Statistical Analysis Plan J5C-MC-FOAB (2.0)

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study of LY4100511 (DC-853) for the Treatment of Adult Participants with Moderate-to-Severe Plaque Psoriasis

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

Protocol J5C-MC-FOAB (DCE853201)

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study of LY4100511 (DC-853) for the Treatment of Adult Participants with Moderate-to-Severe Plaque Psoriasis

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Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AM	Ante Meridiem
AR(1)	First order Autoregressive Model
ARH(1)	First order Heterogeneous Autoregressive Model
AST	Aspartate Aminotransferase
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
CTCAE	Common Terminology Criteria for Adverse Events
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
IAC	Internal Assessment Committee
IBD	Inflammatory Bowel Disease
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council for Harmonization
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
PRO	Patient Reported Outcome
PT	Preferred Term
PT-INT	Prothrombin Time International Normalized Ratio
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
SE	Standard Error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
sPGA	static Physician's Global Assessment
TBL	Total Bilirubin
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 LY4100511 in participants with moderate to severe plaque psoriasis. 220 participants who meet the eligibility criteria will be enrolled across 55 to 60 study sites in a CCI in 4 treatment groups (3 LY4100511 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 et al. 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 (WHO 2016).

LY4100511 is an orally administered small-molecule inhibitor of the cytokine IL-17A being developed as a potential oral therapy for the treatment of psoriasis.

Study J5C-MC-FOAB (DCE853201) referred to as FOAB in participants with psoriasis will provide evidence of clinical activity of LY4100511 in a relevant disease population and will facilitate dose selection 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-17A signaling pathway are currently available and highly efficacious in the treatment of psoriasis. Thus, it is feasible that psoriasis participants treated with LY4100511 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. An Internal Assessment Committee (IAC) will review the interim efficacy, safety, and PK (pharmacokinetics)/PD (pharmacodynamics) data in an unblinded fashion. An ad-hoc IAC may be convened for reviewing safety data in an unblinded fashion. This document does not fully cover the details of the planned analyses for the IAC. Details about IAC membership, purpose, responsibilities, and operations will be described in an IAC charter, which will be approved prior to the first IAC meeting.

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 Amendment [b], 18 Mar 2025.
- Electronic case report form (eCRF) 08 May 2025.

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. 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 dose regimens of LY4100511 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 LY4100511 versus Placebo on a binary composite responder endpoint (PASI-75) at Week 12 without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers, emollients, or shampoos, as needed. **Target Population:** Adult participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) compared to placebo administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or shampoos, as needed. **Variable:** Responder is defined as achieving ≥75% reduction in Psoriasis Area of Severity Index score (PASI-75) from baseline to 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 anti-psoriatic prohibited medication* (including an alternative therapy for psoriasis and interacting drugs) or discontinuing the treatment due to treatment-related AE or lack of efficacy. (Composite strategy) **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to any other reasons occur. (Treatment Policy strategy) **Population-Level Summary:** Difference in proportion and unconditional odds ratio of participants achieving response between each dosing regimen of LY4100511 and placebo at Week 12 **Estimand 1b:** As above but with conditional odds ratio as population-level summary

* Prohibited medications are the medications used for treating psoriasis which also have an impact on the efficacy assessments.

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 LY4100511 dose regimens in adult participants with moderate to severe plaque psoriasis	Proportion of participants in each LY4100511 treatment group achieving PASI-75 at Week 12	**Estimand 2a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 (pairwise comparison of each dose) on a binary composite responder endpoint (PASI-75) at Week 12 without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers, emollients or shampoos, as needed. **Target Population:** Adult participants with moderate to severe plaque psoriasis **Treatment Conditions:** Pairwise comparison of all 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or shampoos, as needed. **Variable:** Responder is defined as achieving ≥75% reduction in Psoriasis Area of Severity Index score (PASI-75) from baseline to 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 anti-psoriatic prohibited medication* (including an alternative therapy for psoriasis and interacting drugs) or discontinuing the treatment due to treatment-related AE or lack of efficacy. (Composite strategy) **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to any other reasons occur. (Treatment Policy strategy) **Population-Level Summary:** Difference in proportion and unconditional odds ratio of participants achieving response between all pairwise dosing regimens at Week 12 **Estimand 2b:** As above but with conditional odds ratio as population-level summary
To compare the efficacy of multiple dose regimens of LY4100511 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 to Week 12	**Estimand 3a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 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 prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers or emollients or bland shampoos, as needed. **Target Population:** Adult participants with moderate to severe plaque psoriasis

		Treatment Conditions: Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) compared to placebo administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or 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 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 to Week 12 or receiving any anti-psoriatic prohibited medication* (including an alternative therapy for psoriasis and interacting drugs) or discontinuing the treatment due to treatment-related AE or lack of efficacy. (Composite strategy) **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to any other reasons occur. (Treatment Policy strategy) **Population-level summary:** Difference in proportion and unconditional odds ratio of participants achieving response between each dosing regimen of LY4100511 and placebo at Week 12 **Estimand 3b:** As above but with odds ratio as population-level summary.
To compare the efficacy of multiple dose regimens of LY4100511 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, respectively) at scheduled timepoints up to 4 weeks after last dose	**Estimand 4a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 versus Placebo on a binary composite responder endpoint (PASI-50) at scheduled timepoints without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers or emollients or bland shampoos, as needed. **Target Population:** Adult participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) compared to placebo administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or shampoos, as needed. **Variable:** Responder is defined as achieving ≥50% reduction in Psoriasis Area of Severity Index score (PASI-50) from baseline to scheduled timepoints up to 4 weeks after last dose without the use of other background anti-psoriasis therapy. Non-responder is defined as not achieving PASI-50 at scheduled timepoints or receiving any anti-psoriatic prohibited medication* (including an alternative therapy for psoriasis and interacting drugs) or discontinuing the treatment due to treatment-related AE or lack of efficacy. (Composite strategy) **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to other reasons occur. (Treatment Policy strategy) **Population-Level Summary:** Odds ratio

		Estimand 4b: As above but with PASI-75 as variable **Estimand 4c:** As above but with PASI-90 as variable **Estimand 4d:** As above but with PASI-100 as variable
To compare the efficacy of multiple dose regimens of LY4100511 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 with ≥2 grade improvement from Baseline at scheduled timepoints up to 4 weeks after last dose	**Estimand 5:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 versus Placebo on a binary composite responder endpoint (sPGA score of 0 [(clear)] or 1 [almost clear] with ≥2 grade improvement from Baseline) at scheduled timepoints without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers or emollients or bland shampoos, as needed. **Target Population:** Adult participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) compared to placebo administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or 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 to scheduled timepoints up to 4 weeks after last dose 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 to scheduled timepoints up to 4 weeks after last dose or receiving any anti-psoriatic prohibited medication* (including an alternative therapy for psoriasis and interacting drugs) or discontinuing the treatment due to treatment-related AE or lack of efficacy. (Composite strategy) **Strategies for Intercurrent Events:** As though no discontinuations of treatment due to other reasons occur (Treatment Policy strategy) **Population-Level Summary:** Odds ratio
To compare the efficacy of multiple dose regimens of LY4100511 versus placebo on additional efficacy endpoints in adult participants with moderate to severe plaque psoriasis	Change and percent change in PASI score from baseline to scheduled timepoints up to 4 weeks after last dose	**Estimand 6a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 on a continuous endpoint PASI at scheduled timepoints, as though no discontinuations of treatment due to treatment-related AE or lack of efficacy, or intake of anti-psoriatic prohibited medications* allowing for use of topical bland moisturizers, emollients, or shampoos, as needed. **Target Population:** Participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) compared to placebo administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or shampoos, as needed.

		Variable: Change in PASI score from baseline to scheduled timepoints up to 4 weeks after last dose. **Strategies for Intercurrent Events:** For participants receiving any anti-psoriatic prohibited medication* (including an alternative therapy for psoriasis and interacting drugs) or discontinuing the treatment due to treatment-related AE or lack of efficacy, data occurring after the ICE will be set to missing and assumed missing at random (MAR) (Hypothetical strategy). For all other discontinuation of treatment reasons, data will be analyzed regardless (Treatment Policy strategy). **Population-Level Summary:** Difference in means **Estimand 6b:** as above but for percent change in PASI score from baseline as variable.
To compare the efficacy of multiple dose regimens of LY4100511 versus placebo on additional efficacy endpoints in adult participants with moderate to severe plaque psoriasis	Change and percent change in the percentage of BSA affected from baseline to scheduled timepoints up to 4 weeks after last dose	**Estimand 7a:** This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 on a continuous endpoint BSA at scheduled timepoints, as though no discontinuations of treatment due to treatment-related AE or lack of efficacy, or intake of anti-psoriatic prohibited medications* allowing for use of topical bland moisturizers, emollients, or shampoos, as needed. **Target Population:** Adult participants with moderate to severe plaque psoriasis **Treatment Conditions:** Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) compared to placebo administered orally 4 tablets each morning and 4 tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or shampoos, as needed. **Variable:** Change in BSA score from baseline to scheduled timepoints up to 4 weeks after last dose. **Strategies for Intercurrent Events:** For participants receiving any anti-psoriatic prohibited medication* (including an alternative therapy for psoriasis and interacting drugs) or discontinuing the treatment due to treatment-related AE or lack of efficacy data occurring after the ICE will be set to missing and assumed MAR (Hypothetical strategy). For all other discontinuation of treatment reasons, data will be analyzed regardless (Treatment Policy strategy). **Population-Level Summary:** Difference in means **Estimand 7b:** as above but for percent change in BSA score from baseline as variable
To compare the safety and tolerability of multiple doses of LY4100511 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 8a:** This estimand is intended to provide a population-level estimate of the incidence proportion of treatment-emergent adverse events (TEAEs) **Target Population:** Adult participants with moderate to severe plaque psoriasis. **Treatment Conditions:** Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) compared to placebo administered orally 4 tablets each morning and 4

		tablets each evening for 12 weeks, allowing for use of topical bland moisturizers, emollients, or 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 8b:** As above but with SAE as variable. **Estimand 8c:** As above but with TEAEs leading to permanent treatment discontinuation as variable.
To assess the PK of LY4100511 and intersubject variability in adult participants with moderate to severe plaque psoriasis	Measurement of plasma concentration of LY4100511 at scheduled timepoints	Measurement of plasma concentration of LY4100511 at scheduled timepoints to evaluate steady state maximum concentration ($C_{max,ss}$) and trough concentration ($C_{trough,ss}$) and associated intra-individual variability.

* 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 6.9.1 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 LY4100511 on additional efficacy endpoints in adult participants with moderate to severe plaque psoriasis	Time to First PASI-75 response
To assess the efficacy of LY4100511 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 LY4100511 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 LY4100511 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 LY4100511 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 effect of LY4100511 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-17A and related pathways
To assess exposure-response relationships of LY4100511	• Analyses to explore relations between LY4100511 exposures and efficacy endpoints/pharmacodynamic (PD) biomarker responses

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 2, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to evaluate LY4100511 in adult participants with moderate-to-severe plaque psoriasis.

The approximate duration of the study is up to 20 weeks (142 days), which includes a

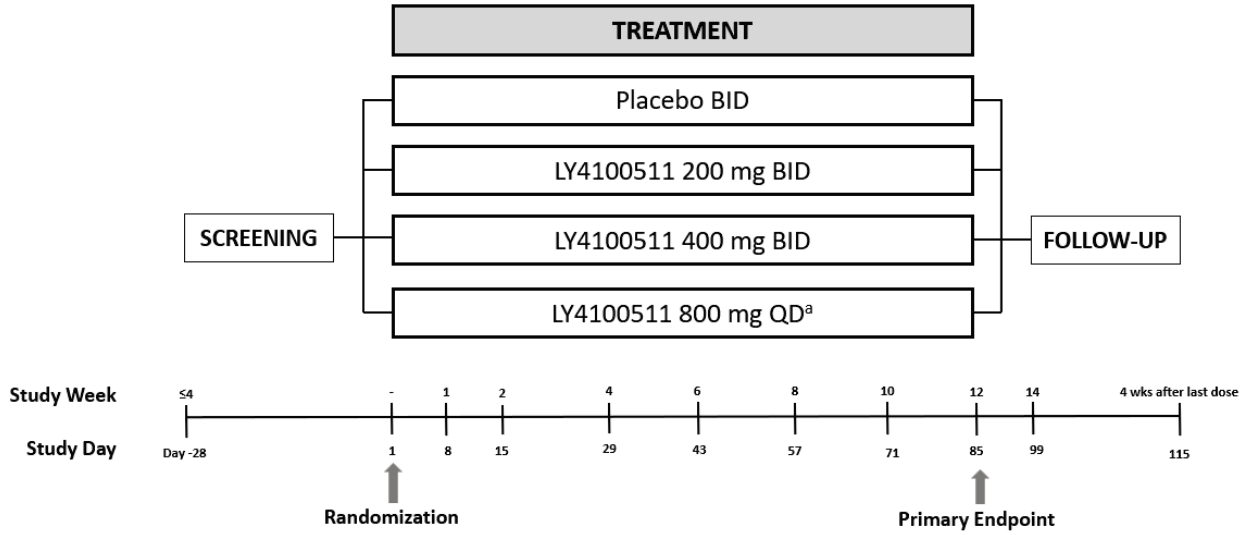
- Screening period: 4 weeks (28 days)
- Treatment period: 12 weeks (84 days), and
- Follow-up period: 4 weeks after last dose (30 days).

This study will evaluate the efficacy, safety, tolerability, and PK of multiple oral doses of LY4100511 in participants with moderate to severe plaque psoriasis.

220 participants who meet eligibility criteria will be randomly allocated in a CCI to 1 of 4 treatment groups. Randomization will be stratified by CCI (Yes/ No) and CCI.

Participants will complete visits for efficacy, safety, PK, and/or PD evaluations on Days 1, 8, 15, 29, 43, 57, 71, and 85, and at Follow-up (Days 99 and 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 LY4100511 is a novel investigational agent with immunomodulatory effects, systemic immunosuppressant agents will be discontinued before dosing to maximize participant safety. Further, to determine whether LY4100511 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.



Abbreviations: BID = twice daily; QD = once daily; wk = week.
[a] Matching placebo administered in the evening.

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	
			LY4100511	Placebo
1	200	Twice daily	55	0
2	400	Twice daily	55	0
3	800	Once daily[a]	55	0
4	Placebo	Twice daily	0	55
Total Approximate Number of Participants			**165**	**55**
			220	

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 number of participants (N) in 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. Baseline data will not be imputed if missing. When data are reported by visit, actual values will be presented regardless of missing baseline data, while changes from baseline analyses require that both baseline and the visit of interest are non-missing.

Unless specified otherwise, all summary and analysis tables will be presented by treatment groups (LY4100511 dose regimens and placebo). Listings of individual participant data will also be produced.

For handling of intercurrent events, non-intercurrent events, and handling of additional missing data, see Section 8, Table 1.

4.1. Date Imputations

Incomplete dates for AEs, prior and concomitant medications/procedures, as well as last dose date 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, and last dose date:
  - 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 220 participants with moderate to severe plaque psoriasis, with approximately 55 participants each to 1 of 3 LY4100511 dose regimens and approximately 55 participants to placebo.

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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.

Participants will be randomly allocated CCI to 1 of 3 LY4100511 dose regimens or placebo, using a stratified, permuted block randomization. Randomization will be stratified by CCI and CCI.

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 LY4100511 or matching placebo. For each dose strength, LY4100511 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 LY4100511. 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. 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 interim efficacy, safety, and PK/PD analyses. 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 Analysis Set

All participants who are randomly assigned a study intervention. Participants will be analyzed according to the treatment group to which they were randomly assigned.

4.4.3. Full Analysis Set (FAS)

All participants who are randomly assigned a study intervention who take at least 1 dose of the double-blind study intervention. Participants will be analyzed according to the treatment group to which they were randomly assigned. All efficacy analyses will be performed using this population.

4.4.4. Safety Analysis Set (SAS)

All participants who are randomly assigned a study intervention who take at least 1 dose of the double-blind study intervention. Participants will be analyzed according to the intervention they receive. If participants receive multiple interventions, the intervention with the highest dose that participants actually receive will be used as an actual intervention. All safety analyses will be performed using this population.

4.4.5. Pharmacokinetics Analysis Set (PKS)

All participants randomly assigned a study intervention and who take at least 1 dose of study intervention and have PK data available. Analyses using the PK populations will group participants according to treatment received. When subjects experience issues which may affect exposure to study drug (e.g., dosing errors etc.), data will be reviewed by the study pharmacokineticist in conjunction with the Sponsor and evaluated for exclusion from the PK analysis set on a case-by-case basis. All data excluded from the PK analysis set will be documented in the data listings.

4.4.6. Biomarker Analysis Set (BMS)

The Biomarker set will consist of all participants who received any study drug (LY4100511 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 of participants who were enrolled, randomized, and screen-failed, as well as the number and percent of 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 7.2.1.1).

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

The number of participants who discontinue treatment will be summarized by treatment group and discontinuation reason as collected on the End of Treatment CRF. In each group, the mean, SD, median, minimum, and maximum time to discontinuation will be presented. Additionally, swimmer plots will be created, comprised of participants who discontinued treatment during the

study, grouped by treatment group and labeled according to reason for discontinuation. Tables and figures will be presented for participants in both the FAS and SAS.

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), baseline 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, Other, Multiple, Not Reported, and Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown), any psoriasis flare in the last 3 months (Yes, No), CCI (Yes, No) collected both in CRF and IRT, and CCI collected in IRT and integrated into the EDC. Percentages will be based on the total number of participants in the FAS.

Summary of difference in CCI (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, and Fitzpatrick Scale of Skin Phototypes will be summarized using descriptive statistics for the FAS. Corresponding listings will also be displayed for the FAS.

Further details of PRO (participant reported outcome) 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 27.1. 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 the 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. Baseline Substance Use

Baseline substance use including current and past smoking status, and caffeine and alcohol intake will be summarized for the SAS.

6.5. 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 and Procedures

Medications will be coded using the World Health Organization (WHO) drug dictionary and procedures will be coded using the MedDRA. The dictionaries will be updated throughout the life of the study so that the latest versions are 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 4 and Preferred Name for the SAS.

A prior procedure is defined as any procedure that is started and completed 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 procedures and the number and percentages of participants with at least one prior procedure will be summarized by treatment group. The number and percentages of all prior procedures will be summarized by treatment group and listed by System Organ Class and Preferred Term for the SAS.

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 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 4 and Preferred Name for the SAS.

A concomitant procedure is defined as any procedure ongoing at the time of first dose of study drug, or any changes to existing procedures during the study, or any new procedures the participant received since the date of first dose of study drug. The total number of concomitant procedures and the number and percentages of participants with at least one concomitant procedure will be summarized by treatment group. The number and percentages of all concomitant procedures will be summarized by treatment group and listed by System Organ Class and Preferred Term for the SAS .

Prohibited medications and anti-psoriatic prohibited medications will be identified through a medication review by the sponsor prior to database lock. For listings of prohibited and permitted medications, see Protocol Sections 6.9.1 and 6.9.2, respectively.

The total number of prohibited medications, the number and percentages of participants with at least one prohibited medication, and the ATC level 4 and Preferred Names will be summarized by treatment group for the SAS, while anti-psoriatic prohibited medications will be summarized similarly but using the FAS.

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

Additionally, psoriasis treatment history of participants with at least one treatment history will be summarized by ATC level 4 and Preferred Name. Percentages will be calculated based on number of participants in the SAS, and summaries will be provided separately for Biologic and Non-Biologic treatments. Listing for the SAS will also be provided.

7.2. Study Treatments

7.2.1. Treatment Exposure and Dose Intensity

7.2.1.1. 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 LY4100511 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.

7.2.1.2. 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).

7.2.1.3. Adherence to Study Drug

Adherence to study drug will be assessed based on tablet counts collected in interactive response technology (IRT).

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, number of tablets taken and level of adherence (%).

8. Efficacy Analysis

Table 1 Estimand Details

		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 LY4100511 versus Placebo on a binary composite responder endpoint (PASI-75) at Week 12 without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers, emollients, or shampoos, as needed.	FAS	Receiving any anti-psoriatic prohibited medication* or discontinuing the treatment due to related adverse event or lack of efficacy ➔ Composite strategy (participants will be imputed as non-responders) Discontinuing the treatment due to any other reason ➔ Treatment policy strategy (observed participant data will be included as is) Any other missing Week 12 data will be imputed using a non-responder imputation (NRI) method, and the missing data will be considered as non-responder.	Fisher's exact test. Participants with no Week 12 data (observed or imputed) will be considered as non-responder.	Sensitivity: Same as main analysis but participants with no Week 12 data will be excluded from the analysis. Supplementary: Same as main analysis but without any censoring or imputing rules.
Estimand 1b	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 versus Placebo on a binary composite responder endpoint (PASI-75) at Week 12 without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to	FAS	Receiving any anti-psoriatic prohibited medication* or discontinuing the treatment due to related adverse event or lack of efficacy ➔ Composite strategy (participants will be imputed as non-responders) Discontinuing the treatment due to any other reason ➔ Treatment policy strategy (observed participant data will be included as is)	a) Cochran-Mantel Haenszel (CMH) test stratified by [redacted] as per IRT (Yes/ No) and [redacted]; strata-adjusted difference in proportions between treatment groups and the 95% CI based on the large sample approximation method for binary data using Mantel-Haenszel strata weights.	Sensitivity: Same as main analysis but participants with no Week 12 data will be excluded from the analysis. Supplementary: Same as main analysis but without any censoring or imputing rules.

	lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers, emollients, or shampoos, as needed.		Any other missing Week 12 data will be imputed using a non-responder imputation (NRI) method, and the missing data 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 and BMI as continuous covariates, and sex as a categorical covariate. The model will be stratified on CCI [redacted] as per IRT (Yes/No) and CCI [redacted] The conditional odds ratio, with Placebo as reference group, and their corresponding 2-sided 95% CI will be presented.	
Estimand 2a / 2b	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 (pairwise comparison of each dose) on a binary composite responder endpoint (PASI-75) at Week 12 without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland	Same as Estimand 1a/1b without the logistic regression. <u>Additional supplementary analysis:</u> A Cochran-Armitage trend test will be conducted to assess a positive trend between LY4100511 dose regimens and PASI-75 at Week 12. The two-sided p-value test against either an increasing or decreasing alternative will be provided				

	moisturizers, emollients, or shampoos, as needed.				
Estimand 3a / 3b	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 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 prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers, emollients, or shampoos, as needed.	Same as Estimand 1a/1b with sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from Baseline.			
Estimand 4a, 4b, 4c, 4d	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 versus Placebo on a binary composite responder endpoint (PASI-50, -75, -90, -100) at scheduled timepoints up to 4 weeks after last dose without the benefit of prohibited concomitant medication or	FAS	Receiving any anti-psoriatic prohibited medication* or discontinuing the treatment due to related adverse event or lack of efficacy ➔ Composite strategy (Participants will be imputed as non-responders at visits following the ICE) Discontinuing the treatment due to any other reason ➔ Treatment policy strategy (observed participant data will be included as is)	Generalized estimating equation (GEE) with PASI-50 (a)/PASI-75(b)/PASI-90(c)/PASI-100(d) up to 4 weeks after last dose as binary response and treatment, visit, CCI [redacted] as per IRT (Yes/No), geographic region (North CCI [redacted] 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	<u>Sensitivity:</u> Same as main analysis with missing values excluded. <u>Supplementary:</u> Same as main analysis but without any censoring or imputing rules.

	discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers, emollients, or shampoos, as needed.		Any other missing Week 12 data will be imputed using a non-responder imputation (NRI) method, and the missing data will be considered as non-responder.	0.2 to retain the covariates in the model: age and BMI as continuous covariates, and sex as a categorical covariate. The conditional odds ratio, with Placebo as reference group, and their corresponding 2-sided 95% CI will be presented.	
Estimand 5	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 versus Placebo on a binary composite responder endpoint (sPGA score of 0 [clear] or 1 [almost clear]) with ≥2 grade improvement from baseline at scheduled timepoints up to 4 weeks after last dose without the benefit of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE, regardless of other treatment discontinuations or the use of topical bland moisturizers, emollients, or shampoos, as needed.	Same as Estimand 4a with sPGA score of 0 (clear) or 1 (almost clear) with ≥2 grade improvement from baseline at scheduled timepoints up to 4 weeks after last dose.			
Estimand 6a	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 on a continuous endpoint	FAS	Receiving any prohibited medication* or discontinuing the treatment due to related adverse event or lack of efficacy ➔	MMRM on PASI percent change from baseline with treatment, visit and PASI score baseline, CCI [redacted] (as per IRT) and CCI [redacted] as covariates and a treatment by visit interaction. The following	<u>Supplementary:</u> Same as main analysis but without any censoring rules.

	(PASI) at scheduled timepoints up to 4 weeks after last dose, allowing for use of topical bland moisturizers, emollients, or shampoos, as needed.		Hypothetical strategy (participant data occurring after the ICE will be set to missing and assumed MAR) Discontinuing the treatment due to any other reason ➔ Treatment policy strategy (observed participant data will be included as is) Missing data will not be imputed, due to MMRM methodology.	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 and BMI as continuous covariates, and sex as a categorical covariate.	
Estimand 6b	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 on a continuous endpoint (PASI) at scheduled timepoints up to 4 weeks after last dose, allowing for use of topical bland moisturizers, emollients, or shampoos, as needed.	FAS	Receiving any prohibited medication* or discontinuing the treatment due to related adverse event or lack of efficacy ➔ Hypothetical strategy (participant data occurring after the ICE will be set to missing and assumed MAR) Discontinuing the treatment due to any other reason ➔ Treatment policy strategy (observed participant data will be included as is) Missing data will not be imputed, due to MMRM methodology.	MMRM on PASI change from baseline with treatment, visit and PASI score baseline, CCI [redacted] (as per IRT) and CCI [redacted] 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 and BMI as continuous covariates, and sex as a categorical covariate.	<u>Supplementary:</u> Same as main analysis but without any censoring or imputing rules.
Estimand 7a / 7b	This estimand is intended to provide a population-level estimate of the anti-psoriatic effect of LY4100511 on a continuous endpoint (BSA) at scheduled timepoints up to 4 weeks after last dose, allowing for use of topical bland moisturizers,	Same as Estimand 6a/6b with BSA change and percent change from baseline.			

	emollients, or shampoos, as needed.				
Estimand 8a	This estimand is intended to provide a population-level estimate of the incidence proportion of TEAEs.	SAS	No intercurrent events will be considered.	Frequencies and percentages of participants will be presented with no formal statistical testing performed. Treatment emergent adverse events include all events that occur on or after the first date of study drug regardless of any intercurrent events.	Not applicable
Estimand 8b	This estimand is intended to provide a population-level estimate of the incidence proportion of SAEs.	SAS	No intercurrent events will be considered.	Frequencies and percentages of participants will be presented with no formal statistical testing performed. Treatment emergent serious adverse events include all events that occur on or after the first date of study drug regardless of any intercurrent events.	Not applicable
Estimand 8c	This estimand is intended to provide a population-level estimate of the incidence proportion of TEAEs leading to permanent treatment discontinuation.	SAS	No intercurrent events will be considered.	Frequencies and percentages of participants will be presented with no formal statistical testing performed. Adverse events leading to permanent treatment discontinuation include all events that occur on or after the first date of study drug regardless of any intercurrent events.	Not applicable

* Prohibited medications are the medications used for treating psoriasis and also having an impact on the efficacy assessments.
Note: CCI [redacted] (as taken from IRT) and CCI [redacted] will be used as covariates

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 anti-psoriatic prohibited medication or discontinuing the treatment due to related adverse event or lack of efficacy prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for any other reason (i.e. not related to the study intervention) PASI score reported after the treatment discontinuation will be used as reported (Treatment policy). Participants without Week 12 PASI score (due to missed visit) will be considered as non-responder.

A 2-sided, 2-sample Fisher's exact test will be performed to assess a difference between active treatment groups (LY4100511) versus Placebo in PASI-75 at Week 12 for the following comparisons on the FAS:

Comparison 1

H_0: PASI-75 at Week $12_{LY4100511\ 800mg}$ = PASI-75 at Week $12_{\ Placebo}$
H_1: PASI-75 at Week $12_{\ LY4100511\ 800mg}$ ≠ PASI-75 at Week $12_{\ Placebo}$

Comparison 2

H_0: PASI-75 at Week $12_{\ LY4100511\ 400mg}$ = PASI-75 at Week $12_{\ Placebo}$
H_1: PASI-75 at Week $12_{\ LY4100511\ 400mg}$ ≠ PASI-75 at Week $12_{\ Placebo}$

Comparison 3

H_0: PASI-75 at Week $12_{\ LY4100511\ 200mg}$ = PASI-75 at Week $12_{\ Placebo}$
H_1: PASI-75 at Week $12_{\ LY4100511\ 200mg}$ ≠ PASI-75 at Week $12_{\ Placebo}$

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.

8.1.1.2. Sensitivity Analyses

Participants without Week 12 PASI score (due to missed visit) will be excluded from the analysis.

The main analysis of estimand 1a will be repeated.

8.1.1.3. Supplementary Analyses

The main analysis will be performed on the observed data without any imputation or censoring rules.

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 lack of efficacy prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for any other reason (i.e. not related to the study intervention) PASI score reported after the treatment discontinuation will be used as reported (Treatment policy). Participants without Week 12 PASI score (due to missed visit) will be considered as non-responder.

Cochran-Mantel-Haenszel (CMH) tests stratified by CCI [redacted] as per IRT (Yes/No) and CCI [redacted] will be performed to assess a difference between active treatment groups (LY4100511) versus Placebo in PASI-75 at Week 12 as mentioned in 8.1.1.1. The CMH tests will be performed on the FAS.

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 (LY4100511– Placebo) with its corresponding 95% CI based on the large sample approximation method for binary data using Mantel-Haenszel strata weights (Mantel, Haenszel 1959) 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 on the FAS. Treatment and baseline PASI score will be included as constant covariates in the model. The following covariates will be tested using backward elimination with a significance level of 0.2 to retain the covariates in the model: Sex, Age and BMI as continuous covariates. The model will be stratified on CCI [redacted] as per IRT (Yes/No) and CCI [redacted]. The conditional odds ratio, with Placebo as reference group, their corresponding 2-sided 95% CI and p-value will be presented.

8.1.2.2. Sensitivity Analyses

Participants without Week 12 PASI score (due to missed visit) will be excluded from the analysis.

The CMH tests in the main analysis of estimand 1b will be repeated.

8.1.2.3. Supplementary Analyses

The main analysis will be performed on the observed data without any imputation or censoring rules.

8.1.3. Efficacy Subgroup Analyses

Subgroup analyses of the estimand 1b main analysis approaches will be made to assess consistency of the intervention effect across the following subgroups:

- Age group (<45, ≥45)
- Sex (Male, Female)
- Ethnicity [Hispanic or Latino (including Not Reported), not Hispanic or Latino]
- Race [White, Non-White (including Multiple and Not Reported)]
- Body mass index (<30, ≥30)
- CCI [redacted] as per IRT (Yes/No)

CCI [redacted]

Descriptive statistics will be provided for each treatment and stratum of a subgroup as outlined, regardless sample size in the FAS. Similar to Estimand 1b, 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 (LY4100511– Placebo) with its corresponding 95% CI will be presented in the active treatment groups compared to the placebo group.

Categorical variable will be analyzed with a logistic regression model that contains the same set of covariates and utilizes the same backward elimination approach as described in Section 8.1.2.1. Note that each model will not include the subgrouping variable of interest as a stratifier or covariate. Within each subgroup category, the conditional odds ratio, with Placebo as reference group, their corresponding 2-sided 95% CI and p-value will be presented.

If the number of participants in any subgroup category is less than approximately 10% of the total population, then the subgroup categories may be redefined prior to unblinding the study. Additional subgroup analyses may be performed as deemed necessary.

8.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are analyzed as follow:

8.2.1. Proportion of participants in each LY4100511 treatment group achieving PASI-75 at Week 12 (Estimand 2a/2b)

The primary endpoint for Estimand 2a/2b is the same as Estimand 1a/1b.

8.2.1.1. Estimand 2a

8.2.1.1.1. Main Analysis Approach

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or lack of efficacy prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for any other reason (i.e. not related to the study intervention) PASI score reported after the treatment discontinuation will be used as reported (Treatment policy). Participants without Week 12 PASI score (due to missed visit) will be considered as non-responder.

A Fisher's exact test 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 $_{\text{LY4100511 800mg}}$ = PASI-75 at Week 12 $_{\text{LY4100511 200mg}}$
H_1: PASI-75 at Week 12 $_{\text{LY4100511 800mg}}$ ≠ PASI-75 at Week 12 $_{\text{LY4100511 200mg}}$

Comparison 2

H_0: PASI-75 at Week 12 $_{\text{LY4100511 800mg}}$ = PASI-75 at Week 12 $_{\text{LY4100511 400mg}}$
H_1: PASI-75 at Week 12 $_{\text{LY4100511 800mg}}$ ≠ PASI-75 at Week 12 $_{\text{LY4100511 400mg}}$

Comparison 3

H_0: PASI-75 at Week 12 $_{\text{LY4100511 400mg}}$ = PASI-75 at Week 12 $_{\text{LY4100511 200mg}}$
H_1: PASI-75 at Week 12 $_{\text{LY4100511 400mg}}$ ≠ PASI-75 at Week 12 $_{\text{LY4100511 200mg}}$

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.

8.2.1.1.2. Sensitivity Analyses

Participants without Week 12 PASI score (due to missed visit) will be excluded from the analysis. The main analysis of estimand 2a will be repeated.

8.2.1.1.3. Supplementary Analyses

The main analysis will be performed on the observed data without any imputation or censoring rules.

8.2.1.1.4. Additional Supplementary Analyses

A Cochran-Armitage trend test will be conducted to assess a positive trend between LY4100511 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 2b

8.2.1.2.1. Main Analysis Approach

A participant receiving any prohibited medication or discontinuing the treatment due to related adverse event or lack of efficacy prior to Week 12 visit will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for any other reason (i.e. not related to the study intervention) PASI score reported after the treatment discontinuation will be used as reported (Treatment policy). Participants without Week 12 PASI score (due to missed visit) will be considered as non-responder.

CMH tests stratified by CCI [redacted] as per IRT (Yes/No) and CCI [redacted] will be performed to assess the statistical significance of a difference between active treatment groups in PASI-75 at Week 12 as mentioned in 8.2.1.1.1. The CMH tests will be performed on the FAS.

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) will be presented.

8.2.1.2.2. Sensitivity Analyses

Participants without Week 12 PASI score (due to missed visit) will be excluded from the analysis. The main analysis of estimand 2b will be repeated.

8.2.1.2.3. Supplementary Analyses

The main analysis will be performed on the observed data without any imputation or censoring rules.

8.2.2. Proportion of participants achieving a sPGA score of 0 or 1 with ≥2 grade improvement from Baseline to Week 12 (Estimands 3a and 3b)

Participants with sPGA score of 0 or 1 with ≥2 grade improvement from baseline will be plotted over time by treatment group. A listing with all sPGA scores will be provided for the FAS.

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 to Week 12 on FAS (see Sections 8.1.1.1 and 8.1.2.1).

8.2.2.2. Sensitivity Analyses

Similar missing data strategy as applied in the sensitivity analyses provided for Estimand 1a/b 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 to Week 12 on FAS. (see Sections 8.1.1.2 and 8.1.2.2).

8.2.2.3. Supplementary Analyses

Similar methods and intercurrent event strategies as applied in the supplementary analyses provided for Estimand 1a/b 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 to Week 12 on FAS. (see Sections 8.1.1.3 and 8.1.2.3).

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 4a, 4b, 4c, 4d)

8.2.3.1. Main Analysis Approach

A participant receiving any anti-psoriatic prohibited medication or discontinuing the treatment due to related adverse event or lack of efficacy at scheduled visits up to 4 weeks after last dose will be considered as a non-responder (Composite strategy). If a participant discontinued treatment for any other reason (i.e. not related to the study intervention) PASI score reported after the treatment discontinuation 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, CCI [redacted] as per IRT (Yes/No), CCI [redacted], 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 and BMI as continuous covariates, and sex as a categorical covariate. 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 4 weeks after last dose by treatment group for the FAS. (Estimand 4a)
- Participants achieving ≥75% reduction in PASI score (PASI-75) at scheduled timepoints up to 4 weeks after last dose by treatment group for the FAS. (Estimand 4b)
- Participants achieving ≥90% reduction in PASI score (PASI-90) at scheduled timepoints up to 4 weeks after last dose by treatment group for the FAS. (Estimand 4c)
- Participants achieving 100% reduction in PASI score (PASI-100) at scheduled timepoints up to 4 weeks after last dose by treatment group for the FAS. (Estimand 4d)

The number and percentage of participants who are defined as PASI-50, PASI-75, PASI-90, and PASI-100 responders will be presented by treatment group.

The conditional odds ratio, with placebo as reference group, and their corresponding 2-sided 95% CI will be presented. In case of non-convergence, the unconditional odds ratio between each active

treatment and placebo will be estimated and Fisher's exact test will be performed 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.

8.2.3.2. Sensitivity Analyses

Participants without PASI score at each scheduled visit (due to missed visit) will be excluded from the analysis.

The main analysis of estimands 4a, 4b, 4c, 4d will be repeated.

8.2.3.3. Supplementary Analyses

The main analyses will also be performed on the observed data without any imputation or censoring rules.

8.2.4. Proportion of participants achieving a sPGA score of 0 or 1 with ≥2 grade improvement from Baseline at scheduled timepoints (Estimand 5)

Proportion of participants with sPGA score of 0 or 1 with ≥2 grade improvement from Baseline at scheduled timepoints up to 4 weeks after last dose 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 4a 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 4 weeks after last dose on FAS (see Section 8.2.3.1).

8.2.4.2. Sensitivity Analyses

Similar missing data strategy as applied in the sensitivity analysis provided for Estimand 4a 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 4 weeks after last dose on FAS (see Section 8.2.3.2).

8.2.4.3. Supplementary Analyses

Similar methods and intercurrent event strategies as applied in the supplementary analysis provided for Estimand 4a 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 4 weeks after last dose on FAS (see Sections 8.2.3.3).

8.2.5. Change and percentage change from Baseline in PASI score at scheduled timepoints (Estimands 6a and 6b)

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 6a

The endpoint is the percentage change from baseline in PASI score at scheduled timepoints up to 4 weeks after last dose on FAS.

8.2.5.1.1. Main Analysis Approach

A mixed model repeated measures (MMRM) of percentage change from baseline in PASI score at scheduled timepoints up to 4 weeks after last dose, 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 as a continuous covariate, and sex as a categorical covariate. 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 due to related adverse event or lack of efficacy will be set to missing (Hypothetical strategy). For all other discontinuation of treatment reasons, available data will be analyzed regardless (Treatment policy 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 up to 4 weeks after last dose. Contrasts will be used to compare LY4100511 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 $_{\text{LY4100511 800mg}} = \mu$ at Week 12 $_{\text{Placebo}}$
H_1: μ at Week 12 $_{\text{LY4100511 800mg}} \neq \mu$ at Week 12 $_{\text{Placebo}}$

Comparison 2

H_0: μ at Week 12 $_{\text{LY4100511 400mg}} = \mu$ at Week 12 $_{\text{Placebo}}$
H_1: μ at Week 12 $_{\text{LY4100511 400mg}} \neq \mu$ at Week 12 $_{\text{Placebo}}$

Comparison 3

H_0: μ at Week 12 $_{\text{LY4100511 200mg}} = \mu$ at Week 12 $_{\text{Placebo}}$
H_1: μ at Week 12 $_{\text{LY4100511 200mg}} \neq \mu$ at Week 12 $_{\text{Placebo}}$

where $\mu_{\text{LY4100511 xx}}$ and μ_{placebo} denotes the true mean percentage change from baseline in PASI at each scheduled visit for each LY4100511 dose regimens and placebo, respectively. (xx= 800mg, 400mg, 200mg)

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

8.2.5.1.2. Supplementary Analyses

The main analysis will be performed on the observed data without any imputation or censoring rules.

8.2.5.2. Estimand 6b

8.2.5.2.1. Main Analysis Approach

The endpoint is the change from baseline in PASI score up to 4 weeks after last dose.

Similar methods and intercurrent event strategies as applied in the main analysis provided for Estimand 6a (see Sections 8.2.5.1.1).

8.2.5.2.2. Supplementary Analyses

The main analysis will be performed on the observed data without any imputation or censoring rules.

8.2.6. Change and percentage change from Baseline in the percentage of BSA affected at scheduled timepoints (Estimand 7a/7b)

The endpoint is the percentage change from baseline in BSA score up to 4 weeks after last dose (Estimand 7a) and change from baseline in BSA score up to 4 weeks after last dose (Estimand 7b).

Percentage change from baseline in BSA will be plotted over time by treatment group in the FAS.

8.2.6.1. Main Analysis Approach

Similar methods and intercurrent event strategies as applied in the main analysis provided for Estimand 6a/6b analysis will be used (see Sections 8.2.5.1.1 and 8.2.5.2.1).

8.2.6.2. Supplementary Analyses

The main analysis will be performed on the observed data without any imputation or censoring rules (see Sections 8.2.5.1.2 and 8.2.5.2.2).

8.3. Exploratory Efficacy Endpoints

8.3.1. Time to First PASI-75 Response

The time from first dose of study drug to first PASI-75 response will be analyzed using CIF with the competing risk of events related to the study intervention (use of prohibited medication, discontinuation of treatment due to related adverse event, or lack of efficacy). The number of events, median time along with 95% CI and cumulative incidence at each scheduled visit along with 95% CI will be presented and CIF plot will be provided for participants in the FAS.

The following censoring rules will be used for different scenarios:

Time to first PASI-75 response: The earliest date and outcome is assessed for each participant. Events related to the study intervention (use of prohibited medication, discontinuation of treatment due to related adverse event, or lack of efficacy) are considered competing events for this analysis.

Situation	Date	Outcome
PASI-75: No study intervention-related event	Date of first PASI-75	Event

PASI-75: study intervention-related event (use of prohibited anti-psoriatic medication, discontinuation of treatment due to related adverse event, or lack of efficacy)	Earliest of: Date of study related event, or date of treatment discontinuation due to study-related event, or date of first dose of study drug if anti-psoriatic prohibited medication is ongoing at the first day of treatment.	Competing Event
No PASI-75: No post-baseline PASI score	Date of first dose	Censored
No PASI-75: Discontinuation of treatment for non-study intervention-related event	Date of end of treatment, date of treatment discontinuation or date of analysis of cut-off, whichever is earlier	Censored

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). Proportion of participants achieving BSA ≤1% will be plotted over time by treatment group.

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.

BSA, DLQI, Itch NRS, and Skin Pain NRS observed scores will be presented in separate listings in the FAS.

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

AEs are recorded in the electronic case report forms (eCRFs). Where changes in severity are recorded in the eCRF, each separate severity of the AE will be reported in the listings. Only the most severe will be used in the summary tables.

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 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

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 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 does not support a reasonable possibility that the event is caused by the study drug after alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention were taken into consideration.
- Related: Evidence supports a reasonable possibility that the event is caused by the study drug after alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention were taken into consideration.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

If an AEs relationship evaluation is missing, the data will be summarized as related, however the relationship will remain missing in listings.

9.1.3. Severity of Adverse Event

The severity of AEs will be graded using 3 severity levels: "mild", "moderate", and "severe". If an AEs severity is missing, it will be presented as "severe" in tables but as missing severity in listings. 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

9.1.5. Adverse Events of Special Situation Report

An adverse event of special situation report (AESSR) are all overdoses, medication errors, misuse and abuse associated with study treatment. Listings of all AESSRs will be provided including start and end dates, and a summary detailing the situation for the SAS.

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.

Laboratory values 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. The number and proportion of participants with CTCAE Grades for each laboratory test (hematology and clinical chemistry) will be presented by visit as well as the end of treatment 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
- Glutamate dehydrogenase
- 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 on the 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; 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 breaths/min; and Low is defined as <10 breaths/min when baseline is between 10 and 24 breaths/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 will be displayed for the SAS.

9.8. Hepatic Safety

Criteria for abnormal hepatic tests involve 5 laboratory analytes: Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), total bilirubin (TBL), Alkaline Phosphatase (ALP), and Prothrombin Time International Normalized Ratio (PT-INR). Analyses for the change from baseline to last visit that occurred on or before the date of treatment discontinuation and shift tables are described in Section 9.2. This section describes additional evaluations for the topic. The central laboratory reference ranges will be used for laboratory assessments.

This table summarizes actions to take based on abnormal hepatic laboratory or clinical changes:

If this laboratory value is observed…	**Then…**		
	Initiate or continue close hepatic monitoring	**Initiate comprehensive evaluation**	**Interrupt or discontinue study intervention**
ALT or AST ≥2x ULN	X		
ALP ≥2x ULN	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥5x ULN	X	X	X
ALP ≥2.5x ULN	X	X	
ALT or AST ≥3x ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x ULN	X	X	X
ALP ≥2.5x ULN and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x ULN with hepatic signs or symptoms[a]	X	X	X

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.
[b] In participants with Gilbert's syndrome, the threshold for TBL may be higher.

The number and percent of participants with the following laboratory will be presented in a table by treatment group for the SAS.

- ALT: The number and percentage of participants with a measurement greater than or equal to 1 time (1X), 2 times (2X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) the performing lab upper limit of normal (ULN) during the postbaseline period will be summarized for all participants with a postbaseline value.

- AST: The number and percentage of participants with a measurement greater than or equal to 1 time (1X), 2 times (2X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) the performing lab upper limit of normal (ULN) during the postbaseline period will be summarized for all participants with a postbaseline value.

- ALP: The number and percentage of participants with a measurement greater than or equal to 2 times (2X), 2.5 times (2.5X), and 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) the performing lab ULN during the postbaseline period will be summarized for all participants with a postbaseline value.

- TBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2X), 5 times (5X), 8 times (8X), and 10 times (10X) the performing lab ULN during the postbaseline period will be summarized for all participants with a postbaseline value.

- PT-INR: The number and percentage of participants with a measurement greater than or equal to 1.5 times (1.5X), 5 times (5X), 8 times (8X), and 10 times (10X) the performing lab ULN during the postbaseline period will be summarized for all participants with a postbaseline value.

A shift table summarizing the maximum treatment-emergent values observed post-baseline for ALT, AST, ALP, TBL, and PT-INR will be presented by treatment group for the SAS. Treatment-emergent is defined as maximum post-baseline value worse than baseline value. Unscheduled assessments will be included in this table for maximum post-baseline value.

Individual participant data will be plotted for the following sets of laboratory parameters; Maximums will be chosen regardless of the timing between the 2 maximum values. A table will be provided for each set of laboratory parameters.

- Maximum ALT or AST (xULN) vs Maximum TBL (xULN)
- Maximum ALP (xULN) vs Maximum TBL (xULN)
- Maximum ALT or AST (xULN) vs Maximum PT-INR (xULN)

The following boundaries will also be plotted on each applicable graph to create 4 quadrants on each graph:

- ALT/AST: 3x ULN
- TBL: 2x ULN
- ALP: 2x ULN
- PT-INR: 1.5x ULN

The number and percent of participants within each of the 3 relevant quadrants of the plots (right upper, left upper, right lower) created by the specified boundaries above will be presented by treatment group.

Listings will be provided for participants with ALT or AST ≥ 2x ULN and separately for participants with ALP or TBL ≥ 2x ULN.

The number and percentage of study participants with any one of the MedDRA preferred terms from any of the SMQs below will be summarized in addition to the percentages for each MedDRA preferred term individually.

Liver-related events will be summarized using the MedDRA Preferred Terms (PTs) contained in the following Standardized MedDRA Queries (SMQs):

- Broad and narrow terms in the Liver-related investigations, signs and symptoms SMQ (20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009)
- Broad and narrow terms in the Hepatitis noninfectious SMQ (20000010)
- Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (20000013), and
- Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015)

Hepatic monitoring events will be summarized using patient-level narratives for the SAS.

9.9. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs. Hypersensitivity follow-up and medical history data will be presented in two separate listings for the SAS.

All SMQ, FMQ, and any customized algorithms will be defined prior to database lock by the Sponsor.

9.9.1. Potential Hypersensitivity Reaction Analysis

The main planned hypersensitivity analysis is potential overall hypersensitivity reactions. This analysis uses the FMQ to identify potential relevant events:

- Hypersensitivity FMQ Algorithm, which includes
  - Any Narrow Terms (Category A);
  - 2 or more algorithmic Broad Terms (that is, it excludes broad terms that do not satisfy the algorithm). Two broad terms from two different categories (Category B, C or D) within 7 days of each other
- Customized query (to add or remove PTs relevant to the program)

9.9.2. Potential Anaphylactic Reaction Analysis

The Anaphylactic reaction SMQ algorithm includes events that met one of the following criteria:

a) Narrow term from the Anaphylactic reaction SMQ (all narrow terms are considered algorithmic terms) [Category A];
b) Two broad terms from different categories (for example, upper airway/respiratory [Category B] + angioedema/topical reaction [Category D], OR upper airway/respiratory [Category B] + systemic reactions [Category C], OR angioedema/topical reactions [Category D] + systemic reactions [Category C]) may, taken together, satisfy particular criteria laid out in detail in the SMQ documentation. In this case, *both* terms are included

as Anaphylactic reaction algorithm terms, if *both* of the events are within 2 days of each other.

All terms identified through the FMQs, SMQs and/or Customized Query will be then evaluated by 2 blinded assessors (1 business unit medical representative and 1 GPS medical representative responsible for the study). Cases which the blinded assessors agree are hypersensitivity or anaphylactic reaction events will be documented in an Excel spreadsheet (also called Hypersensitivity Tool). Cases with discordant assessments will require assessment by a third blinded medical assessor from the Hypersensitivity Working Group. The final assessments will be recorded in the Hypersensitivity Tool that will be maintained for documentation. The terms recorded in the Hypersensitivity Tool as a hypersensitivity or anaphylactic reaction event will be provided in the final Tables and Listings.

Hypersensitivity and anaphylactic reactions will be summarized separately as the frequency and percent of participants in the SAS by search methodology and PT.

10. Pharmacokinetics

PK listings will be presented using the safety analysis set and PK analysis set, and participants not included in the PK analysis set will be flagged. Individual PK concentration-time profiles will be presented graphically using the safety set (participants receiving placebo will not be presented), and participants not included in the PK analysis set will be highlighted. Participants without any estimable PK parameters will not be presented in the listing of PK parameters (eg, placebo participants). PK tables, mean figures and all statistical analyses will be presented using the PK analysis set.

10.1. Data Handling

10.1.1. Pharmacokinetic Profile Exclusions

Where participants experience issues pertaining to a specific dose of study drug over the duration of the study which may affect exposure to study drug during the affected visit (e.g., emesis within 2 x median T_{max}, dosing errors, etc.), individual PK profiles will be reviewed and evaluated by the study pharmacokineticist, in conjunction with the Sponsor, on a case-by-case basis for exclusion from treatment summaries and/or the PK analysis set. All exclusions will be documented throughout the affected data listings.

Note: median T_{max} is defined as the earliest median T_{max} attained across all visits and treatment groups for parent drug.

10.1.2. Data Rounding

Data rounding specifications for PK data are documented in the PK TLF shells.

10.1.3. Below the Limit of Quantification

Plasma concentrations that are Below the Limit of Quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics and estimation of all PK parameters.

10.1.4. Missing Data

All missing concentration data will be presented as missing in concentration data listings and excluded from the estimation of concentration summary statistics. However, for the estimation of PK parameters the following imputations will be made:

- Missing predose concentrations observed before administration of the first dose will be imputed as zero. This imputation is performed automatically by the analysis software.

Otherwise, missing results will be treated as missing and not imputed.

10.1.5. Summary Statistics

Summary statistics to be presented for each output are as follows:

- Plasma concentrations: number of participants (N), number of non-missing observations (n), number of BLQ, arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum.
- Plasma PK parameters: N, n, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. T_{max} will be summarized using number of observations, median, minimum, and maximum only.

Where only one observation is observed (ie, n=1), only the number of observations, arithmetic mean, median, minimum, and maximum will be presented.

10.2 Plasma Concentrations

Serial blood samples will be collected at the following time points for PK assessment:

Study Day	Event	CCI
1	Predose[a]	
	Postdose	
	Postdose	
8	Predose[a]	
15	Predose[a]	
	Postdose	
	Postdose[b]	
29	Predose[a]	
57	Predose[a]	
	Postdose	
	Postdose[b]	
85 or ET	Postdose	

a Predose samples must be drawn CCI of study intervention.
b Postdose samples CCI on Day 15 and Day 57.
c Record the dosing times for the last 2 doses prior to PK sampling with the exception of Day 1.
[d] Approximately CCI (BID cohorts) CCI (QD cohort) CCI (BID) CCI (QD) dose.

PK collections that have an actual sampling time that deviates from the predefined collection time windows will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Predose concentrations (including Ctrough parameters) on Day 8, 15, 29, 57 and 85, will be excluded for the following:

- when the predose sample is taken post dose
- when a sample date or time is not recorded
- when the preceding dose, or dose date and time is missing, the preceding morning dose for QD dosing or the preceding evening dose for BID dosing regimens

Predose samples collected in error after dosing and any subsequent post-dose samples (Day 15 and Day 57) will be excluded from the calculation of concentration summary statistics and may be included in the estimation of PK parameters using the actual time relative to dosing.

All data excluded from the PK analysis set will be documented in the data listings.

Individual plasma concentrations will be presented in data listings and summarized separately by treatment, study day and time point.

Individual plasma concentrations will be plotted by actual time on both linear and semi-logarithmic scales. Arithmetic mean plasma concentrations will be plotted by treatment and study day and nominal time on both linear and semi-logarithmic scales with all dose levels overlaid on the same plots, where applicable.

10.3 Plasma Pharmacokinetic Parameters

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ) or SAS® (SAS Institute Inc., Cary, North Carolina) Version 9.4 or higher. Summary statistics will be tabulated for maximum observed concentration (C_{max}) and time to attain maximum observed plasma concentration (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 8, 15, 29, 57 and 85 schedule of visits. The following PK parameters will be calculated for LY4100511, where data permit. :

C_{max}	Maximum observed concentration (Day 1, 15 and 57).
T_{max}	Time of maximum observed concentration.
AUC_{0-4}	AUC from time 0 to 4 hours post-dose, calculated using the linear trapezoidal rule (Day 15 and 57).
C_{trough}	Concentration at the end of the dosing interval (pre-dose concentration following the first dose, on Days 8, 15, 29, 57 and 85).

Actual sampling times will be used for the estimation of all plasma PK parameters, and all concentrations associated with scheduled sampling times will be included in the analysis (including concentrations collected outside predefined collection windows). Unscheduled PK samples and Early Termination PK samples will not be included in the estimation of PK parameters.

Plasma PK parameters will be presented in data listings and summarized separately by treatment and study day.

A listing of all plasma samples collected will also be presented.

11. Pharmacodynamics

11.1. Biomarker Analysis

11.1.1. Serum Pharmacodynamic (PD) Biomarkers

Serum PD Biomarker endpoints include serum protein levels (pg/mL) of the following biomarkers: IL-17AA, IL-17AF and IL-19. All summaries described in this section will include participants in the Biomarker Set (BMS).

Summaries of mean serum protein levels and mean percent change from baseline in serum protein levels of each serum biomarker will be presented at: Day 1 (pre-morning dose; baseline), Day 8 (pre-morning dose), Day 15 (pre-morning dose, and 4 hours post-morning dose), Day 29 (pre-morning dose), Day 57 (pre-morning dose, and 4 hours post-morning dose), Day 85 (excluding ET), and Day 115. The summaries will include the least squares means and standard errors from the mixed effects model described below for serum protein levels and percent change from baseline for each serum biomarker and timepoint.

Means (+/- standard errors) of serum protein levels and percent change from baseline in serum protein levels (IL-17AA, IL-17AF, and IL-19) will be plotted over time by treatment group, excluding ET visit. Specifically, *least square means* (*+/- standard errors*) *of* the mean estimated from a mixed effects model using an unstructured covariance matrix. 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. Model fitting will be performed using log10 transformed serum protein levels. For IL-19, the dashed horizontal line indicates the upper limit of normal (21 pg/mL).

The following scatter plots will be presented:

- Baseline PASI score (Y-axis) versus serum protein levels (X-axis) of: 1) baseline IL-17AA; 2) baseline IL-17AF; 3) baseline IL-19
- Percent change in PASI score from baseline to Week 12 (Y-axis) versus serum protein levels (X-axis) of: 1) baseline IL-17AA; 2) baseline IL-17AF; 3) baseline IL-19
- PASI score (Y-axis) at Week 12 versus serum protein levels of IL-19 (X-axis) at Week 12
- Percent change in IL-19 from baseline to Week 8 (pre-morning dose) (Y-axis) versus Trough concentrations of LY4100511 at Week 8 (pre-morning dose) (X-axis)

Scatter plots will include all treatment groups on each graph, with groups represented by distinct colors or symbols. Additionally, the line of linear correlation, correlation coefficient, and P-value from Spearman's r correlation test will be included when appropriate. Tabular summaries of all correlation tests will be presented by treatment group and total.

Mean serum protein levels of IL-19, IL-17AA and IL-17AF at baseline and Week 12 will be presented by PASI-75 at Week 12 (responder vs non-responder) and treatment group, along with associated box whisker plots comparing responders vs non-responders by treatment group.

A listing of time matched PASI scores, and serum protein levels of IL-17AA, IL-17 AF and IL-19 will be provided for all biomarker samples collected and sorted by treatment group, including samples collected at early termination (ET) visit.

11.1.2. Skin Biopsy

Skin biopsy endpoints include Histology-Epidermal thickness (μm), and the changes of the following Immunohistochemistry markers: KRT-16 (level 0-4), Ki67 (number of cells) and CD3 (level 0-4).

Summaries of all endpoints in this section will be presented for Day 1 (Lesional and Non-Lesional) and Day 85 (Lesional only), including approximately 25 participants per treatment group in the Biomarker Analysis Set (BMS).

Mean (+/- standard error) of all endpoints will be plotted over time (Day 1 Non-lesional, Day 1 Lesional, Day 85 Lesional) by treatment group. Mean (+/- standard error) of percent change from baseline (Day 1 Lesional and Day 85 Lesional) in all endpoints will be plotted by treatment group. Specifically, least square means (+/- standard error) of the mean estimated from a mixed effects model using an unstructured covariance matrix. 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. Model fitting will be performed using log10 transformed serum protein levels.

Following scatter plots will be presented:

- PASI score at baseline (Y-axis) versus all skin biopsy endpoints at baseline (Day 1 Lesional).
- PASI score at Week 12 (Y-axis) versus all skin biopsy endpoints at Week 12 (Lesional)

Scatter plots will include all treatment groups on each graph, with groups represented by distinct colors or symbols. Additionally, the line of linear correlation, correlation coefficient, and P-value from Spearman's r correlation test will be included when appropriate. Tabular summaries of all correlation tests will be presented by treatment group and total.

A listing of all time matched PASI scores and skin biopsy endpoints will be provided for all biomarker samples collected and sorted by treatment group.

11.1.3. Exposure-Response Analysis

Scatter plots of PASI score and percentage change from baseline in PASI score (Y-axis) vs C_{trough} will be presented separately by treatment group for the following corresponding timepoints:

- PASI score at Week 4 vs C_{trough} at Week 4
- PASI score at Week 8 vs C_{trough} at Week 8

- PASI score at Week 12 vs C_{trough} at Week 8

Similarly, three additional plots will be presented.

- PASI score at Week 12 vs C_{max} at Week 8
- Percentage change from baseline in PASI score at Week 12 vs C_{max} at Week 8
- IL-19 at Week 8 vs C_{trough} at Week 8

Additional analyses could be conducted based on results observed and possible correlations noted.

12. Interim Analysis

An interim analysis will be performed for internal decision-making purposes. The interim analysis production process will begin when approximately at least 45% (100 participants) of the total participants either have completed or had opportunity to complete 12 weeks of treatment. The efficacy analysis population will be determined according to this date. Following this date and after data cleaning, an additional data extraction will be taken. Any existing and additional participants and data from this additional data extraction will be included in the safety population for the interim analysis.

The primary efficacy objective, partial secondary efficacy, and safety analyses will be performed. The efficacy analyses will be performed using the efficacy data from the 100 participants as described above, and will include all data collected through the date of the additional data extraction. An assessment of unblinded interim data will be conducted by an Internal Assessment Committee (IAC) with a limited number of prespecified members who do not have direct site contact or data entry or validation responsibilities. Only the IAC will be authorized to evaluate unblinded interim efficacy and safety analyses. Prior to the interim data snapshot or final database lock, a limited number of preidentified individuals may gain access to the unblinded data to initiate the final population PK/PD model development processes for interim or final analyses. To minimize bias, the SAP and PK/PD analysis plan will be finalized and approved before any unblinding.

13. **Analysis for Japan Submission**

In support of regulatory submission in Japan, analyses will be conducted on Japanese population defined as participants from Japan sites. A subset of the planned analyses will be reproduced on the Japanese population. The analyses to be included will be documented in a separate list of analyses which should include, but not limited to, disposition, demographics, and selected efficacy, health outcomes, and safety endpoints.

14. **Changes from the Planned Analysis**

There were no changes to the planned analysis.

15. References

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16. Appendices

16.1. Schedule of Activities (SoA)

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Fasting visit		X							X			
Informed consent	X											The ICF must be signed before any tests or procedures are performed. Refer to Protocol Section **Error! Reference source not found.** for additional details.
Inclusion/exclusion criteria; confirmation of eligibility	X	X										Confirm prior to randomization and administration of first dose of study intervention.
Demographics	X											Includes ethnicity (where permissible), year of birth, sex, and race.

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Preexisting conditions and medical history, including relevant surgical history	X											Medical history includes any clinically significant diseases or procedures, and toxicities or allergies related to previous treatment. Collect all ongoing conditions and relevant past surgical and medical history.
Prespecified medical history (indication and history of interest)	X											Includes plaque psoriasis history
Prior treatments for indication	X											All prior treatments for psoriasis (all the topical psoriasis medications: within 1 year from baseline; all biologic/systemic therapies: within lifetime).
Substance use (alcohol, caffeine, tobacco use)	X											

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Concomitant medications	X	X	X	X	X		X		X		X	Collect data on • all medications used in the 28 days before screening through the end of study/early termination visit, and • all biologic treatments for psoriasis since diagnosis and all non-biological psoriasis medications /treatments used in the previous 5 years. Refer to Protocol Section **Error! Reference source not found.**.
AEs	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Protocol Section **Error! Reference source not found.**. Additional data will be collected for infection-related AEs.
Physical evaluation												
Height	X											

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Weight	X	X			X		X				X	
BMI	X											
Physical examination	X	X			X				X			The complete physical examination excludes pelvic, rectal, and breast examinations unless clinically indicated. Assess for TB risk factors, and for signs and symptoms of active TB, including an assessment of peripheral lymph nodes (Protocol Sections **Error! Reference source not found.** and **Error! Reference source not found.**).

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Symptom-directed physical assessment			X	X			X				X	Perform as shown in this schedule and as needed at any visit based on participant status and standard of care. May be performed by qualified personnel per local regulations. Assess for TB risk factors, and for signs and symptoms of active TB, including an assessment of peripheral lymph nodes (Protocol Sections **Error! Reference source not found.** and **Error! Reference source not found.**).
Vital signs	X	X	X	X	X		X		X		X	Includes body temperature (ear or oral), respiratory rate, seated blood pressure, and heart rate. Refer to Protocol Section **Error! Reference source not found.**.

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
ECG (single)	X								X		X	Safety ECGs will be read by the investigator to determine any clinically significant abnormalities that would exclude the participant from further study participation. Refer to Protocol Section **Error! Reference source not found.**.
ECG (triplicate; central)		X		X			X					12-lead ECGs will be performed in triplicate approximately 1 minute apart within 2 hours (±15 min) CCI [redacted] and at 1 hour (±15 min) CCI [redacted]. Refer to Protocol Section **Error! Reference source not found.**.
Medical skin photography (selected sites only)		X			X				X			Refer to Protocol Section **Error! Reference source not found.**.
Participant diary (paper)												
Dispense diary		X										

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Diary review			X	X	X		X		X			The daily dosing diary includes the time and number of tablets taken at each dose administration at home (Protocol Section **Error! Reference source not found.**).
Diary return											X	
Patient-reported outcomes (electronic)												Participant-reported outcome assessments must be completed before all other clinical assessments (except at screening).
Dermatology Life Quality Index (DLQI)		X			X		X		X		X	
Itch NRS		X	X	X	X		X		X		X	
Skin Pain NRS		X	X	X	X		X		X		X	
Clinician-administered assessments (paper)												
Psoriasis Area and Severity Index (PASI) score assessment	X	X	X	X	X		X		X		X	

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Static Physician's Global Assessment (sPGA)	X	X	X	X	X		X		X		X	
Body surface area (BSA) assessment	X	X	X	X	X		X		X		X	
Fitzpatrick Scale of Skin Phototypes		X										
Clinician-administered assessments (electronic)												
C-SSRS Baseline/Screening	X											The C-SSRS "Baseline/Screening" version is to be used at screening.
C-SSRS Since Last Visit		X	X	X	X		X		X		X	"Since Last Visit" version is to be used for all other study visits. Participant-reported outcome assessments must be completed before all other clinical assessments (except at screening).
Laboratory tests and sample collections												
Hematology	X	X	X	X	X		X		X		X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X											

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Fasting glucose		X							X			Participants are required to fast for ≥8 hours before the collection of specimens. If a participant attends these visits in a nonfasting state, the sample should still be collected. This will not be considered a protocol deviation.
Fasting lipid panel		X							X			Participants are required to fast for ≥8 hours before the collection of specimens. If a participant attends these visits in a nonfasting state, the sample should still be collected. This will not be considered a protocol deviation.
High-sensitivity, C-reactive protein		X			X		X		X			
eGFR	X								X			
Serum pregnancy	X											Only for individuals of childbearing potential.

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Urine pregnancy (local)		X			X		X		X		X	The result must be available before the first dose of study intervention for individuals of childbearing potential. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.
Urinalysis	X	X	X	X	X		X		X		X	
Follicle-stimulating hormone	X											Perform as needed to confirm postmenopausal status. Definition in Protocol Section **Error! Reference source not found.**.

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
TB test	X								X			Perform TB test procedure using the QFT-G. The QFT-G may be repeated once if the investigator deems this to be necessary. A PPD test may be performed if central laboratory is unable to determine results of QFT-G. Should the PPD test be necessary, the test must be administered and evaluated by a healthcare professional 48 to 72 hours later. Refer to Protocol Section **Error! Reference source not found.**.
Hepatitis B virus (HBV) screening tests	X											For participants who are positive for HBcAb OR anti-HBc, testing for HBV DNA will be performed. Refer to Protocol Section **Error! Reference source not found.**.

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Hepatitis C virus (HCV) screening tests	X											If HCV antibody test is positive, it must be followed by an HCV RNA test. Refer to Protocol Section **Error! Reference source not found.**.
HIV	X											
Blood PK sampling		X	X	X	X		X		X			Refer to PK sampling schedule (Protocol Section **Error! Reference source not found.**) for predose and postdose timing.
Biomarker samples												
Serum PD sampling		X[a]	X[a]	X[a,b]	X[a]		X [a,b]		X[a]		X[a]	If PD analysis is needed for timepoints not captured by PD sampling other blood samples will be utilized. CCI

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
Skin biopsy (selected sites only)		X							X			Nonlesional and lesional skin plaque biopsies are to be performed on Day 1 predose and only lesional skin plaque biopsies are to be performed on Day 85 approximately CCI [redacted] (QD cohort)/CCI [redacted] (BID cohort[s]) CCI [redacted] and are not required at the ET visit but may be collected at investigator's discretion. Refer to Protocol Section **Error! Reference source not found.**.
Randomization and dosing												
Register visit with IRT	X	X			X		X					
Randomization via IRT		X										
Dispense study intervention (for at home dosing)		X			X		X					

	Screening	Treatment Period								Post-treatment Follow-up		Comments
Visit Number	1	2	3	4	5	6	7	8	9	801	802	
Weeks from randomization	≤4	-	1	2	4	6	8	10	12	2 wks after last dose	4 wks after last dose	All activities should be completed prior to any study intervention administration unless otherwise stated below.
Study Day	Up to 28 days prior to Day 1	1	8	15	29	43	57	71	85 or ET	99	115	Day 85 evaluations are performed in the morning in participants who have completed study treatment or are prematurely discontinued from study.
Visit interval tolerance (days)			±2	±2	±2	±2	±3	±3	±3	±3	±7	
CCI of study intervention in clinic		X	X	X	X		X					Participants will be instructed to bring the study intervention to the clinic and withhold the CCI on study visit days, until after predose laboratory samples have been collected. See details in Pharmacy Manual.
Collect unused study drug and assess study intervention compliance					X		X		X			Perform and enter study intervention accountability in IRT based on unused study drug

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IRT = interactive response technology; NRS = numeric rating scale; PD = pharmacodynamics; PK = pharmacokinetics; PPD = purified protein derivative; QD = once daily; QFT-G = QuantiFERON®-TB Gold Plus panel; TB = tuberculosis; wks = weeks.

Pharmacokinetic Sampling Schedule

Study Day	Event	CCI
1	Predose[a]	

	Postdose	CCI
	Postdose	
8	Predose[a]	
15	Predose[a]	
	Postdose	
	Postdose[b]	
29	Predose[a]	
57	Predose[a]	
	Postdose	
	Postdose[b]	
85 or ET	Postdose	

[a] Predose samples must be drawn CCI of study intervention.
[b] Postdose samples CCI on Day 15 and Day 57.
[c] Record the dosing times for the last 2 doses prior to PK sampling with the exception of Day 1.
[d] Approximately CCI (BID cohorts)/CCI (QD cohort) CCI (BID) CCI (QD) CCI.

16.2. 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.

16.3. Static Physician's Global Assessment (sPGA)

sPGA final scores are recorded on the case report form.

16.4. 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.

16.5. 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'.

16.6. 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'.

16.7. 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?	A lot ❒	Very much ❒ 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.

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Complete with Docusign: DICE DCE853201 SAP Final v2.0.docx
Source Envelope:
Document Pages: 77
Signatures: 3
Envelope Originator:
Certificate Pages: 3
Initials: 0
PPD
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Monrovia, Reykjavik
IP Address: PPD

Record Tracking

Status: Original
20 June 2025 | 04:35
Holder: PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I am the author of this document	Sent: 20 June 2025 | 04:47 Viewed: 20 June 2025 | 04:48 Signed: 20 June 2025 | 04:49
Electronic Record and Signature Disclosure: Not Offered via Docusign		
PPD Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 20 June 2025 | 04:49 Viewed: 20 June 2025 | 04:54 Signed: 20 June 2025 | 04:58
Electronic Record and Signature Disclosure: Accepted: 15 April 2024 | 23:23 ID: PPD		

Signer Events	Signature	Timestamp
PPD Senior Biostatistician II, Biostatistics and Programming Clinical Re PPD 21 CFR Part 11 Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 20 June 2025 | 04:58 Viewed: 20 June 2025 | 06:28 Signed: 20 June 2025 | 06:29
Electronic Record and Signature Disclosure: Not Offered via Docusign		

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	20 June 2025 | 04:47
Certified Delivered	Security Checked	20 June 2025 | 06:28
Signing Complete	Security Checked	20 June 2025 | 06:29
Completed	Security Checked	20 June 2025 | 06:29

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