Statistical Analysis Plan J5B-MC-FHAG Version 1.0

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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DICE Therapeutics, Inc.,
A wholly owned subsidiary of Eli Lilly and Company

Protocol DCE806201

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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Final Statistical Analysis Plan

Version 1.0

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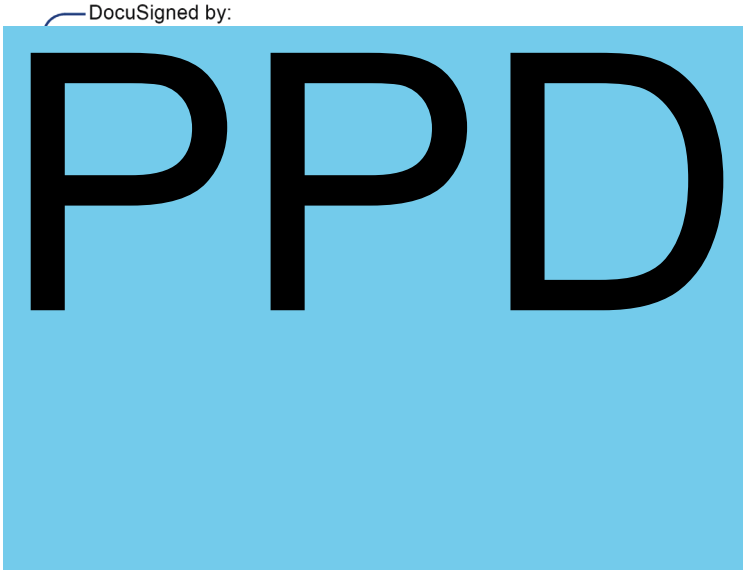

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AM	Ante Meridiem
AR(1)	First order Autoregressive Model
ARH(1)	First order Heterogeneous Autoregressive Model
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the serum concentration-time Curve
AUC0-4	Area Under the Curve from pre-dose to 4-hour post-dose
BID	Bis In Die (twice daily)
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CIF	Cumulative Incidence Function
Cmax	Maximum observed Concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
Ctrough	Concentration obtained immediately before dose administration
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
IBD	Inflammatory Bowel Disease
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
KM	Kaplan-Meier
LS	Least Squared means
MAR	Missing-At-Random
MedDRA®	Medical Dictionary for Regulatory Activities®
MMRM	Mixed Model for Repeated Measures
NRS	Numerical Rating Scale
PASI	Psoriasis Area and Severity Index

PASI-XX	XX% reduction in Psoriasis Area of Severity Index score
PD	Pharmacodynamic
PK	Pharmacokinetic
PM	Post Meridiem
PR	Retrograde P waves
PT	Preferred Term
QD	Quaque Die (once a day)
QRS	Q wave, R wave, and S wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
sPGA	static Physician's Global Assessment
TEAE	Treatment-Emergent Adverse Event
Tmax	Time to attain maximum observed plasma
UN	Unstructured
US	United States
WHO	World Health Organization

1. Introduction

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. 225 participants who meet the eligibility criteria will be enrolled across 60 to 65 study sites in a 1:1:1:1:1 ratio in 5 treatment groups (4 DC-806 dose regimens and placebo).

Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on participants' 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 Organization 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. Participants who experience thick painful plaques in the palms and soles have limited function of hands and feet (Armstrong 2020; Griffiths 2021).

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 participants requiring long-term treatment. There are few oral therapeutic options for participants 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.

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.

The purpose of this Statistical Analysis Plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives and at the same time to ensure that the data listing, summary tables, and figures which will be produced are complete and appropriate to allow valid conclusions regarding the study objectives. This document does not fully cover the details of the planned analyses for the external Independent Data Monitoring Committee (IDMC). The

IDMC charter and a IDMC Table, Listing, and Figure Shells document will outline the sequential nature of these reviews.

This SAP is based on International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use - E3 and E9 Guidelines

This plan should be read in conjunction with the following documents:

- Protocol Version 4.0 – US and Canada, 01 Nov 2023.
- Electronic case report form (eCRF) 28 Aug 2023.

2. Objectives, Estimands and Intercurrent Events

An estimand defines the treatment effect to be tested in terms of the target population, population-level summary measure, treatment conditions to compare, endpoint or variable and strategies for handling intercurrent events (ICEs). ICEs are defined as 'events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest' (ICH E9 (R1)). Part of the estimand statement is to specify the strategy for how each intercurrent event will be managed. Treatment interruption is defined as missing study drug for ≥ 3 consecutive days and/or record any study drug interruption due to an adverse event (AE), adverse event of special interest (AESI) or serious adverse event (SAE). The study objectives along with endpoints, corresponding estimands and rationale for strategies to address intercurrent events are tabulated below.

2.1. Primary Objectives, Endpoints, and Estimands

The primary objectives, corresponding endpoints and estimands are displayed in the below table:

Primary Objectives	Endpoints	Estimands
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 Psoriasis Area of Severity Index score (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, or 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. or emollients, or bland shampoos, as needed **Variable:** Responder is defined as achieving ≥75% reduction in Psoriasis Area of Severity Index score (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* (including an alternative therapy for psoriasis and interacting drugs), or discontinuing the treatment due to related AE or requirement for prohibited medication*. (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 treatment-emergent adverse events (TEAEs), SAEs, and TEAEs leading to discontinuation	**Estimand 2a:** This estimand is intended to provide a population-level estimate of the incidence proportion of treatment-emergent adverse events (TEAEs) **Target Population:** Participants with moderate to severe plaque psoriasis. **Treatment Conditions:** Each of 4 dosing regimens of DC-806 (CCI [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, or emollients, or bland shampoos, as needed **Variable:** Occurrence of 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.

* 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 Protocol Section **Error! Reference source not found.**.

2.2. Secondary Objectives, Endpoints, and Estimands

The secondary objectives, corresponding endpoints, and estimands are displayed in the below table:

Secondary Objectives	Endpoints	Estimands
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:** Participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 4 dosing regimens of DC-806 (CCI [redacted]) compared to each of the lower doses 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, or emollients, or bland shampoos, as needed **Variable:** Responder is defined as achieving ≥75% reduction in Psoriasis Area of Severity Index score (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* (including an alternative therapy for psoriasis and interacting drugs), or discontinuing the treatment due to related AE or requirement for prohibited medication*. (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 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:** 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, or emollients, or bland shampoos, as needed **Variable:** Responder is defined as achieving an sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at Week 12 without the use of other background anti-psoriasis therapy. Non-responder is defined as not achieving an sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at Week 12 or receiving any prohibited medication* (including an alternative therapy for psoriasis and interacting drugs), or discontinuing the treatment due to related adverse event or requirement for prohibited medication* (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 4b:** 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 ≥50%, ≥75%, ≥90%, and 100% reduction in PASI score (PASI-50, PASI-75, PASI-90, and PASI-100,	**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 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:** Participants with moderate to severe plaque psoriasis

	respectively) at scheduled timepoints up to Week 12	**Treatment Conditions:** Each of 4 dosing regimens of DC-806 (CCI [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, or emollients, or bland shampoos, as needed **Variable:** Responder is defined as achieving ≥50% reduction in Psoriasis Area of Severity Index score (PASI-50) at scheduled timepoints up to Week 12 without the use of other background anti-psoriasis therapy. Non-responder is defined as not achieving PASI-50 at scheduled timepoints or receiving any prohibited medication* (including an alternative therapy for psoriasis and interacting drugs), or discontinuing the treatment due to related adverse event or requirement for prohibited medication* (Composite strategy) **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to other reasons occur. (Hypothetical strategy) **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
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 or 1 at scheduled Timepoints up to Week 12	**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 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:** Participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 4 dosing regimens of DC-806 (CCI [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, or emollients, or bland shampoos, as needed **Variable:** Responder is defined as achieving an sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at scheduled timepoints up to Week 12 without the use of other background anti-psoriasis therapy. Non-responder is defined as not achieving an sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at scheduled timepoints up to Week 12 or receiving any prohibited medication* (including an alternative therapy for psoriasis and interacting drugs), or discontinuing the treatment due to related adverse event or requirement for prohibited medication* (Composite strategy) **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to other reasons occur (Hypothetical strategy) **Population-Level Summary:** Odds ratio

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	Change and percent change from Baseline in PASI score at scheduled timepoints up to Week 12	**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* and regardless of treatment interruption **Target Population:** Participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 4 dosing regimens of DC-806 (CCI [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, or emollients, or bland shampoos, as needed **Variable:** Change and percentage change from baseline of PASI score at 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*. (Hypothetical strategy). All data post ICE will be set to missing **Population-Level Summary:** Difference in means **Estimand 7b:** as above but for absolute change in PASI score from baseline as variable.
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	Change and percent change from Baseline in the percentage of BSA affected at scheduled timepoints up to Week 12	**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* and regardless of treatment interruption **Target Population:** Participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 4 dosing regimens of DC-806 (CCI [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, or emollients, or bland shampoos, as needed **Variable:** Change and percentage change from baseline of BSA at 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*. (Hypothetical strategy). All data post ICE will be set to missing **Population-Level Summary:** Difference in means **Estimand 8b:** as above but for absolute change in BSA score from baseline as variable

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	**NA**

* 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 of the protocol.

2.3. Exploratory Objectives and Endpoints

The exploratory objectives with corresponding endpoints are displayed in the below table:

Exploratory Objectives	Exploratory Endpoints
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
To assess the efficacy of DC-806 on additional efficacy endpoints in adult participants with moderate to severe plaque psoriasis	Proportion of participants achieving BSA≤1% psoriasis involvement at Week 12
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 scheduled timepoints up to Week 12
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 scheduled timepoints up to Week 12
To assess improvement by DC-806 in psoriasis symptoms in adult participants with moderate to severe plaque psoriasis	Change from Baseline in Skin Pain NRS at scheduled timepoints up to Week 12
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
To assess exposure-response relationships of DC-806	• Analyses to explore relations between DC-806 exposures and efficacy endpoints/pharmacodynamic (PD) biomarker responses

3. Investigational Plan

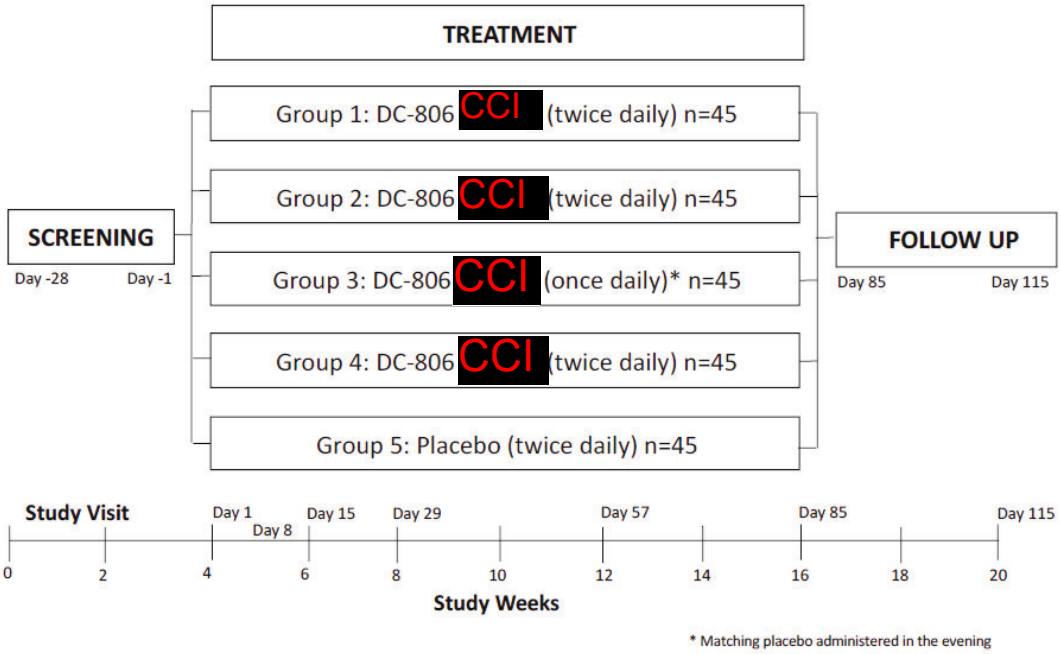
3.1. Overall Study Design and Plan

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.

225 participants who meet eligibility criteria will be randomly allocated in a 1:1:1:1:1 ratio to 1 of 5 treatment groups. CCI [redacted] The approximate duration of the study is up to 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).

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 to maximize participant safety. Further, to determine whether DC-806 exerts a potent anti-psoriatic effect in the absence of background therapy, participation requires that participants discontinue therapy (except for topical bland moisturizers or emollients, or bland shampoos during the study, as needed) before dosing.



3.2. Treatments

The treatments would be provided to the different treatment groups as follows:

Treatment Group	Dose (mg)	Dose Regimen	Approximate Number of Participants	
			DC-806	Placebo
1	CCI	Twice daily	45	0
2	CCI	Twice daily	45	0
3	CCI	Once daily [a]	45	0
4	CCI	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. General Statistical Considerations

Data collected in this study will be presented using summary tables, participant data listings and figures. For ordinal-scaled variables, a combination of presentations may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on the N of the analysis set and number of participants with missing data will also be included. All by-visit summaries will use assessments done at the scheduled visits. If multiple assessments or measurements are done at a single scheduled visit, only the latest such assessment/measurement will be included in the summary. All data will be included in the listings.

Continuous variables will be summarized using the number of participants, mean, standard deviation (SD), median, minimum, and maximum values. The minimum and maximum values will be presented to the same level of precision as the data. The mean and median will be presented to one decimal place greater than the level of precision in the data, and the SD will be presented to two decimal places greater than the level of precision in the data. Categorical summaries will include the frequency counts of each category, and the percentage displayed to one decimal place. In the case of a zero count, the percentage will be suppressed to draw attention to the non-zero counts.

Unless otherwise specified, all confidence intervals (CI) will be 2-sided and performed using a 5% significance level. P-values will be displayed in the following format: 0.9999. Any p-value less than 0.0001 will be displayed as <0.0001. Any p-value greater than 0.9999 will be displayed as >0.9999.

The reference date for the calculation of study days will be the date of the first dose at Day 1. For events/assessments on or after the treatment start date, the study day of events/assessments from treatment start date is calculated as the date of event minus the reference date + 1. For events/assessments before the treatment start date, the study day of events/assessments is defined as the date of assessment minus the reference date.

Baseline will be defined as the last non-missing assessment value before the first dose of study drug.

Unless specified otherwise, all summary and analysis tables will be presented by treatment groups (DC-806 dose regimens and placebo). Listings of individual participant data will also be produced.

4.1. Date Imputations

For the purpose of inclusion in prior and/or concomitant medication/procedure and AE tables, incomplete AEs and medications/procedures start, and end dates will be imputed as follows:

- Start Date Imputation of Adverse Events:
  - Imputation of adverse event end date must be done before imputation of event start date.
  - Missing day and month: For participants treated, impute to January 1st, unless year is the same as year of first treatment dose then impute to the date of first treatment dose.
  - Missing day: For participants treated, impute to the 1st of the month, unless month and year are the same as month and year of first treatment dose then impute to the date of first treatment dose.
  - If adverse event end date (imputed or not) is not missing and imputed event start date is after event end date (imputed or not), set the event start date equal to the event end date (imputed or not).
- Start date imputation of prior/concomitant medications:
  - Imputation of medication end date must be done before imputation of medication start date.
  - Missing day and month: For participants treated, impute to January 1st, unless year is the same as year of first treatment dose then impute to the date of first treatment dose.
  - Missing day: For participants treated, impute to the 1st of the month, unless month and year are the same as month and year of first treatment dose then impute to the date of first treatment dose.
- Stop date imputation of adverse events, prior/concomitant medications:
  - Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
  - Missing day: Impute to the last day of the month unless year and month are the same as year and month of last contact date then impute to the last contact date.

4.2. 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.

4.3. Minimization of Bias

4.3.1. 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.

4.3.2. Blinding of Test Product

The Sponsor, participants, Investigators, and study staff responsible for any study procedures, with the exception of circumstances detailed in Section 4.3.3, 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.

4.3.3. 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 case report form (CRF). The date on which the code was broken, together with the identity of the person responsible, must also be documented.

A separate unblinded project team at PPD will be unblinded for IDMC and Interim Analysis purpose. Datasets (and related Tables, Listings, Figures) containing unblinding data will be exclusively handled by unblinded project team members at PPD. An unblinding plan will give full details.

4.4. Analysis Set

The following analysis sets will be used in the statistical analysis. The number and percentage of participants in each of the analysis sets will be presented for the enrolled set in the disposition table, and a corresponding listing will be displayed.

4.4.1. Enrolled Set

The enrolled set will consist of all participants who sign the informed consent form (ICF).

4.4.2. Randomized Set

The randomized set will consist of all participants who are enrolled and randomized to one of the treatment groups.

4.4.3. Full Analysis Set (FAS)

The FAS will consist of all participants who are randomized and received at least 1 dose of study drug (DC-806 or placebo). All analyses using the FAS will group participants according to the randomized treatment. All efficacy analyses will be performed using this population.

4.4.4. Safety Analysis Set (SAS)

The safety analysis set will consist of all participants who are randomized and received at least 1 dose of study drug (DC-806 or placebo). All analyses using the safety analysis set (SAS) will group participants according to the treatment they actually receive. If participants received multiple treatments (e.g. DC-806 and placebo), the treatment with the highest dose that participants actually received will be used as an actual treatment. A randomized but not treated participant will be excluded from the safety analyses.

4.4.5. Pharmacokinetics (PK) Set

The PK set will consist of all participants who received any study drug (DC-806 or placebo) and have any available concentration-time data. Analyses using the PK populations will group participants according to treatment received.

4.4.6. Biomarker Set

The Biomarker set will consist of all participants who received any study drug (DC-806 or placebo) and have both Baseline and ≥1 post-treatment biomarker measurements.

5. Participant Disposition

5.1. Disposition

Participant disposition will be summarized for the enrolled set. A disposition of participants includes the number and percentage of participants who were randomized, participants who screen-failed, participants who completed the study, and participants who discontinued the study.

The reasons for study discontinuation will also be summarized in this table, as collected on the End of Study CRF. The percentages will be based on the number of participants randomized.

Additionally, the disposition of participants includes the number and percentages of participants who were treated, participants who completed study treatment, and participants who discontinued study treatment. The reasons for study treatment discontinuation will also be summarized in this table, as collected on the End of Treatment CRF. The percentages will be based on the number of participants treated. Study duration and treatment duration will be summarized using descriptive statistics. Study duration is defined as date of study completion or date of early study withdrawal - date of randomization +1; treatment duration is defined as date of last administration of study treatment - date of first administration of study treatment +1 (detailed in Section 7.2.2.1).

Participant disposition data will be presented in a listing for the enrolled set. Listings will be provided for the eligibility fulfillment and randomization information.

5.2. Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). An important deviation occurs when there is nonadherence to the protocol or to local regulations or International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines that may or may not result in a significant, additional risk to the participant or impacts the integrity of study data. All deviations will be assessed as important or not important in cooperation with the Sponsor and in accordance with the Protocol Deviation Guidance Document and the Project Plan.

Important protocol deviations will be summarized by category for the FAS. Important protocol deviations will be listed for the FAS.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline information will be presented. The demographic characteristics consist of age (years) at screening, sex, childbearing potential, race, and ethnicity. The baseline characteristics consist of baseline contraception use (women of childbearing potential only), height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2). BMI is calculated as (body weight in kilograms) / (height in meters)^2.
Age (years), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of participants by sex (Male, Female), childbearing potential (Yes, No), contraception use (Yes, No), race (White, Black, or African American, Asian, American Indian, or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other, Unknown, and Not Reported), ethnicity (Hispanic or Latino, Not Hispanic or Latino), previous biologic therapy (Yes, No) collected both in CRF and as per IRT and geographic region (North America/Western Europe vs. Eastern Europe) collected as per IRT. Percentages will be based on the total number of participants in the FAS.

Summary of difference in previous biologic therapy (Yes, No) collected in CRF and as per IRT will be presented for FAS.

Participant demographic and baseline characteristics will be presented in a listing for FAS.

6.2. Baseline Disease Characteristics

A summary of baseline disease information will also be presented for the FAS. Baseline PASI scores (Psoriasis Area and Severity Index score assessment), sPGA score (static Physician's Global Assessment) score, BSA (body surface area) Involvement (%), Itch NRS (Itch numerical rating scale), Skin Pain NRS (Skin Pain numerical rating scale), and DLQI score (Dermatology Life Quality Index) score will be summarized using descriptive statistics for the FAS. Corresponding listings will also be displayed for the FAS.

Further details of PRO scores are provided in the appendices.

6.3. Medical History

6.3.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), initially with Version 25.1. The dictionary will be updated throughout the life of the study so that the latest version is used. The number and percentage of participants with any medical history will be summarized overall and for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of participants in the SAS.

Participants' medical history data including specific details will be presented in a listing for the SAS. Plaque psoriasis history will be presented in a separate listing for the SAS.

6.4. Inclusion and Exclusion Criteria

The specific inclusion and exclusion criteria are listed in the protocol. Details of any inclusion/exclusion criteria not met will be provided in a listing for the Enrolled Set.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) drug dictionary, initially dated September 2022. The dictionary will be updated throughout the life of the study so that the latest version is used.

A prior medication is defined as any medication that is started and stopped prior to the date of first dose of study drug. For partially missing dates, the imputations defined in Section 4.1 will be used. The total number of prior medications and the number and percentages of participants with at least one prior medication will be summarized by treatment group. The number and percentages of all prior medications will be summarized by treatment group and listed by Anatomical Therapeutic Chemical (ATC) level 2 and Preferred Name.

A concomitant medication Is defined as any existing therapy ongoing at the time of first dose of study drug, or any changes to existing therapies during the course of the study, or any new therapies the participant received since the date of first dose of study drug. For partially missing dates, the imputations defined in Section 4.1 will be used. A medication with missing stop date will be assumed to be ongoing (and thus concomitant). The total number of concomitant medications and the number and percentages of participants with at least one concomitant medication will be summarized by treatment group. The number and percentages of all concomitant medications will be summarized by treatment group and listed by ATC level 2 and Preferred Name for SAS.

The same analysis for prohibited medications will also be provided for SAS.

All medications will be listed for the SAS, with an indicator for Prior/Concomitant, and prohibited medications flagged.

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7.2. Study Treatments

7.2.1. Study Drug Interruption

Interruption of treatment is defined as missing study drug for ≥ 3 consecutive days and/or any study drug interruption due to an AE, AESI or SAE. A summary of the number of participants with at least a study drug interruption will be presented overall, for the SAS. In addition, where a participant has a study drug interruption, the number of participants for each reason the study drug was interrupted will be displayed.

7.2.2. Treatment Exposure and Dose Intensity

7.2.2.1. Duration of Treatment

Overall duration of each treatment, in days, will be calculated for each participant in each treatment group. The Day 1 dispensed date will be considered as the date of first dose of study drug. The last date of dose is defined as the last day a participant received drug, as collected on the End of Treatment CRF.

If the date of last dose of study treatment is missing, i.e., participant lost to follow-up, the date of study drug administration and the date of last dose prior to study visit (e.g. latest bottle return date), whichever comes later, will be used to calculate duration of treatment. Duration of treatment will be summarized descriptively by treatment group.

Participants randomized to DC-806 or placebo at Day 1 will have their duration of treatment derived as:

Duration of study drug exposure (days) = Date of last dose – date of first dose + 1.

7.2.2.2. Summary of Dosing

The number of tablets taken for each participant will be determined using the EDC data and is defined as:

Number of Tablets Taken = Number of Tablets Dispensed – Number of Tablets Returned - Number of Tablets Missing

The number of tablets dispensed, tablets returned, tablets missing, tablets taken, bottles dispensed, and bottles not returned will be summarized descriptively by treatment group for overall treatment period, by bottle type (AM/PM).

7.2.2.3. Adherence to Study Drug

Adherence to study drug will be assessed based on tablet counts collected in electronic data capture (EDC).

The level of adherence to the study drug will be derived for each dispensed visit and overall treatment period. The level of adherence (%) for every dispense visit and overall, for each participant, will be computed as: 100 times the total number of tablets taken (the total number of tablets dispensed - the total number of tablets returned - number of tablets missing) over each dispense period or overall treatment period, divided by the intended total number of tablets that should have been taken over the same period.

$$\text{Level of Adherence (\%)} = \left(\frac{\text{Total Number of Tablets Taken}}{\text{Total Number of Intended Tablets}}\right) \times 100$$

For participants who discontinue early, the level of adherence will be assessed through the time of their discontinuation. If a bottle is dispensed and the bottle is returned empty, then the number of tablets returned will be entered as zero. If a bottle is dispensed but not returned (missing), then all records for that dispense period for that study drug will be excluded (i.e., excluded from both denominator and numerator) when calculating level of adherence (%).

Descriptive statistics for the level of adherence (n, mean, SD, median, minimum, and maximum) with the number and percentage of participants belonging to the following adherence categories will be summarized by treatment groups for the SAS:

- $< 80\%$
- $\geq 80\%$ - $\leq 90\%$
- $> 90\%$ - $\leq 100\%$
- $> 100\%$ - $\leq 120\%$
- $> 120\%$.

A by-participant data listing of study drug administration and interruption will be provided including administration date, dose administration status and reason for not administration, dose interruption status and reason for not administration along with dates of dose interruption, and number of missed doses. In addition, another by-participant data listing of study drug accountability records will be provided, including kit number, dispensed/returned dates, bottle number, is bottle returned, number of tablets dispensed, returned, and missing, suspected medication error (i.e., missing ≥3 consecutive days of dosing) and/or overdose occurred, number of tablets taken and level of adherence (%).

8. Efficacy Analysis

		Main Estimation			
	Estimand Description	**Analysis Set**	**Intercurrent Events**	**Analysis Model/Method**	**Sensitivity and Supplementary Analyses**
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 or emollients, or bland shampoos, as needed and regardless of treatment interruption.	FAS	Receiving any prohibited medication* or discontinuing the treatment due to related adverse event or requirement for prohibited medication* ➔ Composite strategy Discontinuing the treatment due to any other reason è Hypothetical strategy Treatment interruption è Treatment policy	Either Fisher's exact or Chi-squared. Participants with no Week 12 data (observed or imputed) will be considered as non-responder.	
Estimand 1b	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 or emollients, or bland shampoos, as needed and regardless of treatment interruption.	FAS	Receiving any prohibited medication* or discontinuing the treatment due to related adverse event or requirement for prohibited medication* ➔ Composite strategy Discontinuing the treatment due to any other reason ➔ Hypothetical strategy Treatment interruption è Treatment policy	Participants with no Week 12 data (observed or imputed) will be considered as non-responder.  b) A logistic regression model will be performed with PASI-	

				75 at Week 12 as binary response and treatment, baseline PASI score (as a continuous covariate) as covariates. The following additional covariates will be tested in the model using backward elimination with a significance level of 0.2 to retain the covariates in the model: age, BMI and weight as continuous covariates, sex, previous biologic therapy and geographic region as discrete covariates. At the very least, previous biologic therapy and geographic region will be retained in the model. The conditional odds ratio, with Placebo as reference group, and their corresponding 2-sided 95% CI will be presented.	
Estimand 2a	This estimand is intended to provide a population-level estimate of the incidence proportion of TEAEs.	SAS	While at risk strategy will be used where the period considered is defined up to the end of the follow up.	TEAE incidence proportion (proportion of participants with TEAE).	None
Estimand 2b	This estimand is intended to provide a population-level estimate of the incidence proportion of SAEs.	SAS	While at risk strategy will be used where the period considered is defined up to the end of the follow up.	SAE incidence proportion (proportion of participants with SAE).	None
Estimand 2c	This estimand is intended to provide a population-level estimate of the incidence proportion of TEAEs leading to permanent treatment discontinuation.	SAS	While at risk strategy will be used where the period considered is defined up to the treatment discontinuation.	TEAE leading to permanent treatment discontinuation incidence proportion (proportion of participants with TEAE).	None
Estimand 3a / 3b	This estimand is intended to provide a population-level estimate of the anti-psoriatic	Same as Estimand 1a/1b without the logistic regression.			

	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.	<u>Additional supplementary analysis:</u> 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 two-sided p-value test against either an increasing or decreasing alternative will be provided			
Estimand 4a / 4b	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.	Same as Estimand 1a/1b with sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline.			
Estimand 5a, 5b, 5c, 5d	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 scheduled timepoints up to Week 12 without the benefit of other background anti-psoriasis therapy regardless of the use of topical bland moisturizers or emollients, or bland shampoos,	FAS	Receiving any prohibited medication* or discontinuing the treatment due to related adverse event or requirement for prohibited medication* ➔ Composite strategy Discontinuing the treatment due to any other reason è Hypothetical strategy Treatment interruption è Treatment policy	Missing values at each visit will be imputed as non-responder. Generalized estimating equation (GEE) with PASI-50 (a)/PASI-75(b)/PASI-90(c)/PASI-100(d) up to Week 12 as binary response and treatment, visit, baseline PASI score (as a continuous covariate) as covariates and a treatment by visit interaction. The following additional covariates will be tested in the model using backward elimination with a significance	

	as needed and regardless of treatment interruption.			level of 0.2 to retain the covariates in the model: age, BMI and weight as continuous covariates, sex, previous biologic therapy and geographic region as discrete covariates. At the very least, previous biologic therapy and geographic region will be retained in the model. The conditional odds ratio, with Placebo as reference group, and their corresponding 2-sided 95% CI will be presented.	
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 scheduled timepoints up to 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.	Same as Estimand 5 with sPGA score of 0 (clear) or 1 (almost clear).			
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* and	FAS	Receiving any prohibited medication* or discontinuing the treatment due to any reason ➔ Hypothetical strategy Treatment interruption è Treatment policy	MMRM on PASI percentage change from baseline with treatment, visit and PASI score baseline, previous biologic therapy and geographic region as covariates and a treatment by visit interaction. The following additional covariates will be tested in the model using backward elimination with a significance level of 0.2 to retain	CCI

	regardless of treatment interruption.			the covariates in the model: age, BMI and weight as continuous covariates, sex, as discrete covariate.	
Estimand 7b	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* and regardless of treatment interruption.	FAS	Receiving any prohibited medication* or discontinuing the treatment due to any reason è Hypothetical strategy Treatment interruption è Treatment policy	MMRM on PASI absolute change from baseline with treatment, visit and PASI score baseline, previous biologic therapy and geographic region as covariates and a treatment by visit interaction. The following additional covariates will be tested in the model using backward elimination with a significance level of 0.2 to retain the covariates in the model: age, BMI and weight as continuous covariates, sex, as discrete covariate.	CCI
Estimand 8a / 8b	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* and regardless of treatment interruption.	Same as Estimand 7a/7b with BSA percentage change and absolute change from baseline.			

* Prohibited medications are the medications used for treating psoriasis and also having an impact on the efficacy assessment.
Note: previous biologic therapy and geographic region used as covariates will be taken from IRT

8.1. Primary Efficacy Endpoint: Proportion of Participants achieving PASI-75 at Week 12 (Estimands 1a and 1b)

The primary endpoint for estimands 1a and 1b is the proportion of participants achieving at least 75% reduction in PASI score from baseline to Week 12 and is defined as PASI-75 as follows:

Percentage change from baseline in PASI score at Week 12 is defined as:

% change of PASI = 100 * (PASI score at Week 12 - PASI score at Baseline) / PASI score at Baseline.

Thus, PASI-75 at Week 12 is defined as a binary variable such that:
PASI-75 = Responder if % change of PASI ≤ -75%;
Non-responder, otherwise.

The number and proportion of participants achieving PASI-75 at Week 12 with corresponding 95% CI will be presented by treatment group for the FAS.

8.1.1. Estimand 1a

8.1.1.1. Main Analysis Approach

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or requirement for prohibited medication prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for reasons other than related adverse event or requirement for prohibited medication, PASI scores after the treatment discontinuation date will be set to missing (Hypothetical strategy). If a participant experienced any treatment interruption, PASI score reported after the treatment interruption will be used as reported (Treatment policy).

Participants without Week 12 PASI score (either due to hypothetical strategy implementation or missed visit) will be considered as non-responder.

A 2-sided, 2-sample Fisher's exact or Chi-squared test will be performed to assess a difference between active treatment groups (DC-806) versus Placebo in PASI-75 at Week 12 for the following comparisons on the FAS:

Comparison 1

H_0: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ = PASI-75 at Week 12 $_{\text{Placebo}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ ≠ PASI-75 at Week 12 $_{\text{Placebo}}$

Comparison 2

H_0: PASI-75 at Week 12 $_{\text{DC-806 600mg}}$ = PASI-75 at Week 12 $_{\text{Placebo}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 600mg}}$ ≠ PASI-75 at Week 12 $_{\text{Placebo}}$

Comparison 3

H_0: PASI-75 at Week 12 $_{\text{DC-806 400mg}}$ = PASI-75 at Week 12 $_{\text{Placebo}}$

H_1: PASI-75 at Week 12 $_{\text{DC-806 400mg}} \neq$ PASI-75 at Week 12 $_{\text{Placebo}}$

Comparison 4

H_0: PASI-75 at Week 12 $_{\text{DC-806 200mg}} =$ PASI-75 at Week 12 $_{\text{Placebo}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 200mg}} \neq$ PASI-75 at Week 12 $_{\text{Placebo}}$

The number and percentage of participants who are defined as PASI-75 responder will be presented by treatment group. The p-value and unconditional odds ratio with its corresponding 95% CI will be presented in the active treatment group compared to the placebo group. All comparisons will be performed in a prespecified hierarchical procedure starting from the highest dose regimen to the lowest dose regimen.

8.1.2. Estimand 1b

8.1.2.1. Main Analysis Approach

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or requirement for prohibited medication prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for reasons other than related adverse event or requirement for prohibited medication, PASI scores after the treatment discontinuation date will be set to missing (Hypothetical strategy). If a participant experienced any treatment interruption, PASI score reported after the treatment interruption will be used as reported (Treatment policy).

Participants without Week 12 PASI score (either due to hypothetical strategy implementation or missed visit) will be considered as non-responder.

The number and proportion of participants with PASI-75 with corresponding 95% CI will be presented by treatment group. The p-value, conditional odds ratio with its corresponding 95% CI, strata-adjusted difference in proportions between treatment groups (DC-608 – Placebo) with its corresponding 95% CI based on the large sample approximation method for binary data using

Mantel-Haenszel strata weights (Mantel, Haenszel 1959) and the Sato variance estimator (Sato 1989) will be presented in the active treatment groups compared to the placebo group.

In addition, a logistic regression model will be performed with PASI-75 at Week 12 as binary response and treatment and baseline PASI score (as a continuous covariate) as covariates on the FAS. The following additional covariates will be tested in the model using backward elimination with a significance level of 0.2 to retain the covariates in the model: age, BMI and weight as continuous covariates, sex, previous biologic therapy (Yes/No) (as per IRT) and geographic region (North America/Western Europe vs. Eastern Europe) (as per IRT) as discrete covariates. At the very least, previous biologic therapy and geographic region will be retained in the model. The conditional odds ratio, with Placebo as reference group, their corresponding 2-sided 95% CI and p-value will be presented.

8.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are analyzed as follow:

8.2.1. Proportion of participants in each DC-806 treatment group achieving PASI-75 at Week 12 (Estimand 3a/3b)

The primary endpoint for Estimand 3a/3b is the same as Estimand 1a/1b.

8.2.1.1. Estimand 3a

8.2.1.1.1. Main Analysis Approach

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or requirement for prohibited medication prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for reasons other than related adverse event or requirement for prohibited medication, PASI scores reported after the treatment discontinuation date will be treated as missing (Hypothetical strategy). If a participant experienced any treatment interruption, PASI score reported after the treatment interruption will be used as reported (Treatment policy).
Participants without Week 12 PASI score (either due to hypothetical strategy implementation or missed visit) will be considered as non-responder.

A Fisher's exact or Chi-squared test based on the observed counts will be performed to assess a difference between active treatment groups in PASI-75 at Week 12 for the following comparisons on the FAS:

Comparison 1

H_0: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ = PASI-75 at Week 12 $_{\text{DC-806 200mg}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ ≠ PASI-75 at Week 12 $_{\text{DC-806 200mg}}$

Comparison 2

H_0: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ = PASI-75 at Week 12 $_{\text{DC-806 400mg}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ ≠ PASI-75 at Week 12 $_{\text{DC-806 400mg}}$

Comparison 3

H_0: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ = PASI-75 at Week 12 $_{\text{DC-806 600mg}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 800mg}}$ ≠ PASI-75 at Week 12 $_{\text{DC-806 600mg}}$

Comparison 4

H_0: PASI-75 at Week 12 $_{\text{DC-806 600mg}}$ = PASI-75 at Week 12 $_{\text{DC-806 200mg}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 600mg}}$ ≠ PASI-75 at Week 12 $_{\text{DC-806 200mg}}$

Comparison 5

H_0: PASI-75 at Week 12 $_{\text{DC-806 600mg}}$ = PASI-75 at Week 12 $_{\text{DC-806 400mg}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 600mg}}$ ≠ PASI-75 at Week 12 $_{\text{DC-806 400mg}}$

Comparison 6

H_0: PASI-75 at Week 12 $_{\text{DC-806 400mg}}$ = PASI-75 at Week 12 $_{\text{DC-806 200mg}}$
H_1: PASI-75 at Week 12 $_{\text{DC-806 400mg}}$ ≠ PASI-75 at Week 12 $_{\text{DC-806 200mg}}$

The number and percentage of participants who are defined as PASI-75 responder will be presented by active treatment group. The p-value and unconditional odds ratio with its corresponding 95% CI will be presented in the lower dose treatment group compared to the higher dose treatment group.

All comparisons will be performed in a prespecified hierarchical procedure starting from the highest dose regimen to the lowest dose regimen.

8.2.1.1.4. Additional Supplementary Analyses

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 two-sided p-value test against either an increasing or decreasing alternative will be provided.

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or requirement for prohibited medication prior to Week 12 visit or participants with missing Week 12 PASI score will be considered as a non-responder.

8.2.1.2. Estimand 3b

8.2.1.2.1. Main Analysis Approach

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or requirement for prohibited medication prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for reasons other than related adverse event or requirement for prohibited medication, PASI scores reported after the treatment discontinuation date will be treated as missing (Hypothetical strategy). If a participant experienced any treatment interruption, PASI score reported after the treatment interruption will be used as reported (Treatment policy).

Participants without Week 12 PASI score (either due to hypothetical strategy implementation or missed visit) will be considered as non-responder.

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The number and proportion of participants with PASI-75 with corresponding 95% CI will be presented by active treatment group. The p-value, conditional odds ratio with its corresponding 95% CI, strata-adjusted difference in proportions between active treatment groups and its corresponding 95% CI based on the large sample approximation method for binary data using Mantel-Haenszel strata weights (Mantel, Haenszel 1959) and the Sato variance estimator (Sato 1989) will be presented.

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8.2.2. Proportion of participants achieving a sPGA score of 0 or 1 with ≥2 grade improvement from Baseline at Week 12 (Estimands 4a and 4b)

Participants with sPGA score of 0 or 1 with ≥2 grade improvement from baseline will be plotted over time by treatment group.

8.2.2.1. Main Analysis Approach

Similar methods and intercurrent event strategies as applied in the main analysis provided for Estimand 1a/1b analysis will be used to evaluate proportion of participants achieving a sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at Week 12 on FAS. (see Sections 8.1.1.1 and 8.1.2.1).

8.2.3. Proportion of participants achieving ≥50%, ≥75%, ≥90%, and 100% reduction in PASI score (PASI-50, PASI-75, PASI-90, and PASI-100, respectively) at scheduled timepoints (Estimands 5a, 5b, 5c, 5d)

8.2.3.1. Main Analysis Approach

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or requirement for prohibited medication will be considered as a non-responder at scheduled timepoints following the event (Composite strategy). If a participant discontinued treatment for reasons other than related adverse event or requirement for prohibited medication, PASI scores reported after the treatment discontinuation date will be treated as missing (Hypothetical strategy). If a participant experienced any treatment interruption, PASI score reported after the treatment interruption will be used as reported (Treatment policy).
Participants without PASI score at each scheduled visit (either due to hypothetical strategy implementation or missed visit) will be considered as non-responder.

The following analyses will be performed using generalized estimating equation (GEE) as an extension of the logistic regression model with treatment, visit and baseline PASI score (as a continuous covariate) as covariates and a treatment by visit interaction. The following additional covariates will be tested in the model using backward elimination with a significance level of 0.2 to retain the covariates in the model: age, BMI and weight as continuous covariates, sex, previous biologic therapy (Yes/No) (as per IRT) and geographic region (North America/Western Europe vs. Eastern Europe) (as per IRT). At the very least, previous biologic therapy and geographic region will be retained in the model. Of note, visits from the earliest timepoint with at least one responder will be included in the model. e.g. if the first responder is on Day 15, all GEE models will include visits from Day 15.

- Participants achieving ≥50% reduction in PASI score (PASI-50) at scheduled timepoints up to Week 12 by treatment group for the FAS. (Estimand 5a)
- Participants achieving ≥75% reduction in PASI score (PASI-75) at scheduled timepoints up to Week 12 by treatment group for the FAS. (Estimand 5b)
- Participants achieving ≥90% reduction in PASI score (PASI-90) at scheduled timepoints up to Week 12 by treatment group for the FAS. (Estimand 5c)
- Participants achieving 100% reduction in PASI score (PASI-100) at scheduled timepoints up to Week 12 by treatment group for the FAS. (Estimand 5d)

The conditional odds ratio, with placebo as reference group, and their corresponding 2-sided 95% CI will be presented.

In case of non-convergence, unadjusted odds ratio will be estimated separately for each scheduled timepoint.

Proportion of participants with PASI-50, PASI-75, PASI-90, and PASI-100 based on descriptive statistics with observed values will be plotted over time by treatment group.

8.2.4. Proportion of participants achieving a sPGA score of 0 or 1 at Scheduled Timepoints (Estimand 6)

Proportion of participants with sPGA score of 0 or 1 with ≥2 grade improvement at scheduled timepoints up to Week 12 from Baseline will be plotted by treatment group.

8.2.4.1. Main Analysis Approach

Similar methods and intercurrent event strategies as applied in the main analysis provided for Estimand 5 analysis will be used to evaluate proportion of participants achieving a sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline at scheduled timepoints up to Week 12 on FAS (see Section 8.2.3.1).

8.2.5. Change and percentage change from Baseline in PASI score at scheduled timepoints (Estimands 7a and 7b)

PASI observed scores will be tabulated by treatment group and visit; the corresponding changes from baseline and percentage change from baseline will be summarized.

8.2.5.1. Estimand 7a

The endpoint is the percentage change from baseline in PASI score up until Week 12.

8.2.5.1.1. Main Analysis Approach

A mixed model repeated measures (MMRM) of percentage change from baseline in PASI score up until Week 12, including terms for treatment, visit, baseline PASI score (as a continuous covariate), a treatment by visit interaction with an unstructured (UN) covariance matrix. The following additional covariates will be tested in the model using backward elimination with a significance level of 0.2 to retain the covariates in the model: age, BMI and weight as continuous covariates, sex, previous biologic therapy (Yes/No) (as per IRT) and geographic region (North America/Western Europe vs. Eastern Europe) (as per IRT) as discrete covariates. At the very least, previous biologic therapy and geographic region will be retained in the model. In case of non-convergence of the MMRM with UN covariance structure, the first order heterogeneous autoregressive model [ARH(1)] will be fitted instead; if this model still fails to converge then the number of covariance parameters will be reduced further and the first order autoregressive model [AR(1)] will be fitted.

The difference in mean change and mean percentage change between treatments with 95% CI at each scheduled timepoint will be estimated. The data collected after use of a prohibited medication, or discontinuation of treatment for any reason will be set to missing (Hypothetical strategy). The FAS will be used for this analysis. The MMRM analysis will assume a missing-at-random (MAR) mechanism for missing data.

The least-square (LS) mean for change from baseline and percentage change from baseline in PASI score at each time point will be presented for each treatment group until Week 12. Contrasts will be used to compare DC-806 dose regimens versus Placebo at each scheduled visit with the two-sided p-value testing H_1 against H_0.

For example, at Week 12:

Comparison 1

H_0: μ at Week 12 $_{\text{DC-806 800mg}} = \mu$ at Week 12 $_{\text{Placebo}}$
H_1: μ at Week 12 $_{\text{DC-806 800mg}} \neq \mu$ at Week 12 $_{\text{Placebo}}$

Comparison 2

H_0: μ at Week 12 $_{\text{DC-806 600mg}}$ = μ at Week 12 $_{\text{Placebo}}$
H_1: μ at Week 12 $_{\text{DC-806 600mg}}$ ≠ μ at Week 12 $_{\text{Placebo}}$

Comparison 3

H_0: μ at Week 12 $_{\text{DC-806 400mg}}$ = μ at Week 12 $_{\text{Placebo}}$
H_1: μ at Week 12 $_{\text{DC-806 400mg}}$ ≠ μ at Week 12 $_{\text{Placebo}}$

Comparison 4

H_0: μ at Week 12 $_{\text{DC-806 200mg}}$ = μ at Week 12 $_{\text{Placebo}}$
H_1: μ at Week 12 $_{\text{DC-806 200mg}}$ ≠ μ at Week 12 $_{\text{Placebo}}$

where $\mu_{\text{DC-806 xx}}$ and μ_{placebo} denotes the true mean percentage change from baseline in PASI at each scheduled visit for each DC-806 dose regimens and placebo, respectively. (xx= 800mg, 600mg, 400mg, 200mg)

Percentage change from baseline in PASI will be plotted over time by treatment group.

CCI

8.2.5.2. Estimand 7b

8.2.5.2.1. Main Analysis Approach

The endpoint is the change from baseline in PASI score up until Week 12.

Similar methods and intercurrent event strategies as applied in the main analysis provided for Estimand 7a (see Sections 8.2.5.1.1).

CCI

8.2.6. Change and percentage change from Baseline in the percentage of BSA affected at scheduled timepoints (Estimand 8a/8b)

The endpoint is the percentage change from baseline in BSA score up until Week 12 (Estimand 8a) and change from baseline in BSA score up until Week 12 (Estimand 8b).

8.2.6.1. Main Analysis Approach

Similar methods and intercurrent event strategies as applied in the main analysis provided for Estimand 7a/7b analysis will be used (see Sections 8.2.5.1.1 and 8.2.5.2.1).

CCI

8.3.2. Quality of Life Assessments

Proportion of participants achieving BSA ≤1% psoriasis involvement at Week 12 will be analyzed similarly to Estimand 1a/1b (see Sections 8.1.1 and 8.1.2).

DLQI, Itch NRS and Skin Pain NRS observed scores will be tabulated by treatment group and visit; the corresponding changes from Baseline and percentage change from Baseline will be calculated and summarized.
DLQI, Itch NRS and Skin Pain NRS scores' mean (±SD) will be plotted over time by treatment group.

9. Safety Analysis

All safety analysis will be based on the safety analysis set (SAS). Participants will be summarized according to the treatment they actually received.

9.1. Adverse Events

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. For partially missing dates, the imputation rules described in Section 4.1 will be followed, and imputed dates will be used to determine whether an AE is treatment-emergent. If the start date is completely missing, then the AE is considered treatment-emergent if the end date (imputed or not) is on or after the date of first dose. If both the start and end dates are completely missing, then the AE is considered treatment-emergent.

All AEs will be coded using the latest MedDRA version available at the end of the study.

9.1.1. Incidence Proportion of Adverse Events

Intercurrent event strategies described in Section 2.1 will be used.

An overall summary table for the SAS with count and percentage of participants with TEAEs and count of events will include:

- TEAEs
- TEAEs related to study drug
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs leading to treatment discontinuation
- TEAEs by greatest severity
- Serious TEAEs
- Serious TEAEs related to study drug
- TEAEs leading to death
- Deaths

A similar overall summary table will be provided for AESIs.

The incidence proportion of AEs will be summarized in tables with count and percentage of participants with AEs and count of events by SOC and preferred term (PT). Unless otherwise specified, at each level of SOC or PT, a participant with multiple events will only be counted once per SOC or PT. AEs will be displayed by treatment received for the SAS.

The following categories of AE will be summarized by SOC and PT:

- TEAEs
- TEAEs by greatest severity
- TEAEs by relationship
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs leading to treatment discontinuation
- Serious TEAEs
- Serious TEAEs by relationship

The following category of AE will be summarized by PT:

- TEAEs
- AESIs

At each level of SOC or PT, if a participant experiences more than one occurrence of the same AE, the occurrence with the greatest severity and the closest relationship with the study drug will be used in summary tables. All AEs will be presented in tables in descending order from the SOC with the highest total incidence proportion (across all treatment groups) to the SOC with the lowest total incidence proportion. Within each SOC, AEs will be sorted in descending order of PT based on the total of all treatment groups.

Listings of AE, AESI, Serious AE, and AEs that led to study drug discontinuation will be provided for the SAS.

9.1.2. Relationship of Adverse Events to Study Drug

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

- 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

For the purposes of summarizing AEs related to study drug, a relationship of 'Possibly Related' or 'Related' will be considered as related to study drug. A relationship of 'Not related' or 'Unlikely related' will be considered as not related to study drug. If an AEs relationship to study drug is missing, the relationship will be assumed to be 'Related'.

9.1.3. Severity of Adverse Event

The severity of AEs will be graded using the most current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 5-point scale:

- 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

If an AEs severity is missing, the severity will be assumed to be Grade 3 (Severe). If a participant experiences more than one occurrence of the same AE, the occurrence with the greatest severity will be used in summary tables.

9.1.4. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate. The following events will be considered AESIs for this study and will be reported using the same process as for SAEs:

- New onset of inflammatory bowel disease (IBD) including ulcerative colitis or Crohn's disease
- Suicidal ideation

9.2. Clinical Laboratory Evaluations

All summaries will be based on SI units. Blood and urine samples collected at the times indicated in the schedule of events (see Appendix 15.1) for clinical laboratory values (hematology, clinical chemistry, coagulation, urinalysis, and virology) will be analyzed by the central laboratory. COVID-19 testing will be performed on site or by the site's local laboratory. Clinical follicle stimulating hormone tests will be performed by the central laboratory. Additional blood, urine, and/or throat swab samples may be taken for safety tests.

Summary tables presenting observed values and changes from baseline will be presented for clinical laboratory tests with numeric values by treatment group for participants in the SAS. One table will be presented for each of hematology, and clinical chemistry parameter categories. Summary of observed values at screening for coagulation will be presented.

A table for categorical urinalysis values over time and screening virology will also be presented.

The number and proportion of participants with normal, high, and low values for each laboratory test (hematology and clinical chemistry) will be presented by visit and treatment group according to the reference ranges in the Central Lab Manual.

The number and proportion of participants with CTCAE Grades for each laboratory test (hematology and clinical chemistry) will be presented by visit and treatment group.

Shift tables summarizing the baseline and post-baseline timepoints results using normal range and CTCAE grading when available for clinical laboratory tests (hematology and clinical chemistry) will be displayed in cross-tabulations. Only during treatment endpoints are considered in this summary. Unscheduled assessments are included in the table for calculation of minimum post-baseline and maximum post-baseline values.

Corresponding box plots by visit and treatment of the observed values will also be presented for hematology parameters:

- Hemoglobin
- White blood cell count

- Neutrophils
- Lymphocytes
- Platelet count
- Erythrocyte sedimentation rate

and clinical chemistry parameters:

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Total Bilirubin
- creatinine
- C-reactive protein
- Estimated glomerular filtration rate
- Gamma glutamyl transferase
- Lactate dehydrogenase
- Total cholesterol
- High-density lipoprotein cholesterol
- Low-density lipoprotein cholesterol
- Triglycerides

Different colors will be used for the treatment groups.

Laboratory test results for all visits including unscheduled assessments will be presented in a listing for the parameter with at least one abnormal value. The listing will be based of SAS.

9.3. Vital Sign Measurements

Body temperature (ear or oral), respiratory rate, seated blood pressure, and heart rate will be assessed at the times indicated in the schedule of events (see Appendix 15.1). Blood pressure and heart rate will be measured after the participant has been resting quietly for ≥5 minutes. Summary tables presenting observed values and changes from baseline will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (˚C), heart rate (beats/min), and respiratory rate (breaths/minute), by treatment group for participants in the SAS. Changes from baseline to each scheduled post-baseline visit will be presented.

Substantial changes from baseline in clinically significant vital signs results will be presented by treatment group based on the following criteria:

- For Systolic Blood Pressure: High is defined as ≥160 mmHg and increase from baseline>40 mmHg; and Low is defined as <90 mmHg and decrease from baseline >20 mmHg.
- For Diastolic Blood Pressure: High is defined as ≥100 mmHg and increase from baseline>20 mmHg; and Low is defined as <60 mmHg and decrease from baseline >10 mmHg; or and Low* is defined as <60 mmHg and decrease from baseline >20 mmHg.
- For Heart Rate: High is defined as >100 beats/min and increase from baseline>20 beats/min; and Low is defined as <60 beats/min and decrease from baseline >20 beats/min.
- For Respiratory Rate: High is defined as >24 beats/min; and Low is defined as <10 beats/min when baseline is between 10 and 24 beats/min.

- For Temperature, High is defined as ≥38 °C; and Low is defined as <35 °C when baseline is between 35 and 38 (excluded) °C.

Scheduled and unscheduled on-treatment assessments are used in the substantial changes from baseline summary outputs.

Vital Sign results for all visits including unscheduled will be presented in a listing for the parameter with at least one abnormal value. The listing will be displayed for the SAS.

9.4. Physical Examination

A full physical examination will be assessed (see Appendix 15.1) on the 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. The number and proportion of participants with abnormal and normal results and those with assessments not done will be presented for the SAS by assessment, visit and treatment group.

A listing will also be displayed for the SAS.

9.5. Electrocardiogram

Triplicate 12-lead Electrocardiogram (ECG) will be done at the visits specified in the schedule of events (see Appendix 15.1). Summary tables will be presented for PR Interval (msec), QRS Duration (msec), QT Interval (msec), and QTcF interval (msec) by treatment group for participants in the SAS. For triplicate ECGs, the average of the triplicate values will be used to determine the value at that time point. The shift of the overall ECG interpretation from baseline over time will be summarized for the SAS. For triplicate ECGs, the best interpretation of the triplicate values at pre-dose on Day 1 will be used; the worst interpretation of the triplicate values will be used at each post-baseline time point.

Substantial changes from baseline in clinically significant electrocardiogram results will be presented by treatment group based on the following criteria:

- QT Interval: New > 450 / New > 480 / New > 500 / Increase from baseline > 30 / Increase from baseline > 60
- QTcF Interval: New > 450 / New > 480 / New > 500 / Increase from baseline > 30 / Increase from baseline > 60
- QRS Duration: Increase > 25% and to a value > 110
- PR Interval: Increase > 25% and to a value > 200

Note: the average value will be used for substantial changes if triplicate ECGs were performed.
Scheduled and unscheduled on-treatment assessments are used in the substantial changes summary outputs.

A corresponding listing on abnormal ECG results for the SAS will also be presented.

9.6. Pregnancy Testing

To ensure participant safety, each pregnancy must be reported to Sponsor within 24 hours of learning of its occurrence and the study drug must be discontinued. Serum and urine pregnancy

tests will be performed for female participants only at the visits specified in the schedule of events (see Appendix 15.1). Pregnancy test results will be presented in a listing for the SAS.

9.7. 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 (five subtypes of suicidal ideation, five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent). 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. The C-SSRS assessments will be done at the visits specified in the schedule of events (see Appendix 15.1). Summary table of the scores for suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent and suicide-related treatment-emergent events will be presented by the worst score for the SAS by treatment group. Shift tables for categories (No suicidal ideation or behavior/Suicidal ideation/Suicidal behavior) and suicidal ideation Scores will also be presented. Only during treatment endpoints including unscheduled assessments are used in the summary outputs.

Two listings (complete and simplified) will be displayed for the SAS.

10. Pharmacokinetics

Plasma samples for concentration of DC-806 obtained from participants who receive DC-806 at various time the following timepoints after the first administration of study drug will be analyzed for the concentration of DC-806 by a validated method:

Day 1: pre-dose, 0.5h, 1h;
Day 8: pre-dose;
Day 15: pre-dose, 0.5h, 1h, 4h;
Day 29: pre-dose;
Day 57: pre-dose, 0.5h, 1h, 4h;
Day 85: 12 h after Day 84 evening dose.

Individual plasma concentrations will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, median, minimum, and maximum) by treatment group, study day and time point.

Individual plasma concentrations will be plotted by actual time on both linear and semi-logarithmic scales. Mean plasma concentrations will be plotted by treatment group on both linear and semi-logarithmic scales with all treatment groups overlaid on the same plots.

Standard PK parameters will be derived by noncompartmental analysis using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ) if sufficient data are available. The following PK parameters will be calculated for DC-806, where data permits: including trough concentration (Pre-dose concentration, C_{trough}). Descriptive statistics will be presented for the analysis.
Summary statistics will be tabulated for maximum observed concentration (C_{max}) and time to attain maximum observed plasma (t_{max}) on Day 1, 15 and 57, Area under the curve from pre-dose to 4-hour post-dose (AUC_{0-4}) on Day 15 and 57 and C_{trough} levels will be reported on day 1,8,15, 29 and 57 schedule of visits (see Appendix 15.1) for the PK Set.

C_{trough}	Concentration at the end of the dosing interval (pre-dose concentration following the first dose, on Days 8, 15, 29 and 57).
C_{max}	Maximum observed concentration (Day 1, 15 and 57).
t_{max}	Time of maximum observed concentration.
AUC_{0-4}	The area under the concentration time curve from time zero to time 4 hours post-dose (Day 15 and 57)

Actual sampling times will be used for the estimation of PK parameters.

Plasma PK parameters will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) by study day.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics. For PK analysis, all BLQ values will be treated as zero, with the exception of BLQ values observed between 2 quantifiable concentrations which will be set to missing.

All PK outputs will be based on the PK Set. Data rounding specifications for PK data are documented in the PK TLF shells.
A listing of all plasma samples collected will also be presented.

11. Pharmacodynamics

These analyses are outside the scope of the study SAP.

12. Changes from the Planned Analysis

No change.

14. References

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15. Appendices

15.1. Schedule of Study Procedures

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

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
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
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	
Clinical 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. Clinical human chorionic gonadotropin testing will be performed centrally to verify urine test results. All WOCBP must have a negative clinical 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 clinical 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.

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.

15.2. PASI (Psoriasis Area and Severity Index score assessment)

The PASI quantifies the severity of a participant's psoriasis based on both, "lesion severity" and the "percent of body surface area (BSA)" affected. PASI is a composite scoring by the investigator of degree of erythema, induration, and scaling (each scored separately) for each of 4 body regions (head and neck, upper limbs, trunk [including axillae and groin], and lower limbs [including buttocks]), with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.
The PASI score ranges from 0 (no psoriasis on the body) to 72 (the most severe case of psoriasis), with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The sum of severity scores for erythema, thickness, and scaling is multiplied by the degree of involvement for each anatomic region, and then multiplied by a constant corresponding to the region's percentage of body surface area (0.1, 0.3, 0.2, and 0.4 for the above 4 regions, respectively). The resultant values for each anatomic region are then summed to yield the PASI score. The PASI score will be set to missing if any severity score or degree of involvement is missing.
To be classified as a PASI-75 responder, a participant must achieve a ≥ 75% improvement from baseline. Percentage change from baseline will be rounded to one decimal place (i.e., xx.x%) and then compared to 75% to determine whether the required improvement is achieved.

The following formula is used to calculate the PASI score:
$PASI = 0.1 (E_h + I_h + S_h) A_h + 0.2 (E_u + I_u + S_u) A_u + 0.3 (E_t + I_t + S_t) A_t + 0.4 (E_l + I_l + S_l) A_l$
Where E = erythema, I = induration, S = scaling, A = area score, h = head/neck, u = upper limbs, t = trunk, and l = lower limbs.

15.3. Static Physician's Global Assessment (sPGA)

sPGA scoring system is based on response to treatment as measured by lesion erythema, induration, and scale, with score assignments that range from clear, almost clear, mild, moderate, to severe.

The scores are assigned as follows:

Erythema Score	Evidence
0	No evidence of erythema but post inflammatory hyper/hypopigmentation changes may be present
1	Faint Erythema

2	Light Red Coloration
3	Moderate Red Coloration
4	Bright Red Coloration

Induration Score	**Evidence**
0	No Evidence of Plaque Elevation
1	Minimal plaque elevation, barely palpable
2	Mild plaque elevation, slight but definite plaque elevation, indistinct edge
3	Moderate plaque elevation, elevated with distinct edges
4	Severe plaque elevation, hard/sharp borders

Scaling Score	**Evidence**
0	No Evidence of Scaling
1	Minimal; occasional fine scaling
2	Mild; fine scale predominates
3	Moderate; coarse scale predominates
4	Marked; thick scale predominates

The sPGA score is the average of the erythema, induration and scaling score. The total average score should be rounded to the nearest whole number.

15.4. Body Surface Area of Involvement (BSA)

Body surface area affected by plaque psoriasis (%) will be assessed for each major section of the body (head, trunk, arms, and legs) and will be reported as a percentage of all major body sections combined.

15.5. Itch Numerical Rating Scale (Itch NRS)

The Itch Numerical Rating Scale is an 11-point scale from 0 to 10 to evaluate itch intensity. Participants are asked to rate the overall severity of their itch in the past 24 hours from 0 = 'No itch' to 10 = 'Worst itch imaginable'.

15.6. Skin Pain Numerical Rating Scale (Skin Pain NRS)

The Skin Pain Numerical Rating Scale is an 11-point scale from 0 to 10 to evaluate itch intensity. Participants are asked to rate the overall severity of their itch in the past 24 hours from 0 = 'No pain' to 10 = 'Worst pain imaginable'.

15.7. Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a self-administered questionnaire designed to measure the health-related quality of life of adult participants suffering from a skin disease. The DLQI consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, and school, personal relationships, and treatment. Each question is answered by a tick box: "not at all", "a little", "a lot" or "very much". Each question is scored from 0 to 3 and the scores summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). All questions relate "to the last week".

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score: ☐
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒		Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes ❒ No ❒		Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot ❒ A little ❒ Not at all ❒		

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

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PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Uploaded Signature Image Signature ID: C3FB9D70-CE32-43BC-BA16-1B42BE1A16B7 Using IP Address: 134.238.38.235 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10 January 2024 | 22:40 Viewed: 10 January 2024 | 22:41 Signed: 10 January 2024 | 22:42
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
PPD PPD PPD 21 CFR Part 11 Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: 71F14FEE-17D5-4C79-819B-F9F78CE6B695 Using IP Address: 134.238.38.235 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 10 January 2024 | 22:42 Viewed: 10 January 2024 | 23:06 Signed: 10 January 2024 | 23:11
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: A3243723-06BE-40BF-93DD-1AF2C06803C9 Using IP Address: 192.184.216.145 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10 January 2024 | 23:11 Viewed: 11 January 2024 | 04:21 Signed: 11 January 2024 | 04:23
Electronic Record and Signature Disclosure: Accepted: 11 January 2024 | 04:21 ID: b5a3776d-9b9f-4eed-8b94-671abe841766		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	10 January 2024 | 22:40
Certified Delivered	Security Checked	11 January 2024 | 04:21
Signing Complete	Security Checked	11 January 2024 | 04:23
Completed	Security Checked	11 January 2024 | 04:23

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

PPD has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, POL-00392, Appropriate Use of Electronic Records and Electronic Signatures