Same as in E1a • **Population-Level Summary:** Difference in the response rates at Week 12 **Estimand 4b:** As above but with odds ratio as population-level summary
	Proportion of participants achieving ≥50%, ≥75%, ≥90%, and 100% reduction in PASI score (PASI-50, PASI-75, PASI-90, and PASI-100, respectively) at all scheduled timepoints	**Estimand 5a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of DC-806 versus Placebo on a binary composite responder endpoint (PASI-50) at all scheduled timepoints without the benefit of other background anti-psoriasis therapy regardless of the use of topical bland moisturizers or emollients or bland shampoos as needed and regardless of treatment interruption • **Target Population:** Same as in E1a • **Treatment Conditions:** Same as in E1a • **Variable:** Same as in E1a, but for PASI-50 at all scheduled timepoints up to Week 12 • **Strategies for Intercurrent Events:** Same as in E1a • **Population-Level Summary:** Odds ratio **Estimand 5b:** As above but with PASI-75 as variable **Estimand 5c:** As above but with PASI-90 as variable **Estimand 5d:** As above but with PASI-100 as variable

Objectives	Endpoints	Estimands
	Proportion of participants achieving an sPGA score of 0 or 1 at all scheduled timepoints	**Estimand 6:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of DC-806 versus Placebo on a binary composite responder endpoint (sPGA score of 0 [clear] or 1 [almost clear]) at all scheduled timepoints without the benefit of other background anti-psoriasis therapy regardless of the use of topical bland moisturizers or emollients or bland shampoos as needed and regardless of treatment interruption • **Target Population:** Same as in E1a • **Treatment Conditions:** Same as in E1a • **Variable:** Same as in E1a, but for sPGA score of 0 or 1 with ≥2 grade improvement from Baseline at all scheduled timepoints up to Week 12 • **Strategies for Intercurrent Events:** Same as in E1a • **Population-Level Summary:** Odds ratio
	Change and percent change from Baseline in PASI score at all scheduled timepoints	**Estimand 7a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of DC-806 on a continuous endpoint (PASI) as though no discontinuations of treatment for any reason occur, as though no intake of prohibited medications [a], and regardless of treatment interruption • **Target Population:** Same as in E1a • **Treatment Conditions:** Same as in E1a • **Variable:** Change and percent change from baseline of PASI score at all scheduled timepoints up to Week 12 • **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to any reason and as though no intake of prohibited medications [a] (hypothetical strategy). All data after an intercurrent event will be set to missing. • **Population-Level Summary:** Difference in means **Estimand 7b:** As above but with absolute change in PASI score from baseline as variable
	Change and percent change from Baseline in the percentage of BSA affected at all scheduled timepoints	**Estimand 8a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of DC-806 on a continuous endpoint (BSA) as though no discontinuations of treatment for any reason occur, as though no intake of prohibited medications[a] and regardless of treatment interruption • **Target Population:** Same as in E1a • **Treatment Conditions:** Same as in E1a • **Variable:** Change and percent change from baseline of BSA at all scheduled timepoints up to Week 12. • **Strategies for Intercurrent Events:** Same as in E7a • **Population-Level Summary:** Difference in means **Estimand 8b:** As above but with absolute change in BSA score from baseline as Variable

Objectives	Endpoints	Estimands
To assess the PK of DC-806 and intersubject variability in adult participants with moderate to severe plaque psoriasis	Measurement of plasma concentration of DC-806 at scheduled timepoints	N/A
Exploratory		
To assess the efficacy of DC-806 on additional efficacy endpoints in adult participants with moderate to severe plaque psoriasis	• Time to PASI-75 response at Week 12 • Proportion of participants achieving BSA ≤1% psoriasis involvement at Week 12	N/A
To assess improvement by DC-806 in quality-of-life assessments in adult participants with moderate to severe plaque psoriasis	Change from Baseline in DLQI at all scheduled timepoints	N/A
To assess improvement by DC-806 in psoriasis symptoms in adult participants with moderate to severe plaque psoriasis	• Change from Baseline in Itch NRS at all scheduled timepoints • Change from Baseline in Skin Pain NRS at all scheduled timepoints	N/A

Objectives	Endpoints	Estimands
To assess the PD of DC-806 in adult participants with moderate to severe plaque psoriasis	• Measurement of serum biomarkers at scheduled timepoints • Assessment of histologic biomarkers from tissue biopsies of psoriatic skin plaques collected at scheduled timepoints • Measurement of gene expression level of key regulators of IL-17 and related pathways	N/A
To assess exposure-response relationships of DC-806	Analyses to explore relations between DC-806 exposures and efficacy endpoints/PD biomarker responses	N/A

AE = adverse event; BID = twice daily; BSA = body surface area; DLQI = Dermatology Life Quality Index; E1a = Estimand 1a; IL-17 = interleukin-17; N/A = not applicable; NRS = numerical rating scale; PASI-XX = XX% reduction in Psoriasis Area of Severity Index score; PD = pharmacodynamic; PK = pharmacokinetics; QD = once daily; SAE = serious adverse event; sPGA = static Physician's Global Assessment; TEAE = treatment-emergent adverse event

a. Prohibited medications are the medications used for treating psoriasis and also having an impact on the efficacy assessment, and are a subset of the medications listed in Section 6.7.1.

4.0 STUDY DESIGN

4.1 Overall Design and Investigational Plan

This is a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2, dose-ranging study to evaluate the efficacy and safety of DC-806 in participants with moderate to severe plaque psoriasis. This study will evaluate the efficacy, safety, tolerability, and PK of multiple oral doses of DC-806 in participants with moderate to severe plaque psoriasis.

Participants who meet eligibility criteria will be randomly allocated in a 1:1:1:1:1 ratio to 1 of 5 treatment groups (Table 1). CCI

CCI

Participants will complete visits for efficacy, safety, PK, and/or PD evaluations on Days 1, 8, 15, 29, 57, and 85, and at Follow-up (Day 115). Participants may also be required to return to the clinic for additional (unscheduled) safety follow-up visits as deemed necessary by the Investigator. Participants will be closely monitored for AEs throughout the study.

Since DC-806 is a novel investigational agent with immunomodulatory effects, systemic immunosuppressant agents will be discontinued before dosing in order to maximize participant safety. Further, in order to determine whether DC-806 exerts a potent anti-psoriatic effect in the absence of background therapy, participation requires that participants discontinue therapy (with the exception of topical bland moisturizers or emollients, or bland shampoos during the study, as needed) before dosing (refer to washout periods listed in Section 5.2).

Table 1. Study Design

Treatment Group	Dose (mg)	Dose Regimen	Approximate Number of Participants	
			DC-806	Placebo
1	CCI	Twice daily	45	0
2		Twice daily	45	0
3		Once daily [a]	45	0
4		Twice daily	45	0
5	Placebo	Twice daily	0	45
Total Approximate Number of Participants			**180**	**45**
			225	

a. Matching placebo administered in the evening

4.2 Scientific Rationale for Study Design

This study is a randomized, double-blind, -placebo controlled, parallel-group, dose-ranging study. The study population includes participants 18 to 70 years of age with moderate to severe chronic plaque psoriasis. The population selected for this study reflects a standard population for moderate to severe psoriasis trials with new treatment interventions like DC-806.

Placebo control will be used in this study to address potential confounding factors, such as potential Investigator bias in safety and efficacy assessments, or regression to the mean in endpoint scoring. In addition, due to the nature of psoriasis and the outcome measures used, a placebo arm is necessary to obtain reliable efficacy measurements. Moreover, the inclusion of a placebo group is in accordance with health authority guidelines (European Medicines Agency, Committee For Medicinal Products For Human Use 2004), provides an accurate determination of efficacy and safety findings attributable to DC-806, minimizes bias, and is a standard requirement to ascertain study sensitivity due to the seasonal and fluctuating character of chronic plaque psoriasis.

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in patients with psoriasis.

4.3 Dose Selection Rationale

The rationales of selecting these different dose regimens are:

- To evaluate a wide exposure range to characterize the exposure-response relationship and define the therapeutic window for DC-806
  - C_{trough} concentrations will cover an exposure range of ~8-fold
- To identify exposure driver(s) for efficacy or safety (if any) and determine the appropriate "exposure target" for future studies
- Both QD and BID regimens will be evaluated to understand the contribution of "time above target" in achieving the desired clinical benefit
  - Identify a feasible QD regimen that is efficacious and safe

4.4 End of Study Definition

End of Study is defined as the date when all participants have had a Follow-up Visit (Day 115), Early Termination Visit, or have otherwise been discontinued from the study. Primary completion is defined as the last date on which data for the primary endpoints are collected.

The Sponsor may decide to terminate the study at any time, if appropriate (Section 7.1).

5.0 STUDY POPULATION

The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol. Participant eligibility should be reviewed and documented by an appropriate member of the Investigator's study team before participants are included in the study.

5.1 Inclusion Criteria

Participants are eligible to be included in this study only if all of the following criteria apply:

Age

1. Must be 18 to 70 years of age, inclusive, at the time of signing the ICF

Type of Participant and Disease Characteristics

2. Must have a BMI of 18 to 40 kg/m^2
3. Must meet all of the following psoriasis criteria:
   - Clinical diagnosis of plaque psoriasis for ≥6 months before the Baseline visit
   - Stable moderate to severe chronic plaque psoriasis, defined as ≥10% BSA psoriasis involvement, sPGA score of ≥3, and PASI score ≥12 at the Screening and Baseline visits
   - Candidate for phototherapy or systemic therapy, as assessed by the Investigator

Sex and Reproductive Status

4. Male or female

   Contraceptive use by female participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (Section 10.5).

   - Female participants must be postmenopausal or permanently sterilized, or, if a WOCBP, must be willing to use a highly effective method of contraception during the study and for ≥30 days after last dose of study drug
   - Female participants must not be pregnant, lactating, or planning pregnancy during the study and for ≥30 days after last dose of study drug

Informed Consent

5. Participants or their legally authorized representative must voluntarily sign and date an informed consent approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), before the initiation of any screening or study-specific procedures
6. Participants must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures
7. Participants must be willing to discontinue topical and/or systemic therapies for psoriasis before the first dose of study drug
8. Participants must agree to avoid prolonged exposure to the sun and to refrain from the use of tanning booths, sun lamps, and other sources of ultraviolet light during the study

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have had a clinically significant flare of psoriasis during the 12 weeks before the Baseline visit, as assessed by the Investigator
2. History of erythrodermic psoriasis, generalized or localized pustular psoriasis, predominantly guttate psoriasis, medication-induced or medication-exacerbated psoriasis
3. Have any known or suspected diagnosis of inflammatory conditions other than psoriasis and psoriatic arthritis, including but not limited to rheumatoid arthritis, sarcoidosis, IBD (Crohn's disease or ulcerative colitis), or systemic lupus erythematosus. Participants with a diagnosis of psoriatic arthritis requiring and/or are currently receiving systemic immunosuppressant medical treatment (including corticosteroids, immunosuppressants, biologics) are excluded from the study.
4. Have any active skin disease other than psoriasis that could interfere with the assessment of psoriasis
5. History of chronic infections including HIV or viral hepatitis (HBV, HCV):
   - Positive test for HIV

     OR
   - Positive test for hepatitis B surface antigen (hBsAg): participants who are hBsAg negative, hepatitis B core antibody (hBcAb) positive, and hepatitis B surface antibody (hBsAb) positive at Screening will have reflex testing for HBV DNA by polymerase chain reaction (PCR); participants who have HBV DNA above the lower limit of quantification are excluded

     OR
   - Positive test for hepatitis C antibody and a positive confirmatory test for HCV RNA (detectable HCV by PCR)

6. History of active TB
    - Participants with a positive IGRA or a purified protein derivative test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the participant has no evidence of active TB
    - If a negative purified protein derivative test has been documented in the 3 months before Screening, it does not need to be repeated
    - If presence of latent TB is established, participants are not required to be treated with prophylactic anti-TB therapy before or during the study, if the participant is considered low risk for reactivation per Investigator judgment
7. History or evidence of active infection (including but not limited to COVID-19 infection) and/or febrile illness within 7 days, serious infections leading to hospitalization and intravenous antibiotic treatment within 90 days, or serious infection requiring antibiotic treatment within 30 days before the first dose of study drug
8. History of malignancy or lymphoproliferative disease except resected cutaneous squamous cell or basal cell carcinoma that has been treated without recurrence
9. Participant has previously received a solid organ transplant
10. Presence of active suicidal ideation, or positive suicide behavior using the "Baseline /Screening" version of the C-SSRS and with either of the following criteria:
    - History of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) within 5 years before the Screening visit; participants with a history of a suicide attempt >5 years ago should be evaluated by a mental healthcare professional (eg, locally licensed psychiatrist, psychologist, or master's level therapist) before enrolling into the study
    - Suicidal ideation in the past month before the Screening visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Baseline/Screening" version of the C-SSRS at Screening
11. History or evidence of hepatic impairment (eg, history or presence of ascites, encephalopathy, prolonged prothrombin time, hypoalbuminemia, or hyperbilirubinemia); history of any current serious or unstable illnesses including renal, gastrointestinal, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease or other conditions that, in the Investigator's opinion, could interfere with the analyses of safety and efficacy in this study
12. Have undergone major surgery within 12 weeks before the first dose of study drug or planned to be performed during the study (eg, hip replacement, aneurysm removal, stomach ligation) as assessed by the Investigator
13. Have a history of alcohol or substance abuse within 6 months before the first dose of study drug that in the opinion of the Investigator will preclude participation in the study
14. History of an allergic reaction or hypersensitivity to constituents of the study drug (and its excipients) and/or other products in the same class

Prior/Concomitant Therapy

15. Participant has received a live or attenuated vaccine within the 6 weeks before the first dose of study drug
16. Participant has experienced primary failure (no response at approved doses after ≥3 months of therapy) to one or more therapeutic agents targeted to IL-17 (including but not limited to secukinumab, ixekizumab, brodalumab, bimekizumab)
17. Received anti-TNFα inhibitor(s) or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, alefacept) within 12 weeks or 5 half-lives (whichever is longer) before the first dose of study drug
18. Received any therapeutic agent directly targeted to IL-17 (including but not limited to secukinumab, ixekizumab, brodalumab, and bimekizumab) within 16 weeks or 5 half-lives (whichever is longer) before the first dose of study drug
19. Received ustekinumab, risankizumab, tildrakizumab, guselkumab, efalizumab, mirikizumab, or other IL-23 inhibitors within 24 weeks or 5 half-lives (whichever is longer) before the first dose of study drug
20. Received rituximab within 1 year before the first dose of study drug (or within 6 months if B cells have returned to pretreatment level or normal reference range [local laboratory] if pretreatment levels are not available)
21. Received any systemic nonbiologic therapy for psoriasis, including but not limited to methotrexate, cyclosporine, corticosteroids, oral retinoids, deucravacitinib, apremilast, and fumaric acid derivatives within 4 weeks before the first dose of study drug
22. Received phototherapy, laser therapy, tanning booth, or extended sun exposure that could affect psoriasis disease severity or interfere with disease assessments within 4 weeks before the first dose of study drug
23. Received topical medications including but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, urea, alpha- or beta-hydroxyl acids, and medicated shampoos (eg, those that contain >3% salicylic acid, corticosteroids, coal tar or vitamin D3 analogues) within 2 weeks before the first dose of study drug; participants are allowed to use bland (containing no psoriasis treatment) emollients and bland shampoos during the study
24. Received an experimental antibody or biologic therapy within the previous 6 months or 5 half-lives (whichever is longer), or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug, or is currently enrolled in an investigational study
25. Systemic use of known strong and moderate CYP3A4 inhibitors or strong CYP3A4 inducers from Screening through the end of the study (refer to Section 0)

Diagnostic Assessments

26. A 12-lead ECG at Screening that demonstrates clinically significant abnormalities or criteria associated with QT interval abnormalities, including prolongation of QTcF interval (>500 msec)
27. Laboratory values meeting the following criteria within the Screening period before the first dose of study drug:
    - Serum AST ≥2×ULN
    - Serum ALT ≥2×ULN
    - Serum total, direct, or indirect bilirubin ≥2.0 mg/dL; except for participants with isolated elevation of indirect bilirubin relating to a confirmed diagnosis of Gilbert syndrome
    - Serum albumin ≤3.5 g/dL
    - Prothrombin time ≥4 seconds or International Normalized Ratio ≥1.7
    - Estimated GFR by simplified 4-variable MDRD formula <45 mL/min/1.73m^2
    - Total white blood cell count <3000/µL
    - Absolute neutrophil count <1500/µL
    - Platelet count <100,000/µL
    - Hemoglobin <9 g/dL
28. In the opinion of the Investigator or Sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's enrollment in the study

Other Exclusion Criteria

29. Participants who are incapacitated, prisoners or involuntarily incarcerated, in compulsory detention for treatment of either a psychiatric or physical illness, or in other situations that render the participant vulnerable according to local regulations
30. Participants who are employees of the Sponsor or third-party organizations involved in this study or are Investigator-site personnel directly affiliated with this study and/or their immediate families (defined as a spouse, parent, child, or sibling, whether biological or legally adopted)

5.3 Lifestyle Considerations

1. On study visit days during the Treatment Period, participants must not administer study drug until instructed to do so by the Investigator or designated study staff; the study staff need to ensure patient-reported outcomes and clinical assessments are performed/completed before study drug is administered

2. The Investigator or designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (Section 10.5.1) and will confirm that the participant has been instructed in its consistent and correct use. In addition, the Investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

3. Dietary Restrictions: On certain study visit days (as per the Schedule of Assessments, Section 1.3), participants must comply with fasting requirements for ≥ 8 hours (water permitted)

4. Caffeine and Tobacco: Participants will abstain from using tobacco products or ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for ≥30 minutes before pulse rate and blood pressure measurements

5. Immunizations: It is recommended that all participants should be up to date with respect to standard-of-care vaccinations (in accordance with local practice/guidelines); vaccination of participants with live components is prohibited within the 6 weeks before the first dose of study drug

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who do not subsequently receive study drug. There is no requirement to enter screen-failed participants into the electronic case report form (eCRF).

6.0 STUDY TREATMENTS

Detailed information on the formulation, packaging, and handling of DC-806 and matching placebo tablets is provided in the Pharmacy Manual and the DC-806 IB.

6.1 Study Drugs

6.1.1 DC-806

The investigational medicinal product (IMP) for this study is DC-806. DC-806 is a small molecule inhibitor of the cytokine IL-17A in development for the treatment of patients with psoriasis. CCI

CCI

6.1.2 Placebo

Placebo tablets will be the same size, shape, and color as the active tablets and will consist of the compendial excipients present in the active tablets. Placebo tablets are supplied in the same packaging configuration as the active tablets.

6.2 Administration of Study Drug

Participants will receive study drug (DC-806 or matching placebo) tablets to be taken at home. On Days 1, 15, 29, and 57 during the Treatment Period, the participant will receive a kit (or kits) containing a bottle of 64 tablets for morning administration and another bottle of 64 tablets for evening administration (ie, approximately 2 weeks of treatment per kit) containing the appropriate combination of active and matching placebo study drug to provide their randomized dose regimen. Participants will take 4 tablets each morning and 4 tablets each evening, approximately 12 hours after the morning dose. Participants will be asked to take study drug at approximately the same time each day as it was administered the previous day (±2 hours). Study drug can be taken with or without food except on study Day 1 when fasting is required before the morning dose (Schedule of Assessments, Section 1.3).

In the case of a missed dose, participants will be instructed not to take a "catch-up dose" but to resume dosing with the next regularly scheduled dose. Participants should then continue with the remaining doses as normal. Participants will be provided with a daily dosing diary to document the time and number of tablets taken at each dose administration during periods of home dosing.

To facilitate PK analyses, doses of study drug (DC-806 or matching placebo) tablets will be administered in the clinic on study visit days. Participants will be instructed to bring all medications back to the unit and not to dose at home on the morning of study visits.

Detailed instructions for dose administration will be provided in a Pharmacy Manual.

6.3 Duration of Treatment

The approximate duration of the study is 20 weeks (142 days), which includes a 4-week Screening Period (28 days), a 12-week Treatment Period (84 days), and a 4-week Follow-up Period (30 days).

The first act of recruitment is the first screening activity (ie, signing of the first informed consent) and will be considered the start of the study. Investigators will be solely responsible for recruitment of participants at their sites (eg, there will not be a centralized recruitment vendor involved in this study).

Participants will receive the first dose of study drug on Day 1 and the last dose on Day 84. Participants will complete study visits on Days 1, 8, 15, 29, 57, and 85, and a Follow-up Visit on Day 115.

End of Study is defined as the day when all participants have had a Follow-up Visit, Early Termination Visit, or have otherwise been discontinued from the study. Primary completion is defined as the last date on which data for the primary endpoints are collected.

At the end of the study, the Sponsor will NOT continue to provide study drug to participants/Investigators unless the Sponsor chooses to extend the study.

6.4 Preparation, Handling, Storage, and Accountability

All study drug stored at the study site must be stored in a secure, environmentally controlled (temperatures 15°C to 25°C), and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff, as described in the Pharmacy Manual.

Once dispensed, participants will be advised to store study drug safely, out of reach of children, and at room temperature.

Detailed instructions for study drug storage and final disposition of used and unused study drug will be provided in a Pharmacy Manual.

6.5 Minimization of Bias

6.5.1 Randomization and Participant Numbering

Each participant will be assigned a unique screening number chronologically assigned upon consent.

Participants who complete the study Screening assessments and meet all the eligibility criteria will be assigned a unique participant number and randomization number before the first dose. This will be different from the screening number and participants will receive the corresponding product according to a randomization scheme. Random allocation of participants will be managed by a central Interactive Response Technology (IRT) system.

CCI

6.5.2 Blinding of Test Product

The Sponsor, participants, Investigators, and study staff responsible for any study procedures, with the exception of circumstances detailed in Section 6.5.3, will be blinded to whether the participant receives DC-806 or matching placebo.

For each dose strength, DC-806 and a placebo will both be of the same weight, shape, size, and color to ensure blinding is maintained.

6.5.3 Unblinding

Participants, Investigators, and all study site personnel who evaluate participant status, CRO personnel who will review eCRFs, other Sponsor agents (with the exception of the IRT provider), and Sponsor personnel involved in study conduct will be blinded to treatment assignments.

The Investigator will be unblinded to study drug allocation only if the identity of the study drug is essential for participant management in the case of an SAE, although there is no antidote for DC-806.

When possible, the Investigator will contact the Sponsor or contract research organization Medical Monitor to discuss the medical details and options for unblinding before breaking the blind. In the event that the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual participant's treatment allocation.

The treatment assignment will be unblinded through the IRT system. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken, together with the identity of the person responsible, must also be documented.

6.6 Study Drug Compliance

Dose administration will be completed by the participant at the study site under the supervision of study staff and at home when not attending the clinic for study visits. Study staff will complete drug accountability, review daily dosing diaries, and assess compliance at each study visit. Any significant noncompliance will be discussed with the Sponsor. Details on management of drug accountability and compliance are provided in the Pharmacy Manual.

6.7 Prior and Concomitant Medication

All medications (including prescription medication, over-the-counter medication, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a participant within 28 days before Screening and all concomitant medications taken after informed consent will be recorded in the eCRF. In addition, all biologic treatments for psoriasis

since diagnosis, and all non-biologic psoriasis medications or treatments taken within the 5 years before Screening, will be recorded in the eCRF.

6.7.1 Prohibited Prior and Concomitant Therapy

- Anti-TNFα inhibitor(s) or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, alefacept) within 12 weeks or 5 half-lives (whichever is longer) before the first dose of study drug and during the study
- Any therapeutic agent directly targeted to IL-17 (including but not limited to secukinumab, ixekizumab, brodalumab, and bimekizumab) within 16 weeks or 5 half-lives (whichever is longer) before the first dose of study drug and during the study
- Any IL-23 inhibitor (including but not limited to ustekinumab, risankizumab, tildrakizumab, guselkumab, efalizumab, mirikizumab) within 24 weeks or 5 half-lives (whichever is longer) before the first dose of study drug and during the study
- Rituximab within 1 year before the first dose of study drug (or within 6 months if B cells have returned to pretreatment level or normal reference range [local laboratory] if pretreatment levels are not available) and during the study
- Any systemic nonbiologic therapy for psoriasis (including but not limited to methotrexate, cyclosporine, corticosteroids, oral retinoids, deucravacitinib, apremilast, and fumaric acid derivatives) within 4 weeks before the first dose of study drug and during the study
- Topical psoriasis medications (including but not limited to corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, urea, alpha- or beta-hydroxyl acids, and medicated shampoos [eg, those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues]) within 2 weeks before the first dose of study drug and during the study. EXCEPTION: Participants are allowed to use bland (ie, containing no psoriasis treatment) emollients and bland shampoos during the study.
- Use of tanning booths, sun lamps or other ultraviolet light sources during the study; due to the potential to affect psoriasis with ultraviolet light exposure, participants must also avoid prolonged exposure to the sun
- Live or attenuated vaccine within the 6 weeks before the first dose of study drug and during the study
- Any experimental antibody or biologic therapy within the previous 6 months or 5 half-lives (whichever is longer), or any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) before the first dose of study drug or during the study
- Systemic use of known strong and moderate CYP3A4 inhibitors, or strong CYP3A4 inducers from Screening through the end of the study (refer to Section 0)

6.7.2 Permitted Concomitant Medication

The following concomitant medications are permitted during the study:

- Bland emollients and bland shampoos without other active ingredients indicated to treat psoriasis, or other additives which could affect psoriasis
- Corticosteroid inhalers and intranasal sprays, and ophthalmic corticosteroids are permitted for participants receiving a stable dose for ≥3 months before Screening
- Acetaminophen/paracetamol, ibuprofen, and other nonsteroidal anti-inflammatory drugs
- Medications listed as part of birth control methods will be allowed (refer to Section 10.5)
- Hormone replacement therapy
- If coadministration with substrates of CYP3A4, CYP2C8, P-glycoprotein, breast cancer resistance protein, or organic-anion-transporting polypeptide-1B1 is unavoidable, and when minimal concentration changes may lead to serious adverse reactions, the dosage of the substrate should be reduced in accordance with the approved prescribing information; a list of common CYP3A4, CYP2C8, P-glycoprotein, breast cancer resistance protein, and organic-anion-transporting polypeptide-1B1 sensitive substrates can be found at the following site: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Other concomitant medications taken at a stable dose for ≥3 months before Screening for concurrent medical conditions (other than psoriasis), which are not listed in Section 6.7.2, may be permitted at the Investigator's discretion.

Concomitant medications considered necessary for a participant's safety and wellbeing may be given at the discretion of the Investigator during the study. Following consultation with the Sponsor, the Investigator will determine whether the participant should continue in the study.

The following will be allowed as needed for treatment of flare: use of topical antibiotics in the event of secondary infections of lesions; topical moisturizers, bland emollients, bland or nonprescription shampoos; acetaminophen/paracetamol; or aspirin. Participants who do not respond to treatment or whose disease worsens should be managed based on Investigator's judgment and in accordance with local standard of care. Participants will be instructed to consult the Investigator or other appropriate study personnel at the site before taking any new medications or supplements.

7.0 DISCONTINUATION OF STUDY DRUG, PARTICIPANT DISCONTINUATION/WITHDRAWAL, AND DISCONTINUATION OF STUDY

7.1 Discontinuation of Study Drug

Participants will be prematurely discontinued from study drug for any of the following reasons:

- Participant experiences an AE as described below:
  - Any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above AE that is assessed as related to study drug and/or no alternative etiology is found.
  - Any CTCAE Grade 2 AE that is assessed as related to study drug and/or no alternative etiology is found, is persistent, and falls into any of the following System Organ Classes: "Blood and Lymphatic Disorders" or "Cardiac Disorders".

  If the event is deemed to be not related to study drug by the Investigator, the subject may continue study drug upon approval by the CRO Medical Monitor and Sponsor.
- Any AE, laboratory abnormality or intercurrent illness that, in the opinion of the Investigator or Sponsor, indicates that continued participation in the study is not in the best interest of the participant
- Clinical laboratory value meeting any of the following criteria:
  - Hepatotoxicity as described in Section 10.4.1
  - Absolute neutrophil count <500 cells/μL, confirmed by repeat testing with new sample
- Development of erythrodermic, guttate psoriasis
- Participants who develop malignancy other than nonmelanoma skin cancer or carcinoma in-situ of the cervix must be discontinued from study drug; information including histopathological results should be queried for the confirmation of the diagnosis
- Participant who develops active TB or pulmonary nontuberculous mycobacterial infection during the study
- Newly diagnosed IBD during the study must be prematurely discontinued from study drug and be followed-up until resolution of active IBD symptoms; participant should be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist
- Participants must be referred immediately to a mental health professional (eg, locally licensed psychiatrist, psychologist, or master's level therapist) and must be withdrawn from the study for:
  - Active suicidal ideation as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS
  - Any suicidal behavior since last visit

  Participants with active suicidal indication as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS must be referred immediately to a mental health professional and may be withdrawn from the study based upon the Investigator's judgment.

The mental health consultation must be recorded in source documentation.

- Confirmed QTcF interval of >500 ms
- Pregnancy
- Significant deviation from the protocol that is considered, in the opinion of the Investigator or Sponsor, to jeopardize the participant's safety
- Requirement for prohibited medication
- Upon the participant's request (withdrawal of consent)
- At the discretion of the Investigator or Sponsor
- Termination of the study for any reason by the Sponsor

Participants who prematurely discontinue study drug treatment due to an AE or laboratory abnormality should continue to be followed for all regularly scheduled visits as outlined in Section 1.3, and adhere to all study procedures (except for dispensing study drug, efficacy and participant-reported outcomes assessments, PK/PD sample collection, and skin biopsies [if applicable]) until the AE or laboratory abnormality resolves or stabilizes, unless they have decided to discontinue the study participation entirely (withdrawal of informed consent).

For a participant who prematurely discontinues study drug, every effort will be made to ensure the participant completes Early Termination procedures (if applicable) as soon as possible after discontinuation of study drug and as detailed in the study Schedule of Assessments (Section 1.3). The scheduled safety follow-up visit will also be performed, if possible, if the Early Termination visit has been performed before the scheduled follow up period.

7.2 Participant Discontinuation or Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of withdrawal from the study, if possible, Early Termination procedures (if applicable) as detailed in the study Schedule of Assessments (Section 1.3) should be performed as soon as possible. A safety follow-up visit will also be performed as per the Schedule of Assessments (Section 1.3) at the specified time after the last dose of study drug is administered. The participant will be permanently discontinued from both study drug administration and from the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3 Participant Replacement

Participants who withdraw or are withdrawn from the study for reasons not related to study drug may be replaced at the discretion of the Sponsor.

7.4 Lost to Follow Up

A participant 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 site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods); these contact attempts should be documented in the participant's source data records.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study

7.5 Discontinuation of Study

The Sponsor (or designee) reserves the right to discontinue/terminate the study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity. The Sponsor may identify significant safety issues that pose an unacceptable risk to study participants during the ongoing review of safety data (eg, through periodic aggregate safety reviews by the Sponsor safety team or during review of unblinded safety data by the IDMC [as outlined in Section 9.6]).

Study site participation may be discontinued if the Sponsor (or designee), Investigator, or IRB/IEC of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and International Council for Harmonisation (ICH) Good Clinical Practices (GCP).

Should the study be terminated and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative and the Investigators, IRB/IEC, and regulatory authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the participants and assure appropriate therapy and follow-up.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Every effort should be made to ensure that protocol required assessments and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the Investigator that may make it unfeasible to perform an assessment. In these cases, the Investigator must take all steps necessary to ensure the safety and wellbeing of the participant.

Guidance on the conduct of study procedures in the context of COVID-19 or other virus/infection or public health related travel restrictions or emergency is described in Section 10.6. When a protocol required assessment cannot be performed, the Investigator will document the reason for the missed assessment and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

Guidance on study procedures, their timing, and expected order of completion are summarized in the Schedule of Assessments (Section 1.3), Section 8.0, and the Study Reference Manual. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Assessments (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. The Investigator (or delegate) will obtain informed consent from each participant, in accordance with the procedures described in Section 10.1.3.

Participants who are found to be ineligible for entry into the study based on the criteria in Section 5.0 may be rescreened only once, at the discretion of the Investigator. If the participant had a complete initial screening evaluation including hepatitis and HIV serology, IGRA and/or purified protein derivative test, and ECG, these tests will not be required to be repeated for rescreening provided the conditions noted in Section 5.0 are met, there are no changes in the participant's medical history that would warrant retesting, and ≤90 days have passed. Refer to the Study Reference Manual for detailed instructions on rescreening procedures.

8.1 Efficacy Assessments

Efficacy will be assessed through PASI, sPGA, BSA, Itch NRS, Skin Pain NRS, and participant-reported DLQI. Detailed instructions on collection methods for efficacy assessments are provided in the Study Reference Manual.

8.1.1 Participant-reported Outcomes (PROs)

In-clinic PRO assessments (DLQI, Itch NRS, Skin Pain NRS) must be completed before any other study assessments at each study visit except at Screening (refer to the Study Reference Manual). Participants must be given a quiet, private place to complete these assessments.

8.2 Safety Assessments

8.2.1 Physical Examinations

A full physical examination will involve assessment of the following: general appearance; ears, nose and throat; head, neck and thyroid; cardiovascular; dermatological, respiratory; lymph nodes; abdomen; musculoskeletal and nervous system.

A targeted physical examination will involve assessment of the following: cardiovascular; dermatological, respiratory; abdomen and, any other system if deemed necessary.

Any new or worsening changes from Baseline should be recorded as TEAEs, if appropriate.

8.2.2 Vital Signs

Vital signs include body temperature (ear or oral), respiratory rate, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for ≥5 minutes.

8.2.3 Body Weight, Height, and BMI

The participant's body weight and height will be recorded, and BMI will be calculated. Measurements will be taken in normal indoor clothing with shoes removed.

8.2.4 Electrocardiograms

12-lead ECGs will be measured after the participant has been in the supine position for a minimum of 5 minutes. Single 12-lead safety ECGs (Screening, Day 85/Early Termination, and Day 115 will be read by the Investigator to identify any clinically significant abnormalities that would exclude the participant from further study participation. Triplicate ECGs will be obtained approximately 1 minute apart at predose and at 1 hour after dosing on Days 1, 15, and 57. Blood draws should be avoided in the period immediately before ECG measurement and activity should be controlled as much as possible to minimize variability due to effects of physiologic stress.

8.2.5 Clinical Safety Laboratory Assessments

Available blood and urine sample results will be reviewed by the Investigator (or designee) before the participant is dosed on Day 1.

A list of the laboratory parameters measured is presented in Section 10.2.

8.2.5.1 Hematology, Clinical Chemistry, Coagulation, Urinalysis and Virology

Site standard collection and processing procedures for blood and urine samples will be adhered to throughout the study. Scheduled blood samples for fasting lipid panel and fasting glucose will be taken following a ≥8 hour fast (water is permitted). Laboratory tests will be performed by the central laboratory.

8.2.5.2 COVID-19 Antigen Test (nasal swab)

COVID-19 testing will be performed on site or by the site's local laboratory. Site standard collection and processing procedures for samples will be adhered to throughout the study.

8.2.5.3 Pregnancy Test

Pregnancy tests (urine dipstick and serum testing at Screening and urine dipstick testing only at all other time points) will be performed for all female participants of childbearing potential. Site standard collection and processing procedures for samples will be adhered to throughout the study.

8.2.5.4 Follicle Stimulating Hormone Test

Serum follicle stimulating hormone tests will be performed by the central laboratory to confirm postmenopausal status at Screening. Site standard collection and processing procedures for blood samples will be adhered to throughout the study.

8.2.5.5 Abnormal Laboratory Findings

In cases where laboratory findings are outside the normal range and the Investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, appropriate actions will be taken (eg, the participant will not be entered into the study or the participant may be withdrawn from the study). The participant will be referred to their general practitioner or other appropriate provider for further care. The same will apply if the results of the HBsAg, hepatitis C virus antibody, or HIV test are positive and in addition the Investigator will ensure that adequate counselling is available, if requested.

Abnormal results at follow-up assessments will also require repeat testing if the Investigator believes the results may be of clinical significance (Section 10.4). Any clinically significant abnormality, including changes from Baseline (predose Day 1 or the last nonmissing value predose), should be reported as an AE.

Additional blood, urine, and/or throat swab samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the Investigator.

8.2.5.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is utilized to prospectively assess and directly classifies suicidal ideation and behavior into 11 categories. The C-SSRS assesses lifetime and current suicidal thoughts and behaviors across these categories based on an increasing severity of a 1 to 5 rating scale. At the Screening visit, questions will be in relation to lifetime experiences. At all subsequent evaluations, the questions will be in relation to the last assessment. The C-SSRS 'Baseline/ Screening version is to be used at Screening and C-SSRS 'Since Last Visit' version is to be used for all other study visits. The C-SSRS will be completed by the Investigator or by a qualified designee.

8.2.6 Adverse Events

The definition of an AE can be found in Section 10.3. AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue study drug (Section 10.3).

8.2.6.1 Time Period and Frequency for Collecting AE Information

Investigators will seek information on AEs at each participant contact. All AEs, whether reported by the participant or noted by study staff, will be recorded in the participant's medical record and on the Adverse Event eCRF.

After **informed consent** has been obtained **but before initiation of study drug**, only SAEs caused by a protocol-mandated intervention (eg, invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 10.3.5 for instructions for reporting SAEs).

After initiation of study drug, all AEs will be reported until end of study at the Follow-up Visit or until an Early Termination visit.

Investigators are not obligated to actively seek AEs after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related (probable related or possible related) to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.2.6.2 Method of Detecting AEs

The method of recording, evaluating, and assessing causality of AEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.4 and Section 10.3.5.

Care will be taken not to introduce bias when detecting AEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Examples of nonleading questions include the following:

"How have you felt since your last clinic visit? "

"Have you had any new or changed health problems since you were last here?"

8.2.6.3 Follow-up of AEs

After the initial AE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (Section 8.2.8) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 0). Further information on follow-up procedures is provided in Section 10.3.3.

8.2.6.4 Regulatory Reporting Requirements for SAEs

Prompt notification of a SAE by the Investigator to the Sponsor (via PPD Pharmacovigilance) is essential so that regulatory obligations and ethical responsibilities towards the safety of participants and the safety of the IMP under clinical investigation are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IMP under clinical Investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SUSARs) from the Sponsor will review and then file it as appropriate and will notify the IRB/IEC, if appropriate, according to local requirements.

8.2.7 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after first dose of study drug and until 30 days after the last dose as outlined in Section 10.5.3. If a pregnancy in a female participant or the partner of a male participant is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.5.3. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.2.8 Adverse Events of Special Interest

The following AEs, which have been reported with antibody inhibition of IL-17 signaling, will be documented as AESIs:

- New onset of IBD including ulcerative colitis or Crohn's disease
- Suicidal ideation

AESIs will be reported to PPD Pharmacovigilance within 24 hours after awareness at the study site.

8.3 Treatment of Overdose

There is no antidote for DC-806. In the advent of an adverse reaction due to an overdose (ie, taking more than the prescribed number of tablets), supportive and symptomatic treatment is indicated relevant to the clinical scenario. In serious cases, participants should be hospitalized for observation and/or further intervention as necessary.

8.4 Pharmacokinetics

Venous blood samples will be withdrawn via an indwelling cannula or by venipuncture. Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details for collection and processing procedures for PK samples are provided in the Laboratory Manual.

Plasma samples will be processed from venous blood and analyzed according to a validated method. Analytical methods are validated according to internationally accepted standards. The quality and integrity of the analytical work generated in this study will be evaluated in accordance with the study plan, validated method, and standard operating procedures (SOPs) of the bioanalytical laboratory.

8.5 Pharmacodynamics

Venous blood samples will be withdrawn via an indwelling cannula or by venipuncture. Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details for collection and processing procedures for PD samples are provided in the Laboratory Manual.

Serum samples will be processed from the venous blood and will be analyzed according to the bioanalytical laboratory's methods. The quality and integrity of the analytical work generated in this study will be evaluated in accordance with the study plan and SOPs of the bioanalytical laboratory.

8.5.1 Blood Sampling

Venous blood samples will be withdrawn via an indwelling cannula or by venipuncture. Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details for collection and processing procedures for blood samples are provided in the Laboratory Manual.

8.5.2 Skin Plaque Biopsy

Skin plaque biopsies (punch biopsies) will be collected from participants at selected study sites according to the Schedule of Assessments (Section 1.3). Details of skin plaque biopsy collection will be provided in the Study Reference Manual.

Biopsies will be analyzed for exploratory PD biomarkers including immunohistochemistry assessment of biopsy tissues (including but not limited to hematoxylin and eosin staining) and mRNA levels relevant to the IL-17 pathway and psoriasis, including but not limited to gene expression level of selected IL-17 pathway related genes.

9.0 STATISTICAL CONSIDERATIONS

A SAP will be prepared and finalized before database lock and analysis of data. Any deviations from the final SAP will be described and justified in the study report. All statistical analyses will be performed using Statistical Analytics Software (SAS®).

Continuous data will be summarized using the number of participants, mean, standard deviation, median, minimum and maximum values, while categorical data will present the number and percentage of participants within each category. Summaries will be provided by DC-806 dose regimen and placebo). Listings of individual participant data will also be produced.

9.1 Sample Size Determination

This study will randomize approximately 225 participants with moderate to severe plaque psoriasis, with approximately 45 participants each to 1 of 4 DC-806 dose regimens and approximately 45 participants to placebo.

9.2 Analyses Sets

- Enrolled Set: All participants who sign an ICF
- Full Analysis Set: All participants who are randomized and received at least 1 dose of study drug (DC-806 or placebo); participants will be analyzed as per randomized treatment and all efficacy analyses will be performed using this population
- Safety Analysis Set: All participants who received ≥1 dose of study drug (DC-806 or placebo); this population will be used for safety analyses and will be analyzed as per actual treatment received
- Pharmacokinetics Set: All participants who received any study drug (DC-806 or placebo) and have any available concentration-time data
- Biomarker Set: All participants who received any study drug (DC-806 or placebo) and have both Baseline and ≥1 post-treatment biomarker measurements

9.3 General Analyses

Full details of the statistical analyses will be provided in a separate SAP. Statistical analysis will be descriptive and exploratory. Continuous data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) and categorical data will be summarized using the number and percentage of participants in each category. Where confidence limits are appropriate, the confidence level will be 95% (2-sided), unless otherwise stated. Data will be presented by treatment group. Unless otherwise stated, for the purposes of summaries and analyses, Baseline will be defined as the last nonmissing assessment value before the first dose of study drug. Further details regarding selection of Baseline for specific endpoints will be given in the SAP.

9.3.1 Demographic Data and Baseline Characteristics

Demographics and Baseline characteristics (including age, sex, race, ethnicity, height, weight, and BMI), medical history, baseline disease activity, and prior/concomitant medication will be summarized by DC-806 dose regimen and placebo using descriptive statistics. Concomitant medications will be coded using the most current World Health Organisation Drug Dictionary in place at the time of study start. Baseline characteristics refer to those collected at Screening.

9.3.2 Safety Analysis

Safety will be evaluated by presenting summaries of AEs, vital signs, physical examination findings, ECGs, and clinical laboratory evaluations. Safety variables will be tabulated by DC-806 dose regimen and placebo.

Adverse events will be coded using the MedDRA®. The incidence proportion of TEAEs will be presented by system organ class and preferred term, by relationship to study drug, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study drug. A TEAE is defined as an AE that occurs during or after the first study drug infusion and up to and including the Follow-up Visit. In addition, the incidence proportion of serious TEAEs and TEAEs leading to discontinuation of study drug will be presented by system organ class, preferred term, and relationship to study drug.

Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed.

9.3.3 PK Analysis

Summary statistics will be tabulated for C_{max} or C_{trough} levels at different time points. Additional details will be provided in the SAP as necessary.

9.3.4 PD Analysis

Serum concentrations of inflammatory cytokines (eg, IL-17, IL-19, and potentially other IL-17 pathway and psoriasis biomarkers) and gene expression levels of multiple IL-17 pathway related markers in skin before and after DC-806 treatment will be analyzed as exploratory assessments. These analyses are outside the scope of the study SAP.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analyses

PASI-75 score after 12 weeks of treatment will be analyzed using 2-sample Fisher's exact test or Chi-squared test based on observed count to compare response rates in DC-806 dose regimens and placebo. CCI [redacted] CCI [redacted] The odds ratio (odds in a treatment group/odds in placebo group) in the response rates and its corresponding 2-sided 95% CI will be provided.

CCI [redacted]

9.3.5.2 Secondary Efficacy Analyses

Similar analyses as in primary efficacy analyses will be performed to compare any 2 DC-806 dose regimens.

A Cochran-Armitage trend test will be conducted to assess a positive trend between DC-806 dose regimens and PASI-75 at Week 12.

The response rate in PASI-50, PASI-75, PASI-90, and PASI-100 will be summarized by treatment group and visit and will be analyzed using a repeated measure model when applicable. CCI CCI The proportion of participants with an sPGA score of "0" or "1" will be analyzed similarly to the primary analyses. sPGA and DLQI score will be tabulated by treatment group and visit; the corresponding changes from Baseline and percent change from Baseline will be calculated and summarized.

For continuous secondary endpoints (eg, change from Baseline to Week 12 in PASI scores), point estimates and 2-sided 95% CIs for mean change from Baseline within each treatment group will be provided. For binary endpoints (eg, response rate in PASI and sPGA), point estimates of the response rate and 2-sided 95% CIs will be provided using normal approximation within each treatment group.

There will be no adjustment for multiplicity. All comparisons will be performed in a prespecified hierarchical procedure starting from the highest dose regimen to the lowest dose regimen.

CCI

9.5 Handling of Missing Data Points

Full details of procedures for handling missing data will be provided in the SAP. Missing data for safety and PK endpoints will not be imputed. Missing or below the limit of quantification PK concentrations will be handled as described in Section 9.3.3. Missing dermatology data will not be imputed and analysis of these data will include all participants randomized and treated. Summaries of worst post-Baseline values may be included to allow for missing data at individual time points.

9.6 Independent Data Monitoring Committee

Safety and tolerability of study drug will be determined by the IDMC.

The IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of participants enrolled in this study, to ensure the integrity of the blinded nature of the study, and to oversee the planned interim analyses. An IDMC charter will be developed that will specify the roles and responsibilities of the members and interim decision rules. The Sponsor Steering Committee will receive and act on the recommendations from the IDMC. A firewall will be established to ensure the maintenance of the study blind for the Sponsor, the investigational site staff, and study participants and their study partners.

Data summaries and listings will be provided to the IDMC to facilitate their safety assessment at the regularly scheduled times and on an ad hoc basis if needed. The safety review includes serious AEs and AESIs, focusing on early signal detection. Further details on the frequency, content, and methods of data reports to the IDMC will be outlined in the charter of that committee along with the processes and procedures the committee will follow.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and in compliance with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting)
- Applicable laws and regulations, including applicable privacy laws
- 21 July 2011 European Medicines Agency EMEA/CHMP/EWP/192217/2009 Committee for Medicinal Products for Human Use (CHMP) Guideline on bioanalytical method validation
- Regulation [EU] No 536/2014 (Regulation [EU] No 536/2014 Annex I, Section D, no. 17, letter a)

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) will be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The Investigator or his/her designee will explain the nature of the study to the participant and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, General Data Protection Regulation, and the IRB/IEC or study center. The medical record must include a statement that written informed consent was obtained before the participant performed any study procedures and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. An original signed ICF(s) must be provided to the participant or their legally authorized representative.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the site. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Individual participant medical information obtained through this study is considered confidential and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's wellbeing. Each participant will be asked to complete a form allowing the Investigator to notify the participant's primary healthcare provider of his/her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor (or designee), relevant regulatory authority, or IRB.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor (or designee) must be obtained for the disclosure of any confidential information to other parties.

The contract between the Sponsor and the study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5 Committees Structure

Safety and tolerability of study drug will be determined by the IDMC. See Section 9.6 for details of the committee structure.

10.1.6 Dissemination of Clinical Study Data

A clinical study summary report will be provided to the appropriate IRB/IEC and results uploaded to a clinical trials registry within 1 year of the end of the clinical study.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data).

- The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues, protocol deviations and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and/or other study-specific plans
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations)
- Study Monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements
- Data generated by this study must be available for inspection upon request by representatives of national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRB/IEC for each study site, as appropriate
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after end of study unless local regulations or institutional policies require a longer retention period
    - No records may be destroyed during the retention period without the written approval of the Sponsor
    - No records may be transferred to another location or party without written notification to the Sponsor

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

10.2 Appendix 2: Clinical Laboratory Tests

<table>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Virology</th></tr>
<tr><td rowspan="2">Full blood count with differential:
• Red blood cell count
• Mean cell hemoglobin
• Mean cell hemoglobin concentration
• Mean cell volume
• Hematocrit (packed cell volume)
• Hemoglobin
• Platelet count
• White blood cell count
• Neutrophils
• Eosinophils
• Lymphocytes
• Monocytes
• Basophils
• Erythrocyte sedimentation rate</td><td rowspan="3">• Albumin
• Alkaline phosphatase
• Alanine aminotransferase
• Aspartate aminotransferase
• Bicarbonate
• Bilirubin (total, direct and indirect)
• Calcium
• Creatinine
• Creatine kinase
• C-reactive protein
• Estimated glomerular filtration rate
• Follicle stimulating hormone [a]
• Gamma glutamyl transferase
• Glucose — serum (fasting)
• Human chorionic gonadotropin (all WOCBP at screening and follow up)
• High-density lipoprotein cholesterol
• Lactate dehydrogenase
• Low-density lipoprotein cholesterol
• Potassium
• Phosphate (inorganic)
• Protein (total)
• Serum lipids (fasting)
• Sodium
• Total cholesterol
• Triglycerides
• Urea</td><td>• HBsAg
• HBsAb
• HBcAb
• Hepatitis B virus DNA (only if HBsAg negative, HBcAb positive, and HBsAb positive)
• Hepatitis C virus antibody
• Hepatitis C virus RNA (only if Hepatitis C antibody positive)
• HIV-1 and HIV-2 antibodies
• COVID-19 antigen (nasal swab)</td></tr>
<tr><td>• Interferon-Gamma Release Assay (for mycobacterium tuberculosis): QuantiFERON®-TB Gold Plus panel</td></tr>
<tr><td>Coagulation
• Prothrombin time
• Activated partial thromboplastin time
• International normalized ratio</td><td>Urinalysis [b]
• Blood
• Glucose
• Leukocytes
• Protein
• Nitrites</td></tr>
</table>

COVID-19 = coronavirus disease 2019; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; TB = tuberculosis; WOCBP = women of childbearing potential

a. May be performed for postmenopausal female participants to confirm postmenopausal status at discretion of Investigator
b. If urinalysis is positive for protein, blood, nitrite, and/or leukocytes, a microscopic examination (for red blood cell, white blood cell, bacteria, casts, and epithelial cells) will be performed.

10.3 Appendix 3: Adverse Event Definitions

10.3.1 Adverse Events

An AE is any untoward medical occurrence in a participant temporally associated with the use of study drug, whether or not considered related to the study drug.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IMP, action taken regarding the IMP, and outcome.

10.3.1.1 Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication.
    - Overdose, per se, will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent; such overdoses should be reported regardless of sequelae

10.3.1.2 Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2 Serious Adverse Events

If an event is not an AE per the definition above (Section 10.3.1), then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting
        - Complications that occur during hospitalization are AEs; if a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious
        - When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption

- Is a congenital anomaly/birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition; these events should usually be considered serious
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

10.3.3 Emergency Medical Contacts

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PPD Medical Monitor Non-Emergency Contact Information:

PPD

Sponsor Non-Emergency Contact Information:

PPD

10.3.4 Recording and Follow-Up of AEs

10.3.4.1 Recording AEs on the eCRF

- When an AE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event
- There is only 1 eCRF page for recording AEs or SAEs
- Investigators should use correct terminology/concepts when recording AEs on the eCRF; avoid using abbreviations when recording events
- Only 1 medical concept should be recorded in the event field on the eCRF.
    - If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases); however, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF; if a diagnosis is subsequently established, it should be reported as follow-up information
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE eCRF page
- There may be instances when copies of medical records for certain cases are requested by the Sponsor; in this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information; whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE

10.3.4.2 Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following National Cancer Institute CTCAE Version 5.0 (2017) categories:

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 (Moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3 (Severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4 (Severe): life-threatening consequences; urgent intervention indicated
- Grade 5 (Severe): death related to AE

An event is defined as 'serious' when it meets ≥1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (ie, severity should not be confused with seriousness).

10.3.4.3 Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE; the relationship should be classified as follows:
  - Not related: Evidence exists that the AE has an etiology other than the study drug (such as pre-existing condition, underlying disease, intercurrent illness, or concomitant medication)
  - Unlikely related: a causal relationship between the study drug and the AE is not a reasonable possibility
  - Possibly related: The event has a suggestive temporal relationship to the study drug, and an alternative etiology is equally or less likely
  - Related: A temporal relationship exists between the event onset and administration of the study drug; it cannot be readily explained by the participant's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug; in case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge
- An AE is considered causally related to the use of the study drug when the causality assessment is probably or possibly related
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out
- The Investigator will use clinical judgment to determine the relationship
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated
- The Investigator will also consult the DC-806 IB and/or product information for marketed products, in his/her assessment
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor; however, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

10.3.4.4 Follow-up of AEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible; this may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology
- New or updated information will be recorded in the originally completed eCRF
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information

10.3.5 Reporting of AESIs, SAEs, and Pregnancies

10.3.5.1 Events that Occur Before Study Drug Initiation

After informed consent has been obtained, but before initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. The Serious Adverse Event /Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (ie, ≤24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided.

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Contacts for 24-hour emergency reporting can be found on Section 10.3.3.

10.3.5.2 Events that Occur after Study Drug Initiation

After initiation of study drug, AESIs, SAEs, and pregnancies will be reported until end of study at Day 115 or Early Termination. Investigators should record all case details that can be gathered immediately (ie, within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted immediately (ie, ≤24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided in Section 10.3.5.1. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

10.4 Appendix 4: Toxicity Management

The toxicity management of AEs and AESIs includes safety monitoring (review of AEs on an ongoing basis and periodic review of safety by the external IDMC) and may include interruption of study drug dosing with appropriate clinical management if applicable and discontinuation of participants from study drug. The management of specific laboratory parameters is described below (Section 10.4.1).

10.4.1 Management of Hepatotoxicity

For elevations in ALT or AST, the Investigator should assess the participant for potential drug-induced liver injury and apply the standard of care for medical evaluation and treatment following any local guidelines. All abnormal laboratory tests considered clinically significant by the Investigator will be followed to a satisfactory resolution.

For elevations in ALT or AST >2×ULN in participants with normal levels at baseline and any elevation in ALT or AST >3×ULN, obtain repeat ALT, AST, ALP, and total bilirubin within 48 to 72 hours*. Specific toxicity management guidelines are as follows:

- Discontinue study drug if confirmed ALT or AST >3×ULN by repeat testing with new sample AND a total bilirubin >2×ULN (with no evidence of hemolysis and an ALP value <2×ULN or not available)
- Discontinue study drug if confirmed ALT or AST >3×ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain, or tenderness, fever, rash, and/or eosinophilia (>5%)
- If confirmed ALT or AST >3×ULN but ≤5×ULN, total bilirubin ≤2×ULN and participant is asymptomatic, study drug may be continued after consultation with the Sponsor and CRO Medical Monitor
- If confirmed ALT or AST >5×ULN but ≤10×ULN, total bilirubin ≤2×ULN, hold study drug until ALT or AST ≤5×ULN^{+}; study drug may be restarted only if a cause other than the study drug has been established and if liver test returns to baseline. Rechallenge must be in consultation with Sponsor and CRO Medical Monitor. If abnormalities worsen after drug is restarted, study drug must be discontinued.
- Discontinue study drug if confirmed ALT or AST >10×ULN

Obtain repeat ALT, AST, ALP, and total bilirubin approximately every 3 days following receipt of previous laboratory results until ALT and AST are at or below approximate baseline levels for the participant. The frequency of retesting may be decreased to once a week or less if abnormalities are stabilized and participant is asymptomatic. If ALT and/or AST abnormalities worsen or remain >5×ULN for ≥14 consecutive days, study drug should be discontinued.

*+In addition to repeating measurements of ALT, AST, ALP, and total bilirubin for suspected cases of potential drug-induced liver injury, additional laboratory tests should include, but are not limited to; albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, and prothrombin time/international normalized ratio. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine alternative etiology.

+A detailed history including relevant information (eg, review of ethanol, acetaminophen/paracetamol [either by itself or as a coformulated product in prescription or over-the-counter medications], recreational drug use, supplement [herbal] use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals) should be collected. Further testing may be warranted (such as testing for acute viral hepatitis (A, B, C, D, and E) infection, liver imaging (eg, biliary tract), or serum drug levels (eg, acetaminophen/paracetamol). The Investigator should contact the Sponsor to discuss the management of a participant when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF. Study drug should be discontinued if no alternative etiology can be found.

10.4.2 Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the Investigator should assess the participant and apply the standard of care for medical evaluation and treatment following local guidelines as appropriate. Specific toxicity management guidelines for abnormal laboratory values are described below. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. Repeat testing to confirm the abnormality must occur as soon as possible. If a participant experiences a study drug interruption >7 consecutive days during Days 15 through 85, the Sponsor or CRO Medical Monitor should be notified and study drug should be discontinued.

- Hemoglobin
  - If hemoglobin <8 g/dL: interrupt study drug dosing and confirm by repeat testing with a new sample
  - If hemoglobin decreases ≥3.0 g/dL from Baseline without an alternative etiology: interrupt study drug dosing and confirm by repeat testing with new sample
  - If hemoglobin decreases ≥3.0 g/dL from Baseline and an alternative etiology is known: the participants may remain on study drug at the Investigator's discretion
  - If confirmed: continue to withhold study drug until hemoglobin value returns to normal reference range or its Baseline value
- Absolute neutrophil count
  - If confirmed <1000 cells/µL by repeat testing with new sample: interrupt study drug dosing until absolute neutrophil count value returns to normal reference range or its Baseline value
  - If confirmed <500 cells/µL by repeat testing with new sample: discontinue study drug
- Absolute lymphocyte count
  - If confirmed <500 cells/µL by repeat testing with new sample: interrupt study drug dosing until absolute lymphocyte count returns to normal reference range or its Baseline value
- Platelet count
  - If confirmed <50,000 platelets/µL by repeat testing with new sample: interrupt study drug dosing until platelet count returns to normal reference range or its Baseline value
- Serum Creatinine
  - If serum creatinine is >1.5× the Baseline value and >ULN: repeat the test for serum creatinine (with participant in an euvolemic state) to confirm the results; if the results of the repeat testing still meet this criterion; interrupt study drug and restart study drug once serum creatinine returns to ≤1.5× Baseline value and ≤ULN
  - If confirmed serum creatinine ≥2 mg/dL: interrupt study drug and restart study drug once serum creatinine returns to normal reference range or its Baseline value

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Contraception

Female participants who are sexually active and of childbearing potential must use an approved method of highly effective contraception from the time of informed consent until 30 days after their last dose of study drug.

The following highly effective methods of contraception (to be used by female participants of childbearing potential) are acceptable:

- Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine hormone-releasing system
- Implantable intrauterine device
- Surgical sterilization (eg, vasectomy in the male partner, bilateral tubal occlusion/ligation)

The following are <u>not</u> considered highly effective methods of contraception, and thus are <u>not</u> acceptable:

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide.

Alternatively, true abstinence is acceptable when it is in line with the participant's preferred and usual lifestyle. If a participant is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

Female participants who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential unless postmenopausal or permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral oophorectomy. A postmenopausal state is defined as no menses for ≥12 months without an alternative medical cause (e.g.: without hormone replacement therapy). If required by the Investigator, this may be confirmed by follicle stimulating hormone ≥40 IU/L.

No male contraception is required, except in compliance with specific local government study requirements.

10.5.2 Ova/Oocytes Donation

Female participants should not donate ova/oocytes for the duration of the study and for ≥30 days after their last dose of study drug.

10.5.3 Collection of Pregnancy Information

10.5.3.1 Male Participants with Partners Who Become Pregnant

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 30 days of study drug administration. The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study drug. The initial information will be recorded on the appropriate form and submitted to the Sponsor via PPD Pharmacovigilance within 24 hours of learning of the pregnancy.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5.3.2 Female Participants Who Become Pregnant

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor via PPD Pharmacovigilance within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy after signature of a specific informed consent for pregnancy follow-up. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post study, pregnancy related SAE considered related to study drug by the Investigator will be reported to the Sponsor as described in Section 10.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from study drug.

All pregnancies during the study will be reported to PPD Pharmacovigilance, the Sponsor, and the Medical Monitor (contact details are provided in Section 10.3.3).

10.6 Appendix 6: Alternative Measures During Public Emergencies (COVID, etc.)

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from the Sponsor.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.6.1. Telehealth visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Assessments (Section 1.3) or unscheduled visits.

Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the Investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring.

The following assessments should be performed, if possible, during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses
- Review and record any AEs since the last contact
- Review and record any new concomitant medications or changes in concomitant medications since the last contact
- Complete contraceptive check and results of pregnancy testing; confirm that the participant is adhering to the contraception method(s) required in the protocol; refer to Section 10.5 regarding contraceptive guidance
- Administer the C-SSRS and follow-up as necessary per protocol Section 8.2.5.6
- Study participants must be reminded to promptly notify site staff about any change in their health status

10.6.2. COVID-19 Infections

If a participant has COVID-19 during the study, this should be reported as an AE and appropriate medical intervention provided. Temporary interruption of the study drug may be medically appropriate until the participant has recovered from COVID-19. It is recommended that the Investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.6.3. IDMC

The external IDMC will be informed of considerations during Public Health Emergencies such as COVID-19 that may impact participant participation, participant safety, or study operations.

10.7 Appendix 7: Strong/Moderate Inhibitors and Strong Inducers of CYP3A4

Participants taking DC-806 may be affected by drug-drug interactions.

DC-806 is metabolized by CYP3A4. In the presence of a strong/moderate inhibitor of CYP3A4, the systemic exposure of the active metabolite of DC-806 may be increased significantly. **Strong/moderate inhibitors of CYP3A4 should NOT be co-administered with DC-806**. Inducers of CYP3A4 may lower concentrations of active drug, possibly to subtherapeutic concentrations, and their use in participants taking DC-806 should be limited. **Strong inducers of CYP3A4 should NOT be co-administered with DC-806**.

Investigators /site staff should examine each participant's concomitant medications carefully for possible drug-drug interactions.

List of Strong/Moderate Inhibitors and Strong Inducers of CYP3A4

Strong Inhibitors of CYP3A4	Moderate Inhibitors of CYP3A4	Strong CYP3A4 Inducers
Cobicistat	Aprepitant	Apalutamide
Danoprevir and ritonavir	Ciprofloxacin	Carbamazepine
Elvitegravir and ritonavir	Conivaptan	Enzalutamide
Grapefruit juice	Crizotinib	Ivosidenib
Indinavir and ritonavir	Cycosporine	Lumacaftor
Itraconazole	Diltiazem	Mitotane
Ketoconazole	Dronedarone	Phenytoin
Lopinavir and ritonavir	Erythromycin	Rifampin
Paritaprevir and ritonavir and ombitasvir (and/or dasabuvir)	Fluconazole	St. John's wort
Posaconazole	Fluvoxamine	
Ritonavir	Imatinib	
Saquinavir and ritonavir	Isavuconazole	
Tipranavir and ritonavir	Verapamil	
Telithromycin		
Troleandomycin		
Voriconazole		

CYP = cytochrome P450

The list of strong/moderate inhibitors and strong inducers of CYP3A4 above is not exhaustive. In the event of any questions, the Medical Monitor should be consulted. A list of common CYP3A4 inducers and inhibitors can be found at:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

10.8 Abbreviations

AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{0-12}	area under the time-concentration curve from time 0 to 12 hours
AUC_{0-24}	area under the time-concentration curve from time 0 to 24 hours
$AUC_{0-\infty}$	area under the time-concentration curve from time 0 extrapolated to infinity
BD-2	beta definsin-2
BID	bis in die (twice daily)
BMI	body mass index
BSA	body surface area
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed concentration
C_{trough}	Concentration obtained immediately before dose administration
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
F_e	fraction of drug excreted unchanged in urine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IGRA	interferon-γ release assay
IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities®
NOAEL	no-observed adverse-effect level

NRS	numerical rating scale
PASI	psoriasis area and severity index
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
sPGA	static Physician's Global Assessment
PK	pharmacokinetic(s)
PRO	participant-reported outcome
QD	quaque die (once a day)
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcV	QT interval corrected for heart rate using Van de Water's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half life
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th17	T helper 17 cells
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential

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12.0 SUMMARY OF PROTOCOL CHANGES

Protocol No.:	DCE806201
Amendment No.:	2.0 (United States [US] and Canada only)
Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study to Evaluate the Efficacy and Safety of DC-806 in Participants with Moderate to Severe Plaque Psoriasis
Sponsor:	DICE Therapeutics, Inc.

Original Protocol **Date:** 04JAN2023

Protocol Amendment 1.0 **Date:** 08MAR2023

Protocol Amendment 2.0 **Date:** 19JUL2023
(Czechia, Germany, Hungary, Poland, and Spain only)

Protocol Amendment 2.0 **Date:** 20SEP2023
(US and Canada only)

Protocol Amendment 3.0 **Date:** 01NOV2023
(US and Canada only)

12.1.1 Purpose

The purpose of Amendment 3.0 (Version 4.0) (US and Canada only) to the DCE806201 protocol entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study to Evaluate the Efficacy and Safety of DC-806 in Participants with Moderate to Severe Plaque Psoriasis", is to:

- Exclude participants from the study with systemic use of known strong and moderate cytochrome P450 (CYP)3A4 inhibitors, rather than just strong CYP3A4 inhibitors
- Provide information on moderate CYP3A4 inhibitors

12.1.2 Summary of Changes:

This summary of changes provides an overview of key changes and additions made to Amendment 3.0 (Version 4.0) (US and Canada only) versus Amendment 2.0 (Version 3.0) of protocol DCE806201. In addition, other minor editorial revisions have also been made for clarity and consistency.

Section	Topic	Description	Rationale for Change
Synopsis Section 5.2 Section 6.7.1	Exclusion criterion #25	The text was changed to exclude participants from the study with systemic use of known strong and moderate cytochrome P450 (CYP)3A4 inhibitors, rather than just strong cytochrome CYP3A4 inhibitors	Preliminary data from an ongoing drug-drug interaction study evaluating the pharmacokinetics of DC-806, when co-administered with a strong CYP3A4 inhibitor (itraconazole) or a strong CYP3A4 inducer (carbamazepine) identified DC-806 as a sensitive substrate for CYP3A4. Since limited data are available at this stage of the clinical development, co-administration of known moderate CYP3A4 inhibitors will be prohibited from Screening through the end of the study until more information becomes available.
Section 10.7	Strong/Moderate Inhibitors and Strong Inducers of CYP3A4	Information on moderate CYP3A4 inhibitors was added	