

Protocol Amendment J5C-MC-FOAB (b)

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

NCT06602219

Approval Date: 18-Mar-2025

Title Page

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Protocol Title:

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

Protocol Number: J5C-MC-FOAB (DCE853201)

Amendment Number: b

Compound: LY4100511 (DC-853)

Brief Title:

A Phase 2, Dose-Ranging Study of LY4100511 (DC-853) in Adult Participants with Moderate-to-Severe Plaque Psoriasis

Study Phase: 2

Sponsor Name: DICE Therapeutics, Inc., a wholly owned subsidiary of Eli Lilly and Company.

Legal Registered Address: DICE Therapeutics, Inc., 400 East Jamie Court, Suite 300, South San Francisco, California 94080, USA

Regulatory Agency Identifier Numbers:

IND: 169541

EU trial number: 2024-512207-39-00

Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-136751

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment a	12-Dec-2024
Original Protocol	09-Aug-2024

Amendment [b]

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment

The primary rationale for the amendment is to include the statistical comparison of response by dose. Additional changes are to clarify the protocol relative to Protocol Clarifications Memorandums.

The following table outlines a high-level description of changes with a brief rationale.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis Objectives, Endpoints, and Estimands	Added a secondary objective to compare the efficacy of various LY4100511 dose regimens.	To clarify the comparison of the endpoint across the dose levels.
3. Objectives, Endpoints, and Estimands		
1.3. Schedule of Activities (SoA)	TB test row: - added “*” to X at Visit 9 - updated Comments to include “*Only if there are signs of TB infection (Section 8.2.6), including presence of risk factors for TB.”	For clarification.
2.2. Background	Nonclinical efficacy revised to read, “In an IL-17 sensitive, inflammatory disease model in CCI, LY4100511 ameliorated disease CCI.”	To update the nonclinical efficacy results.
	Drug-drug interaction potential CCI deleted “No clinical drug-drug interaction data for LY4100511 is available at this time.”	To update preliminary results from ongoing drug-drug interaction studies.

Section # and Name	Description of Change	Brief Rationale
2.3.1. Risk Assessment	- Hypersensitivity reactions - added “Cutaneous reactions have been observed in participants receiving LY4100511, and were manifested as pruritus, rash, hot flush, and flushing.” - Added risk of eczematous eruptions	To update the potential risks with IL-17 inhibitors.
4.3. Justification for Dose	Revised the language from “The dose levels tested showed plasma after dosing” to “The dose levels tested showed increasing plasma concentrations after dosing”	For correction.
5.2. Exclusion Criteria	Criterion #40: Prothrombin time row, Result column, updated “≥4 sec” to “≥4 sec prolonged” “≥1.7” to “≥1.5” for International Normalized Ratio	For clarification. For consistency with Section 8.2.9.
5.3.4. Sperm, Ova, and Oocytes Donation	Updated the duration for sperm donation from “≥95 days” to “at least 5 days”	To align with update in Section 10.4.3.
6.9.2. Permitted Medication	Sixth bullet: - updated “organic anion-transporting polypeptide-1B1” to “P-gp” - deleted “and when minimal concentration changes may lead to serious adverse reactions, the dosage of the substrate should be reduced in accordance with the approved prescribing information;” - added “these should be discussed with the sponsor.”	To align with update in Section 2.2.
8.3.1. Timing and Mechanism for Collecting Events	Pregnancy row, Collection Stop column: updated the duration for individuals AMAB from “95 days” to “30 days”	To align with update in Section 10.4.3. The 30-day timeframe has been chosen to ensure that any pregnancy that occurs within 5 days after last dose is captured and followed-up, as conception date may not be known when a pregnancy is first detected.

Section # and Name	Description of Change	Brief Rationale
10.2. Appendix 2: Clinical Laboratory Tests	Clinical Laboratory Tests column: • added superscript “b” to “Urine chemistry”. • updated superscript for “Urinalysis” and the corresponding footnote • updated footnote “b” to read “Only at screening”	To clarify that urine albumin and creatinine will be assayed only at screening.
10.4.3. Contraception Guidance for AMAB	Updated the duration for contraception use and restriction on sperm donation for individuals AMAB from “95 days” to “at least 5 days”	To align with the Clinical Trials Coordination Group contraception guidance for male participants receiving non-genotoxic investigational medicinal products.
10.10. Appendix 10: Abbreviations and Definitions	Added “P-gp”	To update the list of abbreviations.
10.11. Appendix 11: Protocol Amendment History	Added amendment summary of changes table	To update amendment history.
11. References	Updated the list of references	To support the update in Section 2.3.1
Throughout the document	Minor editorial and formatting changes	Minor, therefore not detailed.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Brief Title: A Phase 2, Dose-Ranging Study of LY4100511 (DC-853) in Adult Participants with Moderate-to-Severe Plaque Psoriasis

Regulatory Agency Identifier Numbers:

IND: 169541

EU trial number: 2024-512207-39-00

Rationale:

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 Study 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 interleukin (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.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
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 PASI 75 at Week 12
Secondary	
To compare the efficacy of various LY4100511 dose regimens in adult participants with moderate-to-severe plaque psoriasis	Proportion of participants achieving PASI 75 at Week 12
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 at Week 12 - Proportion of participants achieving $\geq 50\%$, $\geq 75\%$, $\geq 90\%$, and 100% reduction in PASI score (PASI 50, PASI 75, PASI 90, and PASI 100, respectively) at all scheduled timepoints

Objectives	Endpoints
	- Proportion of participants achieving an sPGA score of 0 or 1 at all scheduled timepoints - Mean change and percent change from baseline in PASI score at all scheduled timepoints - Mean change and percent change from baseline in the percentage of BSA affected at all scheduled timepoints
To compare the safety and tolerability of multiple dose regimens of LY4100511 versus placebo in adult participants with moderate-to-severe plaque psoriasis	Summary of safety data, including number and proportion of: - TEAEs - SAEs - discontinuations due to TEAEs
To assess the PK of LY4100511 in adult participants with moderate-to-severe plaque psoriasis	Measurement of plasma concentration of LY4100511 at scheduled timepoints to evaluate steady-state maximum concentration ($C_{\max,ss}$) and trough concentration ($C_{\text{trough},ss}$) and associated intra-individual variability

Abbreviations: BSA = body surface area; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetics; SAE = serious adverse event; sPGA = Static Physician's Global Assessment; TEAE = treatment-emergent adverse event.

Estimand

The primary clinical question of interest is:

What is the difference between each dosing regimen of LY4100511 and placebo in the target patient population in achieving a successful response without the use of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related adverse event (TEAE)?

Rationale for the primary estimand

If a participant used any prohibited concomitant medication for plaque psoriasis, the participant was not receiving sufficient benefits from the study intervention.

If a participant discontinued early from the study intervention due to lack of efficacy or TEAE, the participant experienced a burden of the study intervention that outweighed its benefits.

All remaining intercurrent events (ICEs) are considered unrelated to the study intervention.

Estimand strategy

- Binary endpoints: hybrid of composite variable and treatment policy estimands

Efficacy estimand attributes

- Population:** Adults with moderate-to-severe plaque psoriasis
- Endpoints:** Psoriasis Area and Severity Index (PASI) 50, PASI 75, PASI 90, PASI 100, Static Physician's Global Assessment (sPGA) 0 (clear), sPGA 0/1 (clear or almost clear)
 - Timepoints: Week 12 for all endpoints

- **ICEs:**
 - ICEs related to study intervention include the use of prohibited anti-psoriatic concomitant medication and early discontinuation from the study intervention due to lack of efficacy or a related AE. Participants with ICEs related to study intervention will be considered as a treatment failure (binary endpoints) from the time of the ICE (composite strategy).
 - For all remaining ICEs, a treatment policy strategy will be used. That is, the observed data will be used regardless of whether ICEs unrelated to study intervention have occurred.
- **Population-level summary:** Difference in proportion of participants achieving response between each dosing regimen of LY4100511 and placebo and odds ratio.

Overall Design:

Study FOAB 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.

Brief Summary:

The purpose of this study is to evaluate 3 dose levels of twice daily (BID) or once daily (QD) administered LY4100511 compared with BID administered placebo in participants with moderate-to-severe plaque psoriasis.

Study details include:

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).

Study Population:

In general, an individual may take part in this study if they

- are 18 to 70 years of age, inclusive, at the time of signing the informed consent
- meet all of the following plaque psoriasis criteria:
 - clinical diagnosis of plaque psoriasis for ≥ 6 months before the baseline visit (Day 1/randomization)
 - stable moderate-to-severe plaque psoriasis, defined as $\geq 10\%$ body surface area psoriasis involvement, sPGA score of ≥ 3 , and PASI score ≥ 12 at the screening and baseline visits, and
 - candidate for phototherapy or systemic therapy, as assessed by the investigator.
- have a body mass index of 18 to 40 kg/m² (inclusive).

Number of Participants:

Approximately 220 participants will be randomly assigned in a CCI to placebo, LY4100511 200 mg BID, 400 mg BID, and 800 mg QD, respectively.

Intervention Groups and Duration:

This table lists the interventions used in this clinical study.

Intervention Name	LY4100511	Placebo
Dosage Level(s)	200 mg BID 400 mg BID 800 mg QD ^a	BID
Route of Administration	Oral	Oral
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU

Abbreviations: BID = twice daily; QD = once daily.

^a Matching placebo administered in the evening.

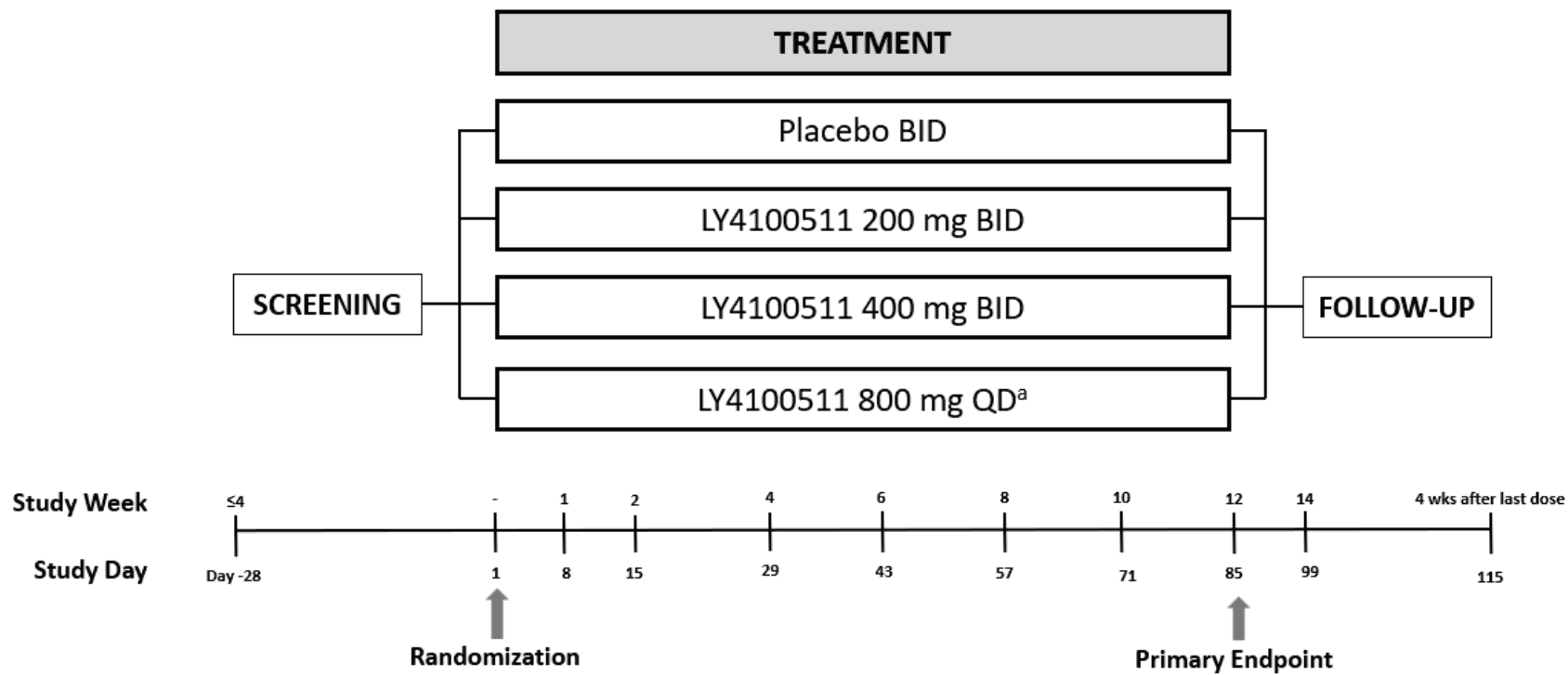
Ethical Considerations of Benefit/Risk:

The safety profile of LY4100511 has been characterized thus far in nonclinical toxicology studies and in Phase 1 studies of healthy adult participants. The safety profile is appropriate to test LY4100511 in a study to characterize the benefit/risk profile in participants with psoriasis. Close monitoring will be conducted in the study on both an individual and trial level to ensure participant safety.

Data Monitoring Committee: No

An Internal Assessment Committee (IAC) will review the interim efficacy and interim and periodic safety data and may include PK (pharmacokinetics) and/or PD (pharmacodynamics) data in an unblinded fashion.

1.2. Schema



Abbreviations: BID = twice daily; QD = once daily; wk = week.

^a Matching placebo administered in the evening.

1.3. 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 Section 10.1.3 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.
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.

	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	
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											
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 Section 6.9 .

	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	
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 Section 10.3.1 . Additional data will be collected for infection-related AEs.
Physical evaluation												
Height	X											
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 (Sections 8.2.1 and 8.2.6).

	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 (Sections 8.2.1 and 8.2.6).
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 Section 8.2.3 .
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 Section 8.2.4 .

	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 (triplicate; central)		X		X			X					12-lead ECGs will be performed in triplicate approximately 1 minute apart within 2 hours (±15 min) CCI and at 1 hour (±15 min) CCI . Refer to Section 8.2.4 .
Medical skin photography (selected sites only)		X			X				X			Refer to Section 8.1.4 .
Participant diary (paper)												
Dispense diary		X										
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 (Section 6.1).
Diary return											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	
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	
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										

	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	
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 Section 10.4.1 .

	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 Section 8.2.6 . *Only if there are signs of TB infection (Section 8.2.6), including presence of risk factors for TB.
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 Section 8.2.7 .
Hepatitis C virus (HCV) screening tests	X											If HCV antibody test is positive, it must be followed by an HCV RNA test. Refer to Section 8.2.8 .
HIV	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	
Blood PK sampling		X	X	X	X		X		X			Refer to PK sampling schedule (Section 1.3.1) 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 [REDACTED]
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] (OD 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 Section 8.7.

	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	
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					
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.

1.3.1. Pharmacokinetic Sampling Schedule

Study Day	Event
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) CCI.

2. Introduction

2.1. Study Rationale

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 Study 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.

2.2. Background

Psoriasis

Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives. Psoriasis is a chronic, relapsing inflammatory disease of the skin with a reported prevalence across countries of 0.09% to 11.4% and affecting approximately 1% to 3% of the world's population (WHO 2016; Michalek et al. 2017). In the United States, 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).

Etiology of psoriasis

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

IL-17A

The IL-17 cytokine family comprises 6 related proteins, IL-17A through IL-17F. In virtually all biological circumstances, cells that synthesize the IL-17A subunit also synthesize the IL-17F subunit, and vice versa, and thus secrete a mixture of IL-17AA, AF, and FF. IL-17B-E are

different enough to not be relevant to LY4100511 or the biology of psoriasis. The combined biological activity of IL-17AA, AF, and FF is referred to simply as IL-17, unless otherwise noted. IL-17 primarily acts on epithelial cells, endothelial cells, and fibroblasts. IL-17 at epithelial surfaces plays an important role in mucosal defense and protective role in regulation of commensal colonization. Absence or impaired IL-17 signaling, either due to genetic deficiency of IL-17 or treatment with anti-IL-17A or anti-IL-17 receptor antibodies may lead to mucocutaneous candidiasis.

In psoriasis, however, aberrant activation of IL-17 signaling pathways within skin keratinocytes promotes the secretion of inflammatory cytokines and anti-microbial peptides, such as beta-defensin 2, resulting in neutrophil recruitment, and aberrant proliferation and differentiation of skin keratinocytes (Fletcher et al. 2020; Prinz et al. 2020).

Advantages of targeting the IL-17 pathway

Antibodies targeting the IL-17 pathway are highly efficacious in the treatment of psoriasis. Secukinumab and ixekizumab recognize the IL-17A subunit and thus neutralize IL-17AA and IL-17AF, whereas another antibody (bimekizumab) recognizes the IL-17A and IL-17F subunits and thus additionally targets IL-17FF.

Oral treatment options include methotrexate, cyclosporine, acitretin, fumaric acid esters, deucravacitinib, and apremilast. Methotrexate is associated with hepatotoxicity, bone marrow suppression, and rarely, pulmonary toxicity. Cyclosporine is associated with renal toxicity. As such, both medications require chronic monitoring and limit long-term use. Acitretin is associated with lipid derangements, pancreatitis, hepatotoxicity, and teratogenicity. Fumaric acid esters are associated with flushing and gastrointestinal side effects as well as lower lymphocyte counts and increased risk of progressive multifocal leukoencephalopathy. Deucravacitinib is a TYK2 inhibitor. TYK2 is a member of the JAK family. Whether TYK2 may be associated with the observed or potential adverse reactions of Janus kinase inhibition is unknown. Apremilast usage is limited due to on-target gastrointestinal tolerability issues, specifically nausea and diarrhea.

Each of these current oral treatment options have safety and tolerability concerns and are less efficacious than antibodies that target the IL-17 pathway.

LY4100511 (DC-853)

LY4100511 is an orally administered small-molecule inhibitor of the cytokine IL-17A. LY4100511 specifically binds to IL-17A and CCI

Nonclinical efficacy

In an IL-17 sensitive, inflammatory disease model in CCI, LY4100511 ameliorated disease CCI

Nonclinical safety

The nonclinical safety of LY4100511 was evaluated in single-dose and repeat-dose toxicity studies up to 13 weeks of duration in rats and dogs; a repeat-dose tolerability study of 10 days duration in rabbits; safety pharmacology evaluations of cardiovascular, respiratory, and neurological function; a genotoxicity battery; and preliminary embryo-fetal development studies in rats and rabbits.

Key findings from definitive, repeat-dose, toxicity studies included CCI [REDACTED]. All human-relevant findings are considered readily monitorable and demonstrated reversibility. LY4100511-related effects to CCI [REDACTED] parameters included CCI [REDACTED] effects:

CCI [REDACTED] at varying time points postdose.

LY4100511 was determined to not have biologically relevant genotoxicity potential. LY4100511 was not associated with malformations or variations in preliminary rat and rabbit embryo-fetal development studies.

Together, the nonclinical toxicology studies support clinical studies of up to 13 weeks of duration.

Clinical safety

The safety and tolerability of LY4100511 in human participants has been evaluated in Phase 1 clinical studies. A Phase 1 first in human study (Study DCE853101) was conducted in 2 parts to evaluate the PK, PD, safety, and tolerability of LY4100511.

The details of the completed Study DCE853101 are presented in this table.

Study Number and Study Parts	Study Design	Endpoints	Population (N)	Dose/Dosing Duration
Study DCE853101, Parts 1 and 2	Part 1: Phase 1, SAD, healthy participants, 6 cohorts (including 1 food-effect cohort)	Safety, tolerability, and PK/PD of LY4100511 after single oral ascending dose(s)	Healthy participants (48). Males and females randomly assigned with 6:2 ratio (6 active and 2 placebo) in each cohort	SAD of LY4100511 CCI [REDACTED] with 7 days of safety follow-up)
	Part 2: Phase 1, MAD, healthy participants, 5 cohorts	Safety, tolerability, and PK/PD of LY4100511 after multiple oral ascending doses	Healthy participants (40). Males and females randomly assigned with 6:2 ratio (6 active and 2 placebo) in each cohort	MAD of LY4100511 CCI [REDACTED] for up to 7 days, with additional 7 days of safety follow-up

CCI [REDACTED]

Based on clinical data from Phase 1 study (DCE853101), LY4100511 at single doses up to CCI [REDACTED] for 7 days was safe and well tolerated in adult healthy participants. No treatment-related discontinuations due to TEAEs were reported. No SAEs were reported. No clinically significant abnormalities in laboratory parameters, physical examination, vital signs, or ECGs were reported. All TEAEs were mild to moderate in severity, with no TEAEs considered treatment related. No dose-dependent trends in the number, severity, or types of TEAEs were noted.

The most common TEAEs, observed in 2 or more study participants following single- or multiple-dose administration of LY4100511 were

- medical device site rash (rash due to Holter or ECG electrode placement in 8 participants)
- headache (8 participants)
- oropharyngeal pain (2 participants)
- dizziness (2 participants)
- nausea (2 participants)
- rhinitis (2 participants), and
- vessel puncture site bruise (2 participants).

Two Phase 1 clinical pharmacology studies are currently ongoing:

- Study J5C-MC-FOAA is a placebo-controlled, Phase 1, participant- and investigator-blinded, single- and multiple-dose study to evaluate safety, tolerability, and pharmacokinetics of LY4100511 in healthy Asian and non-Asian participants.
- Study J5C-MC-FOAG is a Phase 1, single-center, open-label, 3-cohort, fixed-sequence, drug-drug interaction study to assess the pharmacokinetics of LY4100511 when orally administered alone, when coadministered with itraconazole, fluconazole, or carbamazepine in healthy adult participants.

Preliminary safety data are available from the 2 ongoing Phase 1 studies J5C-MC-FOAA (data as of 26-Jul-2024) and J5C-MC-FOAG (data as of 10-Jul-2024). LY4100511 was evaluated at doses up to CCI [REDACTED] as a single dose (SD) and repeated administration of CCI [REDACTED] for 7 days. The TEAEs observed were all mild or moderate in severity, with the exception of 1 SAE of thermal burn, which was deemed severe and unrelated to LY4100511. One participant in study FOAA was withdrawn due to a positive COVID-19 test.

Adverse events observed in the J5C-MC-FOAA study participants, regardless of treatment assignment (LY4100511 or placebo), relatedness, or cohort assignment were: abdominal pain, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatine phosphokinase increased, burning sensation, constipation, COVID-19, diarrhea, dysmenorrhea, flushing, hemorrhoids, headache, hot flush, nausea, oropharyngeal pain, paresthesia, presyncope, pruritus, radius fracture, rash, and thermal burn.

Adverse events observed in J5C-MC-FOAG study participants, regardless of treatment period, relatedness, or cohort assignment were: somnolence, nausea, constipation, vulvovaginitis

trichomonal, headache, viral upper respiratory tract infection, drug eruption, dizziness, sciatica, pyrexia, diarrhea, toothache, cough, and muscle strain.

In Study FOAA, TEAEs observed in participants who received LY4100511 in Cohort 1-3 and were considered by the Investigators as related to study drug were

- headache (2 participants; CCI [REDACTED]),
- alanine aminotransferase increased (2 participants; CCI [REDACTED]),
- aspartate aminotransferase increased (1 participant; CCI [REDACTED])
- rash (1 participant; CCI [REDACTED]),
- hot flush (1 participant; CCI [REDACTED]), and
- pruritus (1 participant; CCI [REDACTED]).

No TEAEs were reported in Study FOAA Cohort 5 (CCI [REDACTED]).

Study FOAA Cohort 4 included 8 participants, of whom 6 received CCI [REDACTED] of LY4100511 SD (a dose which will not be further explored). Four of 6 participants who received LY4100511 had TEAEs that were considered as related to the study drug. These were

- flushing (3 participants, CCI [REDACTED]),
- pruritus (2 participants, CCI [REDACTED]),
- paresthesia (1 participant, CCI [REDACTED]), and
- burning sensation (1 participant, CCI [REDACTED]).

In Study FOAG, TEAEs observed in participants who received LY4100511 and were considered by the Investigators as related to LY4100511 were

- headache (3 participants [CCI [REDACTED]]),
- nausea (1 participant; CCI [REDACTED]),
- somnolence, (1 participant; CCI [REDACTED]), and
- dizziness (1 participant; CCI [REDACTED]).

All safety findings from the Phase 1 trials are transient and clinically manageable. No treatment-related SAEs were reported. To date, LY4100511 at doses up to CCI [REDACTED] is generally well-tolerated with an acceptable safety profile.

Clinical pharmacokinetics

The LY4100511 PK profile was well characterized in the first in human Phase 1 study DCE853101, and in the ongoing Studies J5C-MC-FOAA (FOAA) and J5C-MC-FOAG (FOAG) for doses up to CCI [REDACTED]. After a single oral dose, LY4100511 is rapidly absorbed with a median time of reaching maximum concentration within CCI [REDACTED]. The highest exposure after a single oral dose was observed in the CCI [REDACTED]

CCI [REDACTED] cohort under fasted conditions (FOAA, cohort 3). CCI [REDACTED]

Exposure increased with increasing doses CCI [REDACTED]

CCI [REDACTED] The inter-individual variability in exposure levels ($C_{\max}$ and AUC) at steady-state was relatively small, in a range of CCI [REDACTED]. At steady-state, the mean elimination half-life values for the CCI [REDACTED] were in the range of CCI [REDACTED].

Minimal food effect was observed with minimal impact on AUC and $C_{\max}$ when LY4100511 was administered with food, enabling flexible dosing for outpatient treatment.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Results from Study FOAG suggest that LY4100511 is a sensitive substrate of CYP3A4 in the presence of a strong CYP3A4 inhibitor or inducer, based on the definition from the FDA's guidance (FDA 2023).

CCI [REDACTED] Preliminary clinical data results indicate that LY4100511 is a strong inhibitor of CYP3A4, moderate inhibitor of CYP2C8, and a weak inhibitor of P-gp. Dose adjustment should be considered for concomitant medications that are CYP3A4, CYP2C8, and P-gp substrates in the presence of LY4100511. Refer to the FDA guidance regarding sensitive substrates (FDA 2023).

CCI [REDACTED]

In the Phase 1 study DCE853101, serum levels of IL-17A, the target of LY4100511, were evaluated as a PD biomarker following treatment with LY4100511 for 7 days.

Preliminary data showed a dose-dependent CCI [REDACTED] following LY4100511 treatment. Equivalent daily CCI [REDACTED] doses CCI [REDACTED] demonstrated greater IL-17A protein accumulation CCI [REDACTED].

In contrast, no consistent changes were observed in the placebo group.

The observed increase in IL-17A protein following drug exposure demonstrated LY4100511 target engagement and is consistent with LY4100511 mechanism of action of blocking the interaction between circulating IL-17A and its receptors. CCI [REDACTED]

Similar observations were reported following treatment with monoclonal antibodies that bind to IL-17A (for example, secukinumab) (Bruin 2017) or to IL-17 receptor (for example, brodalumab) (Brodalumab Clinical Pharmacology and Biopharmaceutics Review 2015).

A detailed description of the chemistry, nonclinical pharmacology, and nonclinical safety of LY4100511 is provided in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY4100511 may be found in the IB.

2.3.1. Risk Assessment

Potential risks with LY4100511

Based on LY4100511 nonclinical data, potential toxicity risks include effects to the CCI [REDACTED]. These findings demonstrated reversibility and are considered clinically monitorable. Based on available clinical data from Study DCE853101, no anticipated risks of particular severity require monitoring beyond that of routine monitoring of IL-17 inhibitors and immunomodulatory products in human studies.

Risks with marketed IL-17 inhibitors and monitoring plan

Infections

IL-17 inhibitors have been associated with increased risk of infections, including serious infections and opportunistic infections. To minimize these potential risks, participants with the following medical conditions will be excluded: chronic infections including HIV or viral hepatitis (HBV and HCV), active TB, and acute infections. Participants will be carefully monitored throughout the course of treatment.

A participant who develops active TB will be discontinued from study treatment ([Section 7.1.1](#)).

Inflammatory bowel disease

Participants receiving IL-17 inhibitors may develop or experience worsening of Crohn's disease or ulcerative colitis (ixekizumab prescribing information; secukinumab prescribing information; brodalumab prescribing information). Participants with newly diagnosed IBD (Crohn's disease or ulcerative colitis) during the study will be discontinued from study intervention and referred, as appropriate, to a healthcare professional treating IBD, such as a gastroenterologist ([Section 7.1.1](#)).

Suicidal ideation

In clinical trials, suicidal ideation and behavior has been reported in participants receiving brodalumab and bimekizumab. To evaluate the potential for suicidal ideation, a standard, validated questionnaire (C-SSRS) will be administered to participants at screening and at each subsequent study visit. To minimize this risk, participants with active suicidal ideation or suicide behavior will be excluded. During the study, participants with active suicidal ideation will be discontinued from study treatment and referred immediately to a mental health professional and may be withdrawn from the study based upon the investigator's judgment ([Section 7.1.1](#)).

Malignancies

There are theoretical considerations linking IL-17 immunomodulation with the development of malignant tumors. A history of malignancy or lymphoproliferative disease (except resected cutaneous squamous cell or treated basal cell carcinoma) will also be exclusionary in this study. Participants with a newly diagnosed malignancy during the study will be discontinued from study intervention and referred, as appropriate, to an oncologist.

Hypersensitivity reactions

IL-17 inhibitors have been associated with hypersensitivity or allergic reactions. Participants should be educated about symptoms and signs of hypersensitivity or allergic reactions and reporting of such reactions. If a serious hypersensitivity reaction occurs, study intervention should be discontinued immediately, and appropriate therapy should be initiated ([Section 8.2.12](#)).

Cutaneous reactions have been observed in participants receiving LY4100511, and were manifested as pruritus, rash, hot flush, and flushing.

Eczematous eruptions

Cases of severe eczematous eruptions, including atopic dermatitis-like eruptions, dyshidrotic eczema, and erythroderma were reported in patients receiving other IL-17 inhibitors ([Taltz[®] prescribing information, 2024](#)). The onset of eczematous eruptions was variable, ranging from days to months after the first dose of IL-17 inhibitors. Treatment with study intervention may need to be discontinued to resolve the eczematous eruption, and appropriate therapy should be initiated. Participants should be educated about symptoms and signs of eczematous eruptions and reporting of such events.

Surveillance of drug-induced hepatotoxicity

Although rare, potential for drug-induced hepatotoxicity is under constant surveillance by sponsors and regulators. A panel of standard clinical tests to evaluate liver function will be carefully monitored specifically to mitigate the risk of potential drug-induced liver injury. This study will ensure timely detection, evaluation, and follow-up of laboratory abnormalities in selected liver laboratory parameters to ensure the safety of participants ([Section 8.2.9](#)).

Study procedures

The procedures in this study are typical for a modern dermatology trial. The skin punch biopsy is commonly performed in the clinical setting and is generally well tolerated, with potential risks of pain, bleeding, and infection.

Management of risks

In summary, [Sections 5.1, 5.2, 7.1, and 8.2](#) address mitigation, management, and monitoring of the known potential risks associated with LY4100511.

Participants will be monitored closely with scheduled visits in [Section 1.3](#) wherein safety procedures will be conducted, including AE reporting, vital signs, laboratory tests, physical assessments, and ECGs.

Monitoring of aggregate safety data (including AEs, SAEs, and laboratory measurements) as blinded trial level safety reviews will be conducted by the study team on an ongoing basis, and an IAC will evaluate unblinded safety data, if needed, as described in [Sections 9.4](#) and [10.1.5](#).

2.3.2. Benefit Assessment

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.

2.3.3. Overall Benefit Risk Conclusion

The safety profile of LY4100511 has been characterized thus far in nonclinical toxicology studies and in Phase 1 studies of healthy adult participants. The safety profile is appropriate to test LY4100511 in a study to characterize the benefit/risk profile in participants with psoriasis. Close monitoring will be conducted in the study on both an individual and trial level to ensure participant safety.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
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 PASI 75 at Week 12
Secondary	
To compare the efficacy of various LY4100511 dose regimens in adult participants with moderate-to-severe plaque psoriasis	Proportion of participants achieving PASI 75 at Week 12
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 at Week 12 - Proportion of participants achieving $\geq 50\%$, $\geq 75\%$, $\geq 90\%$, and 100% reduction in PASI score (PASI 50, PASI 75, PASI 90, and PASI 100, respectively) at all scheduled timepoints - Proportion of participants achieving an sPGA score of 0 or 1 at all scheduled timepoints - Mean change and percent change from baseline in PASI score at all scheduled timepoints - Mean change and percent change from baseline in the percentage of BSA affected at all scheduled timepoints
To compare the safety and tolerability of multiple dose regimens of LY4100511 versus placebo in adult participants with moderate-to-severe plaque psoriasis	Summary of safety data, including number and proportion of: - TEAEs - SAEs - discontinuations due to TEAEs
To assess the PK of LY4100511 in adult participants with moderate-to-severe plaque psoriasis	Measurement of plasma concentration of LY4100511 at scheduled timepoints to evaluate steady-state maximum concentration ($C_{\max,ss}$) and trough concentration ($C_{\text{trough},ss}$) and associated intra-individual variability
Exploratory	
Exploratory objectives and endpoints may include, but not be limited to, evaluations of the following at various time points: - to assess the efficacy of LY4100511 on additional efficacy endpoints in adult participants with moderate-to-severe plaque psoriasis - to assess the change from baseline in DLQI - to assess the change from baseline in Itch NRS and Skin Pain NRS	

Objectives	Endpoints
- to assess the change in PD biomarker of LY4100511, and - to assess exposure-response relationships of LY4100511 and its metabolites, if applicable. Additional details will be provided in the SAP.	

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PD = Pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; sPGA = Static Physician's Global Assessment; TEAE = treatment-emergent adverse event.

Estimand

The primary clinical question of interest is:

What is the difference between each dosing regimen of LY4100511 and placebo in the target patient population in achieving a successful response without the use of prohibited concomitant medication or discontinuing the study intervention either due to lack of efficacy or due to a treatment-related AE?

Rationale for the primary estimand

If a participant used any prohibited concomitant medication for plaque psoriasis, the participant was not receiving sufficient benefits from the study intervention.

If a participant discontinued early from the study intervention due to lack of efficacy or a treatment-related AE, the participant experienced a burden of the study intervention that outweighed its benefits.

All remaining ICEs are considered unrelated to the study intervention.

Estimand strategy

- Binary endpoints: hybrid of composite variable and treatment policy estimands

Efficacy estimand attributes

- Population:** Adult participants with moderate-to-severe plaque psoriasis
- Endpoints:** PASI 50, PASI 75, PASI 90, PASI 100, sPGA 0 (clear), sPGA 0/1 (clear or almost clear)
 - Timepoints: Week 12 for all endpoints
- Treatment Condition:** Each of 3 dosing regimens of LY4100511 (200 mg BID, 400 mg BID, 800 mg QD) vs. placebo
- ICEs:**
 - ICEs related to study intervention include the use of prohibited concomitant medication and early discontinuation from the study intervention due to lack of efficacy or a treatment-related AE. Participants with ICEs related to study intervention will be considered as a treatment failure (binary endpoints) from the time of the ICE (composite strategy).
 - For all remaining ICEs, a treatment policy strategy will be used. That is, the observed data will be used regardless of whether ICEs unrelated to study intervention have occurred.
- Population-level summary:** Difference in proportion of participants achieving response between each dosing regimen of LY4100511 and placebo and odds ratio.

4. Study Design

4.1. Overall Design

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
- Post-Treatment Follow-up period: 4 weeks after last dose (30 days).

Refer to the SoA ([Section 1.3](#)) for additional details about the study visits and visit specific-assessments. The study schema is presented in [Section 1.2](#). For randomization ratios and stratification factors, refer to [Section 6.3](#).

4.2. Scientific Rationale for Study Design

Choice of primary endpoint

The PASI 75 is commonly used as a primary endpoint in clinical trials of moderate-to-severe plaque psoriasis ([Papp et al. 2005](#); [Reich et al. 2005](#); [Leonardi et al. 2008](#); [Menter et al. 2008](#)).

Choice of comparator

Placebo control will be used in this study to address potential confounding factors, such as potential investigator bias in safety and efficacy assessments, or regression to the mean in endpoint scoring.

In addition, due to the nature of psoriasis and the outcome measures used, a placebo arm is necessary to obtain reliable efficacy measurements. Moreover, the inclusion of a placebo group is in accordance with health authority guidelines ([EMA 2004](#)), provides an accurate determination of efficacy and safety findings attributable to LY4100511, minimizes bias, and is a standard requirement to ascertain study sensitivity due to the seasonal and fluctuating character of chronic plaque psoriasis.

Duration of the study treatment

The 12-week duration of the treatment period is appropriate for assessing efficacy based on achieving steady-state concentrations after **CCI** of BID or QD dosing with LY4100511 and allowing sufficient time for pharmacological effects to occur. Further, 12-week duration and durability of effect is a common assessment duration for efficacy and safety in psoriasis. This duration is also supported by the nonclinical toxicology data for LY4100511 available at the time this study was designed.

Study population

The study population includes participants 18 to 70 years of age with moderate-to-severe chronic plaque psoriasis. The population selected for this study reflects a standard population for moderate-to-severe psoriasis trials with new treatment interventions such as LY4100511.

Study procedures

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

Collection of race and ethnicity data

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

In Studies DCE853101 and FOAA, dose up to CCI for 7 days were administered in adult healthy volunteers. The dose levels tested showed increasing plasma concentrations after dosing. An increase in serum IL-17A levels was observed after dosing and the IL-17A levels increased with increasing dose, demonstrating target engagement of the study intervention. IL-17A coincidental to PK achieved a steady-state trough level with repeat administration.

One of the objectives of this study is to evaluate a wide exposure range to characterize the exposure-response relation and define the therapeutic window for LY4100511. The target doses for efficacy are a range of doses and regimens that sustain trough plasma levels of LY4100511 near or above the in vitro IC₉₀ for IL-17A binding CCI. Three doses and regimens are selected for evaluation in this study: 200 mg BID, 800 mg QD, and 400 mg BID. CCI

200 CCI 800 CCI single daily dose CCI
400 mg BID CCI

Phase 2 Doses: Projected and Measured Mean Steady-State Trough and Maximum Concentrations versus Target Coverage

Regimen	Mean $C_{ss,max}$ (ng/mL)	Mean $C_{ss,trough}$ (ng/mL)	% Time Above IC_{90} Within a Dose Interval	$C_{ss,trough}/IC_{90}$
200 mg BID ^a	CCI			
800 mg QD ^b				
400 mg BID ^a				

Abbreviations: BID = twice daily; CCI
QD = once daily.

^a Profiles observed from FOAA study MAD CCI.

^b Predicted values were simulated based on LY4100511 PK profiles observed from Part 2 (CCI dosed in fasted condition) of Study DCE853101.

Based on clinical data from completed and ongoing Phase 1 studies, LY4100511 at single and multiple doses up to 400 mg BID and 800 mg QD is generally well-tolerated with an acceptable safety profile.

With the expected variability in PK, the selected doses and regimens should adequately investigate a range of efficacious and safe doses to define the therapeutic window for LY4100511.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA (Section 1.3).

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age

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

Type of participant and disease characteristics

2. Must meet all of the following psoriasis criteria:
 - clinical diagnosis of plaque psoriasis for ≥ 6 months before the baseline visit (Day 1/randomization)
 - stable moderate-to-severe plaque psoriasis, defined as $\geq 10\%$ BSA psoriasis involvement, sPGA score of ≥ 3 , and PASI score ≥ 12 at the screening and baseline visits, and
 - candidate for phototherapy or systemic therapy, as assessed by the investigator.

Weight

3. Must have a BMI of 18 to 40 kg/m² (inclusive).

Sex assigned at birth and contraceptive/barrier requirements

4. Individuals AMAB or AFAB, IOCBP or INOCBP, may participate in this trial.
Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, refer to [Section 10.4](#).

Informed consent

5. Are capable of giving signed informed consent as described in [Section 10.1.3](#), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

6. Are able to swallow oral medication.
7. Must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

8. Must be willing to discontinue topical and/or systemic therapies for psoriasis before the first dose of study intervention.
9. Must agree to avoid prolonged exposure to the sun and to refrain from the use of tanning booths, sun lamps, and other sources of ultraviolet light during the study.

5.2. Exclusion Criteria

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

Medical conditions

Psoriasis

10. Have had a clinically significant flare of psoriasis during the 12 weeks before the baseline visit, as assessed by the investigator.
11. Have a history of erythrodermic psoriasis, generalized or localized pustular psoriasis, predominantly guttate psoriasis, or medication-induced or medication-exacerbated psoriasis.
12. Have any known or suspected diagnosis of inflammatory conditions other than psoriasis and psoriatic arthritis, including but not limited to rheumatoid arthritis, sarcoidosis, IBD (Crohn's disease or ulcerative colitis), or systemic lupus erythematosus.
13. Have a diagnosis of psoriatic arthritis requiring, or are currently receiving, systemic immunosuppressant medical treatment (including corticosteroids, immunosuppressants, and biologics).
14. Have any active skin disease other than psoriasis that could interfere with the assessment of psoriasis.

Previous or current infections

15. Have a current or recent acute, active infection.

For at least 30 days before screening and up to the randomization/baseline visit, participants must have no symptoms or signs of confirmed or suspected infection and must have completed any appropriate anti-infective treatment.

Note: Participants who have an upper respiratory infection or a vaginal candida infection who are being treated only symptomatically and not requiring systemic anti-infectives may be considered for enrollment if other study eligibility criteria are met. Enrollment of participants with other uncomplicated local infections should be discussed with the sponsor's designated medical monitor.

16. Have had any of the following types of infection within 3 months prior to the screening visit (Visit 1) or develops any of these infections before the randomization visit (Day 1/Visit 2):
 - serious (requiring hospitalization, or intravenous or equivalent oral antibiotic treatment, or both)

- opportunistic (as defined in [Winthrop et al. 2015](#))
Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
- chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis)
Note: Participants with only recurrent mild and uncomplicated orolabial herpes, or genital herpes, or both may be discussed with the sponsor's designated medical monitor and considered for enrollment if other study eligibility criteria are met.
- have active TB ([Section 8.2.6](#))
- have or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and the United States CDC, unless such treatment is underway ([Section 8.2.6](#))
- have a current infection with HBV (that is, positive for HBsAg and/or PCR positive for HBV DNA [[Section 8.2.7](#)])
- have a current infection with HCV (that is, positive for HCV RNA [[Section 8.2.8](#)]), and
- have HIV infection.

Malignancy

17. Have a history of malignancy or lymphoproliferative disease.

Exception: Successfully treated basal cell skin carcinoma or squamous cell skin carcinoma, with no evidence of recurrence or metastatic disease within the 3 years prior to baseline.

General

18. Have previously received a solid organ transplant.
19. Have undergone major surgery within 12 weeks before the first dose of study intervention or such surgery is planned to be performed during the study (for example, hip replacement, aneurysm removal, or stomach ligation) as assessed by the investigator.
20. Have the following conditions which in the investigator's opinion, could interfere with the analyses of safety and efficacy in this study:
 - history or evidence of hepatic impairment (for example, history or presence of ascites, encephalopathy, prolonged prothrombin time, hypoalbuminemia, or hyperbilirubinemia), and
 - history of any current serious or unstable illnesses including renal, gastrointestinal, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease or other conditions.
21. Have a history of significant allergies to lidocaine or other topical anesthetics used during skin biopsy.

Alcohol and substance use disorder

22. Have a history of alcohol or substance abuse within 6 months before the first dose of study intervention that in the opinion of the investigator will preclude participation in the study.

Hypersensitivity

23. Have a history or presence of severe allergies, clinically significant multiple or severe allergic reaction to medications, severe posttreatment hypersensitivity reactions, or hypersensitivity to constituents of the study intervention (and its excipients) and/or other products in the same class.

Psychobehavioral

24. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
25. History of a suicide attempt within the 5 years prior to the screening visit. Participants with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare professional (for example, locally licensed psychiatrist, psychologist, or master's level therapist) before enrolling into the study.
26. Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **and** the ideation occurred within the past month,
OR
Have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS **and** the behavior occurred within the past 3 months.

Vaccines

27. Have received any live vaccine (that is, live attenuated) within the 6 weeks before the first dose of study intervention.

Note: The following are not considered live vaccines: RNA vaccines, vaccines with inactive viral elements, and/or nonreplicating viral vector vaccines.

28. Have received a BCG vaccination or treatment within < 4 weeks before randomization (Day 1/Visit 2) or intend to receive BCG vaccination or treatment during the study.

Prior/concomitant therapy

29. Have received any therapeutic agent directly targeting IL-17 (including, but not limited to secukinumab, ixekizumab, brodalumab, and bimekizumab) and discontinued the anti-IL-17 therapy for any of the following reasons:
- did not show adequate response after a treatment of at least 3 months and/or lost response after prolonged therapy.
 - intolerability or toxicity, irrespective of treatment duration.

30. Have received any therapeutic agent directly targeted to IL-17 (including, but not limited to secukinumab, ixekizumab, brodalumab, and bimekizumab) within 16 weeks or 5 half-lives (whichever is longer) before the first dose of study intervention.
31. Have received anti-TNF α inhibitor(s) or agents that modulate B cells or T cells (for example, adalimumab, alemtuzumab, abatacept, or alefacept) within 12 weeks or 5 half-lives (whichever is longer) before the first dose of study intervention.
32. Have received ustekinumab, risankizumab, tildrakizumab, guselkumab, efalizumab, mirikizumab, or other IL-23 inhibitors within 24 weeks or 5 half-lives (whichever is longer) before the first dose of study intervention.
33. Have received rituximab within 1 year before the first dose of study intervention (or within 6 months if B cells have returned to pretreatment level or normal reference range [local laboratory], if pretreatment levels are not available).
34. Have received any systemic nonbiologic therapy for psoriasis, including but not limited to methotrexate, cyclosporine, corticosteroids, oral retinoids, oral vitamin D, JAK and/or TYK2 inhibitors (including but not limited to tofacitinib, baricitinib, upadacitinib, filgotinib, deucravacitinib), apremilast, and fumaric acid derivatives within 4 weeks before the first dose of study intervention.
35. Have received phototherapy, laser therapy, tanning booth, or extended sun exposure that could affect psoriasis disease severity or interfere with disease assessments within 4 weeks before the first dose of study intervention.
36. Have received topical medications, including but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, urea, alpha- or beta-hydroxyl acids, and medicated shampoos (for example, those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues), topical roflumilast, crisaborole, tapinarof, topical JAK inhibitors (including but not limited to ruxolitinib), and topical calcineurin inhibitors within 2 weeks before the first dose of study intervention.

Notes:

- Participants are allowed to use bland (that is, containing no psoriasis treatment) emollients and bland shampoos during the study.
 - Participants receiving a stable dose for ≥ 3 months before screening are allowed to use corticosteroid inhalers and intranasal sprays, and ophthalmic corticosteroids.
37. Have received a biologic therapy or experimental antibody within the previous 6 months or 5 half-lives (whichever is longer), or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) before the first dose of study intervention, or are currently enrolled in an investigational study.

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Diagnostic assessments

39. Have a 12-lead ECG abnormality that, in the opinion of the investigator,

- increases the risks associated with participating in the study
- may confound ECG data analysis
- a QT interval corrected using Fridericia's formula (QTcF)
 - >450 msec for individuals AMAB or
 - >470 msec for individuals AFAB
- short PR interval <120 msec, or PR interval >220 msec
- second- or third-degree atrioventricular block
- intraventricular conduction delay with QRS >120 msec
- right bundle branch block
- left bundle branch block, or
- Wolff Parkinson-White syndrome.

If an ECG parameter is out of range in the screening ECG, the site may perform 2 repeat ECGs and average the 3 results to assess eligibility.

40. Have had laboratory values meeting the following criteria within the screening period before the first dose of study intervention and in the opinion of the investigator or sponsor, any clinically significant laboratory abnormality that would affect the safety of the participant or the interpretation of the study data.

Test	Result
Hematology	
Absolute neutrophil count	<1500 μ L
Platelet count	<100,000 μ L
Hemoglobin	<9 g/dL
Total white blood cell count	<3000 μ L
Clinical chemistry	
ALT, AST, TBL, and ALP	$\geq 1.5 \times \text{ULN}$; except for participants with isolated elevation of indirect bilirubin relating to a confirmed diagnosis of Gilbert's syndrome
Serum albumin	≤ 3.5 g/dL
Prothrombin time	≥ 4 sec prolonged or International Normalized Ratio ≥ 1.5
eGFR, using the CKD-EPI creatinine equation (2021)	≤ 60 mL/min/1.73 m ²

Other exclusions

41. Are incapacitated, prisoners or involuntarily incarcerated, in compulsory detention for treatment of either a psychiatric or physical illness, or in other situations that render the participant vulnerable according to local regulations.
42. Are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

- 43. Are Lilly employees or are employees of a third-party organization involved with the study.
- 44. Are pregnant, intend to become pregnant, or intend to breastfeed during the study.
- 45. Are donating sperm and ova or oocyte ([Section 5.3.4](#)).
- 46. Are unsuitable for inclusion in this study in the opinion of the investigator or the sponsor.

5.3. Lifestyle Considerations

Administration of study intervention

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

Contraception

The investigator or designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods ([Section 10.4.4](#)) and will confirm that the participant has been instructed in its consistent and correct use. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.1. Meals and Dietary Restrictions

On certain study visit days (as per the SoA, [Section 1.3](#)), participants must comply with fasting requirements for ≥ 8 hours (water is permitted).

5.3.2. Substance Use: Caffeine and Tobacco

Participants will abstain from using tobacco products or ingesting caffeine- or xanthine-containing products (for example, coffee, tea, cola drinks, and chocolate) for ≥ 30 minutes before pulse rate and blood pressure measurements ([Section 8.2.3](#)).

5.3.3. Immunizations

It is recommended that all participants should be up to date with respect to standard-of-care vaccinations (in accordance with local practice/guidelines); vaccination of participants with live components is prohibited within the 6 weeks before the first dose of study intervention ([Section 5.2](#)).

5.3.4. Sperm, Ova, and Oocytes Donation

Individuals AMAB should not donate sperm for the duration of the study and for at least 5 days after their last dose of study intervention.

Individuals AFAB should not donate ova or oocytes for the duration of the study and for at least 5 days after their last dose of study intervention.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any reported SAE.

Participants who are found to be ineligible for entry into the study based on the criteria in [Section 5](#) may be rescreened only once, at the discretion of the investigator.

If the participant had a complete initial screening evaluation including hepatitis and HIV serology, IGRA and/or PPD test, and ECG, these tests will not be required to be repeated for rescreening provided the conditions noted in [Section 5](#) are met, there are no changes in the participant's medical history that would warrant retesting, and ≤ 90 days have passed.

Retest of laboratory samples or ECGs does not constitute rescreening. If a screening laboratory or ECG needs to be repeated (for example due to laboratory process error or technical issue with ECG equipment), the medical monitor must be consulted prior to the retest being conducted. The most recent results will be used for eligibility purposes. If inclusion/exclusion criteria were not met after the repeat test, the participant should not be enrolled in the study.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY4100511	Placebo
Dosage Level(s)	200 mg BID 400 mg BID 800 mg QD ^a	BID
Route of Administration	Oral	Oral
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU

^a Matching placebo administered in the evening.

Study intervention will be dispensed at the study visits summarized in SoA ([Section 1.3](#)).

Returned study intervention should not be re-dispensed to the participants.

Timing of dose administration

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

At home administration

Participants will receive LY4100511 or matching placebo tablets (study intervention) for morning and evening administration.

Participants should take study intervention at approximately the same time each day. Fasting is required for prior to certain visits for some study procedures ([Section 1.3](#)).

In clinic administration

To facilitate PK analyses, doses of study intervention will be administered in the clinic (at the study site) on certain study visit days (refer to the SoA [[Section 1.3](#)]). Participants will be instructed to bring all medications back to the unit and not to dose at home CCI [REDACTED].

Missed doses

In the case of a missed dose, participants will be instructed not to take a “catch-up dose” but to resume dosing with the next regularly scheduled dose. Participants should then continue with the remaining doses as normal. A participant should never take a catch-up dose in this circumstance.

Participants will be provided with a daily dosing diary to document the time and number of tablets taken at each dose administration during periods of home dosing.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, or administer study intervention.

At the study site, all study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel. Participants will be provided with a daily dosing diary, which includes at home dosing instructions as well as storage instructions.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention**Method of treatment assignment**

Each participant will be assigned a unique participant ID upon consent.

Random allocation of participants will be managed by a central IRT system.

Randomization ratios and stratification factors

Participants will be randomly assigned in a CCI to placebo, LY4100511 200 mg BID, 400 mg BID and 800 mg QD, respectively.

The randomization will be stratified by:

CCI

6.4. Blinding

This is a double-blind study. Study participants and study personnel are blinded to study intervention. Blinding will be maintained throughout the conduct of the study, as described in the separate blinding plan.

To maintain the blind, a minimum number of sponsor personnel may see the randomization table and treatment assignments before the study is complete.

Emergency unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, sponsor must be notified immediately.

If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify sponsor as soon as possible.

Emergency unblinding may be performed through the IRT. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All unblinding events are managed by the IRT.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be permanently discontinued from study intervention ([Section 7.1.1](#)).

6.5. Study Intervention Compliance

As indicated in [Section 6.1](#), participants will take the study intervention

- at home when not attending the clinic for study visits, or
- at the study site under the supervision of study staff.

Study staff will complete intervention accountability, review daily dosing diaries, and assess compliance at the study visits indicated in the SoA ([Section 1.3](#)). Any significant noncompliance will be discussed with the sponsor. Details on management of intervention accountability and compliance are provided in the Pharmacy Manual.

Participants considered to be poorly compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

A record of the number of the tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

Intervention start and stop dates, including dates for intervention interruption due to AE, will also be recorded in the CRF.

6.6. Dose Modification

Dose modification of study intervention is not allowed.

6.7. Continued Access to Study Intervention after the End of the Study

Study intervention will not be made available to participants after conclusion of the study.

6.8. Treatment of Overdose

For this study, an overdose is defined as any dosage that exceeds the maximum dosage in the protocol. Initiate supportive treatment according to the participant's clinical signs and symptoms, as medically appropriate.

In the event of an overdose, the investigator/treating physician should:

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until resolved clinically or can no longer be detected systemically (at least 2 days)
- obtain a plasma sample for PK analysis, if requested, and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.9. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant in the past 28 days before screening and all biologic treatments for psoriasis since diagnosis, and all nonbiologic psoriasis medications or treatments taken within the 5 years before screening must be recorded in the applicable CRF with the

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All participants should maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically excluded in the protocol.

Participants taking concomitant medications should be on stable dosages at the time of baseline and should remain at stable dosages throughout the study, unless changes need to be made because of AEs.

Participants should be instructed to consult with authorized site personnel before taking any new medications or supplements during the study. Authorized site personnel should consult the sponsor's medical monitor if there are any questions about concomitant therapies during the study.

Refer to [Sections 6.9.1](#) and [10.7](#) for lists of medications that are prohibited in this study, and [Section 6.9.2](#) for medications that are permitted.

Participants who require treatment with concomitant medications that are prohibited in this study will be permanently discontinued from the study intervention ([Section 7.1.1](#)).

6.9.1. Prohibited Medication

The following concomitant medications are prohibited during the study:

Prohibited Medication	Examples (including, but not limited to)	Duration or half-lives for washout (whichever is longer)
Live or attenuated vaccine	Chickenpox, yellow fever, MMR vaccine	Within 6 weeks before the first dose of study intervention and during the study
Anti-TNF α inhibitor(s) or agents that modulate B cells or T cells	Adalimumab, etanercept, alemtuzumab, abatacept, and alefacept	Within 12 weeks or 5 half-lives before the first dose of study intervention and during the study
Any therapeutic agent directly targeted to IL-17	Secukinumab, ixekizumab, brodalumab, and bimekizumab	Within 16 weeks or 5 half-lives before the first dose of study intervention and during the study
Any IL-23 inhibitor	Ustekinumab, risankizumab, tildrakizumab, guselkumab, efalizumab, and mirikizumab	Within 24 weeks or 5 half-lives before the first dose of study intervention and during the study
Rituximab	-	Within 1 year or within 6 months if B cells have returned to pretreatment level or normal reference range (local laboratory) if pretreatment levels are not available before the first dose of study intervention and during the study
Any systemic nonbiologic therapy for psoriasis	Methotrexate, cyclosporine, corticosteroids, oral retinoids, oral vitamin D, JAK and/or TYK2 inhibitors (including but not limited to tofacitinib, baricitinib, upadacitinib, filgotinib, deucravacitinib), apremilast, and fumaric acid derivatives	Within 4 weeks before the first dose of study intervention and during the study
Use of light sources	Phototherapy, laser therapy, tanning booth, or extended sun exposure	Within 4 weeks before the first dose of study intervention and during the study

Prohibited Medication	Examples (including, but not limited to)	Duration or half-lives for washout (whichever is longer)
Topical psoriasis medications	Corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, urea, alpha- or beta-hydroxyl acids, and medicated shampoos (for example, those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues), topical roflumilast, crisaborole, tapinarof, topical JAK inhibitors (including but not limited to ruxolitinib), topical calcineurin inhibitors Exceptions: Participants are allowed to use bland (that is, containing no psoriasis treatment) emollients and bland shampoos during the study. Participants receiving a stable dose for ≥ 3 months before screening are allowed to use corticosteroid inhalers and intranasal sprays, and ophthalmic corticosteroids.	Within 2 weeks before the first dose of study intervention and during the study
Any experimental antibody or biologic therapy	-	Within the previous 6 months or 5 half-lives before the first dose of study intervention and during the study
Any other experimental therapy or new investigational agent	-	Within 30 days or 5 half-lives before the first dose of study intervention and during the study
CCI [REDACTED]	[REDACTED]	Discontinue at screening through end of study

6.9.2. Permitted Medication

Concomitant medications considered necessary for a participant's safety and well-being may be given at the discretion of the investigator during the study. Following consultation with the sponsor, the investigator will determine whether the participant should continue in the study.

The following concomitant medications are permitted during the study:

- Bland emollients and bland shampoos without other active ingredients indicated to treat psoriasis, or other additives that could affect psoriasis
- Corticosteroid inhalers and intranasal sprays, and ophthalmic corticosteroids for participants receiving a stable dose for ≥ 3 months before screening
- Acetaminophen/paracetamol, ibuprofen, and other nonsteroidal anti-inflammatory drugs
- Medications listed as part of birth control methods (refer to [Section 10.4.4](#))
- Hormone replacement therapy



CCI

- For treatment of flare:
 - use of topical antibiotics in the event of secondary infections of lesions
 - topical moisturizers, bland emollients, bland or nonprescription shampoos
 - acetaminophen/paracetamol or aspirin
 - other concomitant medications taken at a stable dose for ≥ 3 months before screening for concurrent medical conditions (other than psoriasis), which are not listed in [Section 6.9.1](#), may be permitted at the investigator's discretion.

Participants who do not respond to treatment or whose disease worsens should be managed based on investigator's judgment and in accordance with local standard of care.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of [Section 10.1](#).

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for an early termination visit and posttreatment follow-up as shown in the SoA.

- Participants who prematurely discontinue study intervention due to an AE or laboratory abnormality will remain in the study to complete procedures for an early termination visit and posttreatment follow-up as shown in the SoA as outlined in [Section 1.3](#), and adhere to all study procedures (except for dispensing study intervention, efficacy and participant-reported outcome assessments, PK/PD sample collection, and skin biopsies, if applicable) until the AE or laboratory abnormality resolves or stabilizes, unless they have decided to discontinue the study participation entirely (withdrawal of informed consent).

A participant should be permanently discontinued from study intervention for the following reasons:

- For safety reasons, in the opinion of the investigator
- Any AE, laboratory abnormality or intercurrent illness that, in the opinion of the investigator or sponsor, indicates that continued participation in the study is not in the best interest of the participant
- **HBV or HCV:** The participant tests positive for HBV DNA (see [Section 8.2.7](#)) or tests positive for HCV RNA ([Section 8.2.8](#)).

Note: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification ([Section 7.1.4](#)). Prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study intervention, the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

- Absolute neutrophil count <500 cells/mL, confirmed by repeat testing with new sample
- Development of erythrodermic, guttate psoriasis
- Malignancy
- Development of HIV infection
- Development of active TB during the study ([Section 8.2.6](#))

- Newly diagnosed IBD; participants with this diagnosis must be followed up until resolution of active IBD symptoms and should be referred, as appropriate, to a healthcare professional treating IBD, such as a gastroenterologist
- Pregnancy: The participant becomes pregnant during the study
- Significant deviation from the protocol that is considered, in the opinion of the investigator or sponsor, to jeopardize the participant's safety
- An investigator, site personnel performing assessments, or participant is unblinded
- Requirement for prohibited medication ([Sections 6.9.1 and 10.7](#))
- Termination of the study for any reason by the sponsor.
- C-SSRS
 - answered “yes” to Question 4 or Question 5 on the “Suicidal Ideation” portion of the C-SSRS, **or**
 - answered “yes” to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

Possible reasons leading to a participant's permanent discontinuation of the study intervention include:

- If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor ([Section 8.2.12](#)).

7.1.2. Hepatic Criteria for Study Intervention Interruption or Discontinuation

See [Section 8.2.9.3](#) for hepatic criteria for study intervention interruption or discontinuation.

7.1.3. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Discontinuation of study intervention should be considered by the investigator and sponsor

- if QTcF >500 msec and confirmed by repeat ECG
- increase from baseline in QTc >60 msec, from at least 2 consecutive readings.

7.1.4. Temporary Discontinuation

Infection-related criteria for temporary withholding

Temporary withholding of study intervention is required if the participant meets any of the following infection-related criteria during the study:

- Serious or opportunistic infections, as defined in [Section 5.2](#). Study intervention is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.
- HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. In this situation, the sponsor's designated medical monitor should be contacted regarding the participant's status. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention as described in [Section 7.1](#).

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon. To minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep participants in the study regardless of study intervention use.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early termination visit and post-treatment follow-up, if applicable, as shown in the SoA ([Section 1.3](#)). If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

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

8.1.1. Primary Efficacy Assessment: Psoriasis Area and Severity Index 75 (PASI 75)

The PASI is an investigator-administered, multi-item scale used to measure the severity of psoriasis ([EMA 2004](#)).

The PASI is based on the area of coverage and severity of plaque characteristics.

Area of coverage is the extent of body surface involvement in 4 anatomical regions,

- head and neck
- trunk
- upper extremities, and
- lower extremities.

Plaque characteristics include

- the severity of desquamation (scaling)
- erythema (redness), and
- plaque infiltration (thickness) in each region.

The assessment yields an overall score of 0 for no psoriasis to 72 for the most severe disease ([Fredriksson and Pettersson 1978](#)).

The primary efficacy endpoint, PASI 75, represents at least a 75% decrease (improvement) from the baseline PASI score. A PASI 75 response is considered clinically meaningful.

8.1.2. Secondary Assessments

8.1.2.1. Clinician-Administered Assessments

Body Surface Area (BSA)

The percentage of BSA is a clinician-administered scale used in adults to evaluate the percent involvement of psoriasis on each participant's body surface. It is assessed on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the participant's hand (including the palm, fingers, and thumb) ([National Psoriasis Foundation 2016](#)).

PASI 50, PASI 90, and PASI 100

Secondary efficacy endpoints, PASI 50, PASI 90, and PASI 100, represent a 50%, 90%, and 100% improvement from the baseline PASI score.

Static Physician's Global Assessment (sPGA)

The sPGA is a clinician-administered, multi-item scale. It determines the participant's psoriasis lesions, overall, at a given time point.

Overall lesions are graded for plaque elevation, scaling, and erythema on a range from clear (0) to severe (4).

8.1.3. Patient-Reported Outcomes

Dermatology Life Quality Index (DLQI)

The DLQI is a simple, patient-reported, 10-item, validated, quality-of-life questionnaire in adults. It covers 6 domains:

- symptoms and feelings
- daily activities
- leisure
- work or studying
- personal relationships, and
- treatment.

The recall period of this scale is over the last week. Response categories include

- not at all (score 0)
- a little (score 1)
- a lot (score 2)
- very much (score 3)

The unanswered (or "not relevant") responses are scored as 0. Scores range from 0 to 30, with higher scores indicating greater impairment of quality of life.

Itch Numeric Rating Scale (NRS)

The Itch NRS is a participant-reported, single-item, 11-point scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable" in adults. Overall severity of

a participant's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016; Newton et al. 2019; Silverberg et al. 2021).

Skin Pain Numeric Rating Scale (Skin Pain NRS)

Skin Pain NRS is a participant-reported, 11-point scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable". Overall severity of a participant's skin pain is indicated by selecting the number that best describes the worst level of skin pain over the past week (Newton et al. 2019; Silverberg et al. 2021).

8.1.4. Exploratory Assessments

Some of the secondary assessments may support exploratory endpoints. Skin samples and serum biomarkers (Section 8.7) will be used for exploratory assessment of efficacy.

Photography

Photographs of lesion sites will be taken as per the SoA (Section 1.3). Agreement to participate in photography of the skin is not a requirement for this study.

Lesions selected should be representative of the overall disease severity. A close-up and more global view of the lesion should be collected. The face or individual distinguishing features (for example, tattoos) should not be included. If the lesion has resolved, any subsequent photos will be collected from the cleared skin in that area.

In the event a participant is unable to complete photography at the scheduled visit, the participant should return for an unscheduled visit as soon as possible to capture the required views. All photographs are to be taken prior to the morning dose.

Detailed instructions for obtaining clinical photographs will be provided.

Use of photographs

The photographs may be included in the CSR, a regulatory submission package, scientific publications, or other public dissemination of clinical data to illustrate disease presentation at baseline and clinical response following treatment with LY4100511. Photographs will be used for visual purposes to illustrate disease state.

These photographs may also be used in advertising and promotional activities including, but not limited to, communication with healthcare professionals and payers, patient education, speaker programs, and digital and print media messaging.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

Safety monitoring

The investigator will monitor the participant safety data throughout the study. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue the study intervention.

The sponsor will monitor the trial safety data, including AEs, SAEs, discontinuations, vital signs, and clinical laboratory results by means of periodic blinded reviews and other appropriate methods. These methods include reviews by a functionally independent safety physician and/or clinical research scientist who regularly reviews SAE reports in real time and across studies, and who reviews applicable clinical safety and epidemiological publications from the literature. If this safety monitoring uncovers an issue that needs to be addressed by unblinding at the individual or group level, the IAC can conduct additional analyses of the safety data. The IAC is an advisory group for this study formed to protect the integrity of the study in unblinded safety data reviews. Refer to [Section 10.1.5](#).

8.2.1. Physical Examinations

A full physical examination will involve assessment of the following:

- general appearance
- ears, nose, and throat
- head, neck, and thyroid
- cardiovascular
- dermatological
- respiratory
- lymph nodes
- abdomen
- musculoskeletal, and
- nervous system.

The complete physical examination excludes pelvic, rectal, and breast examinations, unless clinically indicated.

A symptom-directed physical examination will involve assessment of the following:

- cardiovascular
- dermatological
- respiratory
- abdomen, and
- any other system, if deemed necessary.

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

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

8.2.2. Skin Assessment with Fitzpatrick Scale of Skin Phototypes

The Fitzpatrick Scale of Skin Phototypes is based on an individual's cutaneous reaction to sun exposure and baseline skin pigmentation. Modern Fitzpatrick skin phototypes range from I – VI, with score of I indicating white skin tone, always burns, does not tan and score of VI indicating skin color black, never burns, tans very easily ([High et al. 2012](#)). Investigators will follow the descriptive terms included in the scale when recording the Fitzpatrick skin phototype. Both sun sensitivity and skin tone must be evaluated for this study. Whichever value is higher is the Fitzpatrick scale score for each individual participant.

8.2.3. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3). If warranted, additional vital signs may be measured.

- Vital signs include body temperature (ear or oral), respiratory rate, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for ≥ 5 minutes.
- Temperature should be measured using the same methodology throughout the study. Participants must refrain from using tobacco-, caffeine-, or xanthine-containing products for ≥ 30 minutes before vital signs being recorded.

8.2.4. Electrocardiograms

For each participant:

- A single, 12-lead digital ECG will be collected according to the SoA (Section 1.3). All single ECGs recorded should be stored at the investigational site.
- At scheduled times (refer to the SoA), consecutive ECGs will be obtained in triplicate at approximately 1-minute intervals.

ECGs (single) may be obtained at additional times when deemed clinically necessary (for example, to assess participants' safety).

ECGs must be recorded before collecting any blood samples. Participants must be supine for at least 5 to 10 minutes before ECG collection, and remain supine and awake, during ECG collection.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to the sponsor, or its designee, as an AE via the CRF.

ECGs will be interpreted by the investigator (a physician or qualified designee) at the site as soon as after the time of ECG collection as practical, to determine whether the participant meets entry criteria.

The ECG data collected in single or triplicate will also be reviewed by a central ECG lab cardiologist to assess whether there are any pre-existing concerns for QT prolongation. All digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details). ECG Analysis Reports by the ECG central lab will be posted to common data site. Sites will be informed about the results via email notifications. All ECGs will be stored in a central electronic database.

8.2.5. Clinical Safety Laboratory Tests

Refer to Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within approximately 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in [Section 10.2](#), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE or AE or dose modification, then report the information as an AE.

8.2.6. Tuberculosis Testing and Monitoring

Screening

During screening, all participants are to be assessed for risk factors, symptoms, and signs of TB with all of the following:

- Thorough history to determine the lifetime risk factors for TB infection, for TB progression, and for symptoms and/or signs of active TB, and
- Thorough physical examination for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes
 - Participants with risk factors for TB or signs and/or symptoms of TB should have further assessment (including chest x-ray) according to local practice/guidelines to establish conclusively that the participant has no evidence of active TB.
- Risk factors include:
 - any known history of active or latent TB
 - foreign born person from country with high incidence of TB defined as greater than or equal to 40 cases per 100,000 people per year
 - any history of travel outside USA with temporary or permanent residence in a country with high incidence of TB
 - close contact to someone with TB disease at any time
 - history of homelessness or work or residence in a homeless shelter

- history of incarceration or work in a prison
- history of use or current use of crack cocaine or injecting illegal drugs
- current or past work as a health care professional in direct contact with patients, and
- current or planned immunosuppression, including exclusion criteria 15, 17, 27, chronic steroids use (equivalent of prednisone greater than or equal to 15 mg/day for more than or equal to 1 month), or other immunosuppressive medication use.

Participants with latent or active TB will be excluded. No ongoing treatment for LTBI is allowed. If LTBI is determined and treatment is required, participant will be discontinued from study intervention.

All participants with no history of LTBI or active TB, and no history of positive Mantoux TST using PPD or positive *M tuberculosis* IGRA must have one of the following tests:

- PPD TST, or
- IGRA for *M tuberculosis* (QFT-G).

For details about these tests, refer to [Section 10.8](#).

Diagnosed LTBI

- Participants diagnosed with LTBI are excluded ([Section 5.2](#)).

Monitoring during the study

For all participants, monitoring for TB is to be continuous throughout the study. At a minimum, each participant is to have the following documented at least every 3 months:

- Thorough history to determine any risk factors for TB infection and for TB progression, and symptoms or signs of active TB, and
- Thorough physical examination for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes ([Sections 8.2.1](#) and [8.2.3](#)).

8.2.7. Hepatitis B Testing and Monitoring

As specified in the SoA ([Section 1.3](#)), initial testing for HBV infection includes HBsAg and anti-HBc

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
- If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required.
 - If the screening HBV DNA is positive, the participant is excluded.
 - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study.

Management of enrolled participants with detectable HBV DNA during the study

- If HBV DNA is detected, study intervention will be temporarily withheld or permanently discontinued, as described in [Sections 7.1.4](#) and [7.1.2](#) and the participant should receive appropriate follow-up medical care.

8.2.8. Hepatitis C Testing

As specified in the SoA ([Section 1.3](#)), initial testing for HCV infection includes testing for anti-HCV.

- If anti-HCV is positive, a test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded ([Section 5.2](#)).
- Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.
- If HCV RNA is detected during the study, the study intervention will be discontinued ([Section 7.1](#)), and the participant should receive appropriate follow-up medical care.

8.2.9. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Intervention Interruption or Discontinuation

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 ≥ 2 x ULN	X		
ALP ≥ 2 x ULN	X		
TBL ≥ 2 x ULN ^b	X		
ALT or AST ≥ 5 x ULN	X	X	X
ALP ≥ 2.5 x ULN	X	X	
ALT or AST ≥ 3 x ULN with hepatic signs or symptoms ^a	X	X	X
ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN ^b or INR ≥ 1.5	X	X	X
ALP ≥ 3 x ULN	X	X	X
ALP ≥ 2.5 x ULN and TBL ≥ 2 x ULN ^b	X	X	X
ALP ≥ 2.5 x 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.

8.2.9.1. Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring:

ALT or AST ≥ 2 x ULN or
ALP ≥ 2 x ULN or
TBL ≥ 2 x ULN ^b

^b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests ([Section 10.2](#)), including ALT, AST, ALP, TBL, D. Bil, GGT, CK, and CBC with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize.
- In addition to lab tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the sponsor-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

8.2.9.2. Comprehensive Hepatic Evaluation

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation:

ALT or AST ≥ 5 x ULN or
ALP ≥ 2.5 x ULN or
ALT or AST ≥ 3 x ULN with hepatic signs or symptoms ^a or
ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN ^b or INR ≥ 1.5

^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.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan). Remaining sample collected for hepatic evaluation may be stored as an exploratory biomarker sample. These stored samples will be used for the limited purpose of additional hepatic evaluations for up to 15 years.
- Based on the participant's history and initial results, further testing should be considered in consultation with the sponsor-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.9.3. Study Intervention Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study intervention and continue close monitoring and comprehensive hepatic evaluation as described in [Sections 8.2.9.1](#) and [8.2.9.2](#).

ALT or AST ≥ 3 x ULN with hepatic signs or symptoms ^a or
ALT or AST ≥ 5 x ULN or
ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN ^b or INR ≥ 1.5 or
ALP ≥ 3 x ULN or
ALP ≥ 2.5 x ULN and TBL ≥ 2 x ULN ^b or
ALP ≥ 2.5 x ULN with hepatic signs or symptoms ^a

^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.

Interruption or discontinuation of study intervention should include these actions:

- While the participant is not receiving the study intervention, clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study (that is, data lock) the investigator should consult with the sponsor-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, data lock date).
- All the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study intervention after interruption for a hepatic reason can be considered only in consultation with the sponsor-designated medical monitor and only if the liver test results returned to near baseline and if a self-limited, non-study intervention etiology is identified. Otherwise, the study intervention should be permanently discontinued.

8.2.10. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA ([Section 1.3](#)).

Participants who become pregnant during the study should be permanently discontinued from the study ([Section 7.1](#)). Participants who become pregnant will complete procedures for an early termination visit and posttreatment follow-up, as shown in the SoA.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected as outlined in [Sections 8.3.1](#) and [8.3.2](#).

8.2.11. Suicidal Ideation and Behavior Risk Monitoring

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a semi-structured interview by a trained rater.

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

Timing of collection and AE monitoring

Nonleading AE collection should occur prior to the collection of the C-SSRS.

Only report a suicide-related event discovered during collection of the C-SSRS on the AE form if it is an AE that leads to discontinuation or an SAE.

Follow standard procedures for reporting SAEs.

8.2.12. 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.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in [Section 10.2.1](#). Laboratory results are provided to the sponsor via the central laboratory.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in [Section 10.2.1](#):

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant, or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study ([Section 7](#)).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest as defined in [Section 8.3.3](#) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 7.3](#)).

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in [Section 10.2.1](#).

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Start of study intervention	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of study intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE ^a – after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in participants and partners of participants	After the start of study intervention	30 days after the last dose of study intervention for individuals AMAB; 30 days after the last dose of study intervention for individuals AFAB	Within 24 hours (Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

^a SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Collection of Pregnancy Information

8.3.2.1. Participants Who Become Pregnant

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

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

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in [Section 8.3.1](#). While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.2.2. Participants With Partners Who Become Pregnant

When to collect pregnancy information

In most circumstances, the investigator will attempt to collect pregnancy information from a participant's partner who becomes pregnant while the participant is in this study.

After learning about a pregnancy in the partner of a study participant, the investigator

- will obtain a consent to release information from the pregnant partner directly, and
- within 24 hours after obtaining this consent, will record pregnancy information on the appropriate form and submit it to the sponsor.

The partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and neonate will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

When not to collect pregnancy information

It is not necessary to collect information about a pregnancy in the partner of a study participant in these circumstances:

- the partner of the study participant was not exposed to the study intervention, or
- the participant did not contribute the sperm or ova that resulted in the pregnancy.

8.3.3. Adverse Events of Special Interest

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

- new onset of IBD including ulcerative colitis or Crohn's disease, and
- suicidal ideation.

8.4. Pharmacokinetics

At the visits and times specified in the SoA ([Section 1.3](#)), venous blood samples will be collected to determine the plasma concentrations of LY4100511. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded as well as the date and time of the 2 doses administered immediately preceding the PK sampling must be recorded accurately on the appropriate forms.

Instructions for the collection and handling of blood samples will be provided by the sponsor. Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of LY4100511 will be assayed using a validated bioanalytical assay. Analyses of samples collected from participants while receiving placebo are not planned. A maximum of 4 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Samples collected for analyses of LY4100511 plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Any excess samples collected for PK testing may be used for exploratory analyses, such as bioanalytical methods development, assay validation or cross-validation exercises, protein binding, and/or metabolism work.

Study intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Refer to [Section 10.1.12](#) for details about sample retention and custody.

8.5. Pharmacodynamics

Venous blood samples will be withdrawn by venipuncture at time specified in the SoA ([Section 1.3](#)). Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details for collection and processing procedures for PD samples are provided in the Laboratory Manual.

Sample retention is described in [Section 10.1.12](#).

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Exploratory Biomarkers

Collection visits

Refer to the SoA ([Section 1.3](#)).

Sample use

Samples may be used for exploratory research on the

- drug target
- disease process
- variable response to treatment with LY4100511
- pathways associated with psoriasis
- mechanism of action of LY4100511, or
- research methods or in validating diagnostic tools or assays related to psoriasis or to LY4100511.

Sample confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel.

Sample retention

Refer to [Section 10.1.12](#).

Types of samples

Blood and tissue will be collected for exploratory biomarker research.

Serum samples

Exploratory serum samples for PD biomarkers, including but not limited to, inflammatory cytokines (for example, IL-17) will be analyzed at different timepoints during the 12-week treatment period. Exploratory serum samples may also be analyzed for understanding safety events.

Skin biopsy***Optional procedure***

Agreement to participate in skin biopsies is *not* a requirement for this study.

Sample collection

Skin samples from lesional and nonlesional areas should be collected from different areas but not include the scalp, face, or neck. Collections of lesions should be representative of

- the overall disease severity
- an area or region that is preferably not exposed to the sun, and
- has a size of approximately 12 cm² at baseline or more.

If the lesion has resolved, any subsequent sample will be collected from the cleared skin in that area.

Details of skin plaque biopsy collection will be provided.

Use of local anesthetic for skin biopsies

For the optional skin biopsies at selected sites, a local anesthetic will be used for collection of a 4-mm skin punch biopsy. Sites may follow their site-specific/local standard of care for preparation, management, and follow-up care.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.9. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

The SAP will be prepared and finalized before database lock or analysis of data. Any deviations from the final SAP will be described and justified in the clinical study report.

Continuous data will be summarized using the number of participants, mean, standard deviation, median, minimum and maximum values, while categorical data will present the number and percentage of participants within each category. Summaries will be provided by LY4100511 dose regimens and placebo. Listings of individual participant data will also be produced.

9.1. Statistical Hypothesis

The primary objective is to demonstrate the efficacy of LY4100511 that there is no difference in the primary efficacy of outcome among different dose levels and the placebo at Week 12. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows: LY4100511 at any dose levels is not different from placebo in achieving PASI 75 at Week 12.

9.1.1. Multiplicity Adjustment

There will be no adjustment for multiplicity.

9.2. Analyses Sets

For the purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled set	All participants who sign full informed consent.
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.
Full analysis set	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.
Safety analysis set	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.
PK analysis set	All participants randomly assigned a study intervention and who take at least 1 dose of study intervention and have PK data available.

Note: Details about biomarker analysis set will be specified in the SAP.

The full analysis set is used to analyze endpoints related to the efficacy objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Full details of procedures for handling missing data will be provided in the SAP. Missing data for safety and PK endpoints will not be imputed.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.3.2. Primary Endpoint/Estimand Analysis

PASI 75 score at Week 12 will be analyzed using 2-sample Fisher's exact test to compare the proportion of patients achieving PASI 75 in the treatment groups versus the placebo group at Week 12. The odds ratio and its corresponding 2-sided 95% CI will be provided. Response rates and 2-sided 95% CIs will be estimated using normal approximation between treatment groups.

Participants with missing data will be considered as non-responders. SAP will provide other details.

9.3.3. Secondary Endpoints/Estimands Analysis

Details about secondary estimands analyses will be included in the SAP.

The PASI 50, PASI 75, PASI 90, and PASI 100 response rates will be summarized by treatment group and visit and will be analyzed using a repeated measure model when applicable.

The proportion of participants with an sPGA score of "0" or "1" will be analyzed similarly to the primary analyses. sPGA and DLQI score will be tabulated by treatment group and visit; the corresponding changes from baseline and percent change from baseline will be calculated and summarized.

For binary endpoints (for example, response rate in PASI and sPGA), estimates of the response rate and 2-sided 95% CIs will be provided using normal approximation between treatment groups.

For continuous secondary endpoints (for example, percent change and absolute change from baseline to Week 12 in PASI scores), the difference and 95% CIs between dose groups and placebo for mean change and percent change from baseline will be provided using an MMRM. This method is useful for its robustness in handling missing data and its ability to account for intra-individual correlations in repeated measures. The MMRM method will include fixed effects

of treatment, visit, treatment $\times$ visit interaction, baseline PASI score as a continuous covariate. The previous biologic therapy and geographic region may be included in the model as covariates.

For PK, summary statistics will be tabulated for $C_{\max}$, AUC_{0-4} , or C_{trough} levels by timepoint and by treatment group. LY4100511 concentrations will be evaluated graphically and summarized descriptively across time points. To facilitate the planning of future clinical studies, a model-based approach implemented using nonlinear mixed effects modeling or other appropriate software may be conducted. As appropriate, data from the present study may be combined with data from other studies in model-based analyses.

Additional details will be provided in the SAP as necessary.

9.3.4. Exploratory Endpoints/Estimands Analysis

Exploratory endpoints and analyses will include, but will not be limited to:

CCI

Exploratory PK/PD analyses using both graphical approaches and model-based approaches may be conducted to evaluate the relationship between LY4100511 CCI and CCI (for example, CCI). Additional analyses may be conducted, if they are deemed appropriate.

Details about exploratory analyses will be specified in the SAP.

9.3.5. Safety Analyses

Safety will be evaluated by presenting summaries of AEs, vital signs, physical examination findings, ECGs, and clinical laboratory evaluations. Safety variables will be tabulated by LY4100511 treatment group.

Adverse events analyses

AEs will be coded using the MedDRA[®]. The proportion of TEAEs will be presented by system organ class and preferred term, by relationship to study intervention, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study intervention. In addition, the proportion of serious TEAEs and TEAEs leading to discontinuation of study intervention will be presented by system organ class, preferred term, and relationship to study intervention.

Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (C-SSRS WWW).

C-SSRS data will be listed by participant.

Laboratory analytes and vital signs

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

9.4. Interim Analyses

An interim analysis may be conducted prior to final database lock. The interim data snapshot may be conducted when a pre-specified proportion of participants would have completed Week 12. The interim analysis may include safety, PK, PD, and efficacy data. Analysis details will be provided in the SAP.

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.

An IAC is authorized to evaluate unblinded interim efficacy, safety, and PK/PD analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants ([Section 10.1.5.1](#)).

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.5. Sample Size Determination

This study will randomly assign approximately 220 participants with moderate-to-severe plaque psoriasis, with approximately 55 participants each to 1 of the 3 LY4100511 dose regimens and approximately 55 participants to placebo.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH Good Clinical Practice (GCP) Guidelines, and
- applicable laws and regulations.

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.
- If the investigator or designee becomes aware of a likely significant protocol deviation, they must immediately report it to the Sponsor or Sponsor's designee.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

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

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and

management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulations.

10.1.5. Committees Structure

10.1.5.1. Internal Assessment Committee

In addition to the safety reviews routinely performed by the blinded study team, as described in [Section 8.2](#), an IAC will exist for the purpose of reviewing safety data in an unblinded fashion periodically or on an ad hoc basis.

The IAC will be fully independent from the study team and will include, at a minimum,

- a sponsor physician
- a statistician, and
- a representative from the sponsor global patient safety organization.

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. The IAC will provide guidance for the safe conduct of the study based on the safety and efficacy data reviewed and will provide information to the study team or senior management as prescribed in the IAC charter.

If an efficacy interim analysis is considered necessary, the IAC will be responsible for review of the efficacy data. Refer to [Section 9.4](#) for general information about interim analyses. Details of interim analyses will be provided in the SAP.

Study sites will receive information about interim results only if they need to know for the safety of their study participants.

In addition to the pre-specified reviews of safety data, the IAC will evaluate unblinded safety data if

- 3 or more participants experience similar TEAEs in the same System Organ Class
- these TEAEs are assessed as severe by the investigator and/or meet at least 1 serious criterion, and
- these TEAEs are judged as related to blinded study treatment by the investigator.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, SAP, , and blank or annotated CRFs, will be provided in a secure data-sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct or remote access to source documents.

If the investigator or designee becomes aware of a likely significant protocol deviation, they must immediately report it to the Sponsor or Sponsor's designee.

Data monitoring and management

QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the CSR.

Monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An EDC will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Clinical outcome assessments

Additionally, data will be collected as follows:

- COA data: Some of the clinician-administered questionnaire data will be collected by the investigative site personnel via a paper source document and will be transcribed by the investigative site personnel into the EDC system. Please refer to the [SoA](#) for scales administered via paper.
- electronic COA data: Patient-reported and clinician-administered assessments other than those collected via paper will be directly recorded by the participant and investigative site personnel into an instrument, for example, an electronic tablet. The electronic COA data will

serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data. Please refer to the [SoA](#) for scales administered electronically.

Data collected via the sponsor-provided data capture system(s) will be stored at third party sites. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the site confirmation of source data.

10.1.9. Study and Site Start and Closure

Study start

The study start date is the date on which the clinical study will be open for recruitment of participants.

First act of recruitment

The first act of recruitment is the first screening activity (i.e., signing of the first informed consent).

Study or site termination

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to the following:

- study termination due to discontinuation of further study intervention development
- site termination due to
 - failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
 - inadequate recruitment, evaluated after a reasonable amount of time of participants by the investigator, or
 - total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY4100511 or after LY4100511 becomes commercially available.

Sample Type	Custodian	Maximum Retention Period after Last Participant Visit
Pharmacokinetics	Sponsor or designee	1 year
Exploratory biomarkers	Sponsor or designee	Up to 15 years

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 5](#) of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Clinical Laboratory Tests	Comments
Hematology	Assayed by sponsor-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential WBC (absolute counts) of	
• Neutrophils	
• Lymphocytes	
• Monocytes	
• Eosinophils	
• Basophils	
Platelets	
Clinical chemistry	Assayed by sponsor-designated laboratory.
Albumin	
Alkaline phosphatase	
Alanine aminotransferase	
Aspartate aminotransferase	
Bicarbonate	
Bilirubin (total, direct and indirect)	
Calcium	
Creatinine	
C-reactive protein	
Gamma-glutamyl transferase	
Glucose – serum	
Glutamate dehydrogenase	

Clinical Laboratory Tests	Comments
Lactate dehydrogenase	
Potassium	
Phosphate (inorganic)	
Protein (total)	
Serum lipids	
Sodium	
Urea	
Lipid panel	
High density lipoprotein cholesterol (HDL-C)	Assayed by sponsor-designated laboratory.
Total cholesterol	
Triglycerides	
Low-density lipoprotein cholesterol (LDL-C)	Calculated by sponsor-designated laboratory. LDL will be directly measured if TGL exceeds maximum value for calculation
TB, HIV, and hepatitis serology	Assayed by sponsor-designated laboratory.
Interferon-Gamma Release Assay (for <i>Mycobacterium tuberculosis</i>): QuantiFERON-TB Gold Plus panel	
HIV-1 and HIV-2 antibodies	
Hepatitis C virus (HCV) testing:	
HCV antibody	
HCV RNA	Performed only for participants who test positive for HCV antibody.
Hepatitis B virus (HBV) testing:	
HBV DNA	Performed only for participants who test positive for anti-HBc.
Hepatitis B core antibody (HBc-Ab)	
Hepatitis B surface antigen (HBsAg)	
Hormones (female)	Assayed by sponsor-designated laboratory unless stated otherwise.
Serum pregnancy	
Urine pregnancy	Evaluated locally.
Follicle-stimulating hormone (FSH) ^a	
Urine chemistry^b	Assayed by sponsor-designated laboratory.
Albumin	
Creatinine	
Calculation	Generated by sponsor-designated laboratory.
eGFR (CKD-EPI)	CKD-EPI creatinine equation (2021). Results will be used for eligibility criteria.

Clinical Laboratory Tests	Comments
Coagulation	Generated by sponsor-designated laboratory.
Prothrombin time	
Activated partial thromboplastin time	
International normalized ratio	
Urinalysis^c	Assayed by sponsor-designated laboratory.
Blood	
Glucose	
Leukocytes	
Protein	
Nitrites	
Plasma (EDTA)	

- a May be performed for postmenopausal AFAB participants to confirm postmenopausal status at discretion of investigator.
- b Only at screening
- c If urinalysis is positive for protein, blood, nitrite, and/or leukocytes, a microscopic examination for red blood cell, white blood cell, bacteria, casts, and epithelial cells will be performed.

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

CCI	

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening
 - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
 - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
 - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
 - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
 - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
 - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations:
 - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
 - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

If the participant identifies a product complaint or a problem with the study intervention, investigators will instruct participants to contact the site as soon as possible so that the situation can be assessed.

An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

Device deficiencies are product complaints.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

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.

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 administration will be considered and investigated.

The investigator will also consult the IB in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs**SAE reporting via paper form**

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the SAE coordinator.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in SAE paper form.

10.3.6. Regulatory Reporting Requirements**SAE regulatory reporting**

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Individuals assigned female at birth (AFAB)	Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus, and thus are capable of exposing an egg, embryo, or fetus to study drug or drug effects.
Individuals assigned male at birth (AMAB)	Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus, but are capable of exposing a fetus to study drug or drug effects via their semen. Individuals AMAB are considered to be not of reproductive potential if they have had orchiectomy (orchidectomy) with or without penectomy, confirmed by operative note.
Individuals of childbearing potential (IOCBP) ^a	Adult individuals AFAB are considered IOCBP unless they are INOCBP. Note: Adolescent or adult individuals AFAB who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP.
Individuals not of childbearing potential (INOCBP) ^b	Individuals AFAB are considered INOCBP if they are not capable of producing ova or embryo, and/or are not capable of potentially gestating a fetus. Such individuals include those who • have a congenital anomaly such as Müllerian agenesis, resulting in confirmed infertility • are infertile due to surgical sterilization, or • are menopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Menopausal state ^c	The menopausal state is defined as an individual: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy^c, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone ≥ 40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or

	aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.
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- a IOCBP is inclusive of the concept of women of childbearing potential (WOCBP or WCBP), a term often used in literature and regulatory guidance documents.
- b INOCBP is inclusive of the concept of women not of childbearing potential (WNOCBP).
- c The individual **should not** be taking medications during amenorrhea, such as oral contraceptives, hormone replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Individuals on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of menopausal status before study enrollment.

10.4.2. Contraception Guidance for Individuals AFAB

IOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle must follow the rules in this table.

Must...	Must not...
agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are AFAB, and not plan a pregnancy during the study	- use periodic abstinence methods - calendar - ovulation - symptothermal, or - post-ovulation - declare abstinence just for the duration of a trial, or - use the withdrawal method

IOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle, must follow the rules in this table.

Must...
Agree to use 2 methods of effective contraception, where at least 1 method must be highly effective. These methods of contraception must be used during the study and for at least 5 days after the last dose of the study intervention.

10.4.3. Contraception Guidance for AMAB

The table below describes contraception guidance for individuals AMAB.

Participant Population	Contraception Guidance
All individuals AMAB...	should refrain from sperm donation for the duration of the study and for at least 5 days after the last dose of the study intervention.

Individuals AMAB with partner(s) who are IOCBP ^a ...	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms and at least 1 additional effective method of contraception for the duration of the study and for at least 5 days after the last dose of the study intervention.
Individuals AMAB with partner(s) who are pregnant ^a ...	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms for the duration of the study and for at least 5 days after the last dose of the study intervention.
Individuals AMAB who exclusively engage in sexual relations with other individual(s) who are AMAB, as their preferred and usual lifestyle...	are not required to use contraception.

^a Individuals AMAB who have undergone orchiectomy but not penectomy must use condoms during sex, but the partner who is IOCBP is not required to use an additional form of contraception. Individuals AMAB who have undergone orchiectomy and penectomy are not required to use condoms.

10.4.4. Examples of Different Methods of Contraception

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the INOCBP definition above. • combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation: ○ oral ○ intravaginal (vaginal ring) ○ transdermal (for example, contraceptive patch) (only for individuals <198 pounds or 90 kg) • progestogen-only hormonal contraception associated with inhibition of ovulation: ○ oral ○ injectable ○ implantable • total abstinence • sexual relationships exclusively between individuals who are assigned the same sex at birth • vasectomy (only if it has received medical assessment of the surgical success) – for individuals AMAB in clinical trials and for the partner of an individual AFAB (if only sexual partner)

Methods	Examples
	• fallopian tube implants (if confirmed by hysterosalpingogram) • intrauterine devices (IUD), or • intrauterine hormone-releasing system (IUS)
Effective contraception	• progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action • penile condom with or without spermicide • vaginal condom with or without spermicide • diaphragm with spermicide • cervical sponge with spermicide, or • cervical cap with spermicide Note: Penile and vaginal condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic evaluation testing

Please refer to [Section 8.2.9](#) for guidance on appropriate test selection.

The sponsor-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management. The local laboratory must be qualified in accordance with applicable local regulations. If testing is not available in certain regions based on local requirements, consult with sponsor-designated medical monitor.

Tests assayed by sponsor-designated central laboratory	
Hepatic hematology panel	Hepatitis A virus (HAV) testing:
Hemoglobin	HAV total antibody ^a
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	Hepatitis B virus (HBV) testing:
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA ^b
Basophils	Hepatitis C virus (HCV) testing:
Eosinophils	HCV total antibody ^a
Platelets	HCV RNA ^b
Cell morphology (RBC and WBC)	Hepatitis D virus (HDV) testing:
Hepatic clinical chemistry panel	HDV total antibody ^a
Total bilirubin	HDV IgM antibody
Direct bilirubin	HDV RNA ^b
Alkaline phosphatase (ALP)	Hepatitis E virus (HEV) testing:
Alanine aminotransferase (ALT)	HEV IgG antibody
Aspartate aminotransferase (AST)	HEV IgM antibody
Gamma-glutamyl transferase (GGT)	HEV RNA ^b
Glutamate dehydrogenase (GLDH)	Anti-nuclear antibody (ANA)
Creatine kinase (CK)	Anti-smooth muscle antibody (ASMA) or anti-actin antibody
Hepatic coagulation panel	Immunoglobulin IgA (quantitative)
Prothrombin time, INR (PT-INR)	Immunoglobulin IgG (quantitative)
Urine chemistry	Immunoglobulin IgM (quantitative)
Drug screen	
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	Cytomegalovirus (CMV) testing:
Acetaminophen protein adducts ^c	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA ^b
Ceruloplasmin	Herpes simplex virus (HSV) testing:
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (ethanol, EtOH)	HSV (Type 1 and 2) DNA ^b
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine chemistry	Microbiology culture:
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV antibody	
EBV DNA ^b	

^a If laboratory does not offer total antibody testing, IgG and IgM are acceptable substitutes.

^b Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

^c Availability of acetaminophen protein adducts testing is limited, so testing may be performed at central laboratories, if needed.

10.6. Appendix 6: Country-Specific Requirements

Country-specific requirements for non-EU countries will be described in separate protocol addenda, if any.

10.6.1. European Union

The study will be conducted in accordance with the Regulation (EU) No. 536/2014.

Regulatory reporting requirements

The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to EU regulatory requirements. The sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority, per European Union Clinical Trial Regulation 536/2014 submission of SUSARs to the EudraVigilance database.

Changes related to EMA regulatory feedback

The revised text in the following sections is based on EMA Regulatory feedback and is applicable for participants in study sites in the EU. All additions have been identified by underscore, and deletions are identified by strikethrough.

5.2. Exclusion Criteria

Previous or current infections

16. Have had any of the following types of infection within 3 months prior to the screening visit (Visit 1) or develops any of these infections before the randomization visit (Day 1/Visit 2):

- serious (requiring hospitalization, or intravenous or equivalent oral antibiotic treatment, or both)
- opportunistic (as defined in [Winthrop et al. 2015](#))
- **Note:** Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
- chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis)

Note: Participants with only recurrent mild and uncomplicated orolabial herpes, or genital herpes, or both may be discussed with the sponsor's designated medical monitor and considered for enrollment if other study eligibility criteria are met.

- have active TB ([Section 8.2.6](#))
- have or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and the United States CDC; ~~unless such treatment is underway~~ ([Section 8.2.6](#))
- have a current infection with HBV (that is, positive for HBsAg and/or PCR positive for HBV DNA [[Section 8.2.7](#)])

- have a current infection with HCV (that is, positive for HCV RNA [Section 8.2.8]), and
- have HIV infection.

General

20. Have the following conditions which, in the investigator's opinion, could interfere with the analyses of safety and efficacy in this study:

- history or evidence of hepatic impairment (for example, history or presence of ascites, encephalopathy, prolonged prothrombin time, hypoalbuminemia, or hyperbilirubinemia), ~~and~~
- history of any current serious or unstable illnesses, including renal, gastrointestinal, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease, or other conditions, and
- history of any clinically significant conditions associated with immunosuppression.

Psychobehavioral

25. History of a suicide attempt within the 5 years prior to the screening visit. Participants with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare professional in line with local law (for example, locally licensed psychiatrist, psychologist, or master's level therapist) before enrolling into the study.

7.1.1 Permanent Discontinuation of Study Intervention

A participant should be permanently discontinued from study intervention for the following reasons:

- Diagnosis of LTBI or a positive or indeterminate result in the TB testing during the study.

7.1.4. Temporary Discontinuation

Infection-related criteria for temporary withholding

Temporary withholding of study intervention is required if the participant meets any of the following infection-related criteria during the study:

- Serious or opportunistic infections, as defined in Section 5.2. Study intervention is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.
- HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. In this situation, the sponsor's designated medical monitor should be contacted regarding the participant's status, and an infectious diseases specialist or hepatologist must be consulted by the investigator. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention as described in Section 7.1.

8.2.6. Tuberculosis Testing and Monitoring

Screening

Participants with active TB will be excluded. Participants with a prior history of active or latent TB with documented completion of a full course of anti-TB therapy may be eligible, provided that written approval by a TB specialist or an infectious disease specialist is obtained prior to starting study treatment. Participants with LTBI who have not initiated treatment or are currently receiving treatment for LTBI will be excluded.

~~Participants with latent or active TB will be excluded. No ongoing treatment for LTBI is allowed. If LTBI is determined and treatment is required, participant will be discontinued from study intervention.~~

Diagnosed LTBI

- ~~Participants diagnosed with LTBI are excluded (Section 5.2).~~

10.8. Appendix 8: Tuberculosis Testing

This table describes recommendations for performing and interpreting TB tests. It also provides recommendations on TB retesting

TB Test Type	How to Perform the Test	How to Interpret the Test	When to Retest
PPD TST	- Inject 0.1 mL of tuberculin PPD into the inner surface of the forearm. Notes: - The injection should be made with a tuberculin syringe. - The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. - Measure induration at the site of intradermal injection from 48 to 72 hours after intradermal injection. Notes: - Test must be read during this window of time. Test does not need to be read at the study site but must be read by a trained medical professional, and the result must be provided to the study site before randomization. - The reaction should be measured in millimeters of	- An induration of 5 mm or more is considered positive in persons with - HIV infection - a recent contact with a person with TB disease - fibrotic changes on chest radiograph consistent with prior TB - organ transplants, or - immunosuppression for other reasons (for example, taking the equivalent of >15 mg per day of prednisone for 1 month or longer, or taking TNF alpha antagonists) - An induration of 10 mm or more is considered positive in all other potential clinical trial participants.	- Two-step testing (that is, repeat TST from 1 to 3 weeks after the first TST) is recommended for certain participant groups, including those - receiving immunosuppressant treatment - having a history of temporally remote increased risk of TB infection, or - for whom the first test is negative, and retesting is recommended per local public health, and/or professional medical society recommendations.

TB Test Type	How to Perform the Test	How to Interpret the Test	When to Retest
	induration (palpable, raised, hardened area, or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).		
IGRA for M. tuberculosis QFT-G	Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.	Results are provided by the laboratory assaying the test.	The investigator may discuss retesting with the sponsor's designated medical monitor if - the investigator suspects a false positive IGRA result in a participant with no increased risk of TB infection during lifetime, and - there is no evidence of prior or current TB on physical examination and/or on CXR interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and with documented CXR report). One retest using the same method is allowed for participants with an indeterminate QFT-G result or a borderline PPD test. Participants with 2 indeterminate QFT-G tests or 2 borderline PPD tests are excluded. <u>Participants with an indeterminate test followed by a negative result upon retest may be eligible, provided that written approval by a TB or infectious disease specialist is obtained prior to starting study intervention.</u>

Abbreviations: CXR = chest x-ray; IGRA = interferon gamma release assay; PPD = purified protein derivative; QFT-G = QuantiFERON®-TB Gold Plus panel; TB = tuberculosis; TNF = tumor necrosis factor; TST = tuberculin skin test.

The following sections describe additional requirements according to the European Union Clinical Trial Regulation 536/2014

Archiving of the clinical trial master file

The sponsor and investigator will archive the clinical trial master file for at least 25 years after the end of the trial, unless other union laws require a longer archiving period. However, the medical records of participants should be archived in compliance with national law.

Reporting of serious breaches

The sponsor will notify the concerned Member States of any serious breach of this Regulation or the applicable protocol version at the time of the breach through the EU portal without undue delay, but no later than 7 days after becoming aware of the breach.

Submission of clinical trial results

Regardless of the clinical trial's outcome, the sponsor will upload a summary of the trial results to the Clinical Trials Information System within 1 year after the end of the trial in all concerned Member States in accordance with the European Union Clinical Trial Regulation Annex IV.

10.6.2. Germany

Changes related to “Legally Authorized Representative,” “Legal Guardian,” “Parents”

This section describes protocol changes applicable for adult participants in study sites in Germany.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
7.2. Participant Discontinuation/Withdraw from the Study 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.10. Appendix 10: Abbreviations and Definitions	Deleted references to “legally authorized representative,” “legal guardian,” “parents”	The German Drug Law (Arzneimittelgesetz – AMG) with reference to EU Regulation 536/2014 requires that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.
10.9. Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances	Revision in temporary measures	In Germany, the temporary measures described in the section “Provisions for Changes in Study Conduct During Exceptional Circumstances” are applicable only to “the COVID-19 pandemic.”

The revised text in the following sections show the changes applicable for adult participants at study sites in Germany. Deletions are identified by strikethrough format.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- ~~at the request of the participant’s designee, for example, parents or legal guardian~~

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in [Section 10.3](#):

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant, or, when appropriate, by a caregiver, or surrogate, ~~or the participant’s legally authorized representative.~~

10.9. Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances

In Germany, the temporary measures described in the Section “Provisions for Changes in Study Conduct During Exceptional Circumstances” ([Section 10.9](#)) are applicable only to “the COVID-19 pandemic.”

10.10. Appendix 10: Abbreviations and Definitions

enter	Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~
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10.8. Appendix 8: Tuberculosis Testing

This table describes recommendations for performing and interpreting TB tests. It also provides recommendations on TB retesting.

TB Test Type	How to Perform the Test	How to Interpret the Test	When to Retest
PPD TST	1. Inject 0.1 mL of tuberculin PPD into the inner surface of the forearm. Notes: ○ The injection should be made with a tuberculin syringe. ○ The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. 2. Measure induration at the site of intradermal injection from 48 to 72 hours after intradermal injection. Notes: ○ Test must be read during this window of time. Test does not need to be read at the study site but must be read by a trained medical professional, and the result must be provided to the study site before randomization. ○ The reaction should be measured in millimeters of induration (palpable, raised, hardened area, or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).	● An induration of 5 mm or more is considered positive in persons with ○ HIV infection ○ a recent contact with a person with TB disease ○ fibrotic changes on chest radiograph consistent with prior TB ○ organ transplants, or ○ immunosuppression for other reasons (for example, taking the equivalent of >15 mg per day of prednisone for 1 month or longer, or taking TNF alpha antagonists) ● An induration of 10 mm or more is considered positive in all other potential clinical trial participants.	● Two-step testing (that is, repeat TST from 1 to 3 weeks after the first TST) is recommended for certain participant groups, including those ○ receiving immunosuppressant treatment ○ having a history of temporally remote increased risk of TB infection, or ○ for whom the first test is negative, and retesting is recommended per local public health and/or professional medical society recommendations.

TB Test Type	How to Perform the Test	How to Interpret the Test	When to Retest
IGRA for <i>M. tuberculosis</i> QFT-G	Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.	Results are provided by the laboratory assaying the test.	The investigator may discuss retesting with the sponsor's designated medical monitor if - the investigator suspects a false positive IGRA result in a participant with no increased risk of TB infection during lifetime, and - there is no evidence of prior or current TB on physical examination and/or on CXR interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and with documented CXR report). One retest using the same method is allowed for participants with an indeterminate QFT-G result or a borderline PPD test. Participants with 2 indeterminate QFT-G tests or 2 borderline PPD tests are excluded.

Abbreviations: CXR = chest x-ray; IGRA = interferon gamma release assay; PPD = purified protein derivative; QFT-G = QuantiFERON®-TB Gold Plus panel; TB = tuberculosis; TNF = tumor necrosis factor; TST = tuberculin skin test.

10.9. Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

In an exceptional circumstance, the sponsor's procedures ensure that relevant parties are kept informed of changes to the design and conduct of the study.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "[Remote visits](#)"
- a change in the method of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits***Types of remote visits***

Telemedicine - Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to

- AE review
- concomitant medication review
- C-SSRS (since last visit, as applicable), and
- product complaint (if applicable).

Mobile healthcare - Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor.

Other alternative locations - A local laboratory may be used for laboratory draws.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing in circumstances of urgent testing or re-testing, or if a participant is unable to travel to the investigative site. However, central laboratory testing must be retained for PK analysis.

The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf
- arranging delivery of study supplies, and
- working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location such as an infusion center.

The following requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 28 days.

The following rules will be applied for active, nonrandomized participants whose participation in the study must be interrupted due to exceptional circumstances:

- If screening is interrupted for less than 28 days from screening to randomization visit, the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 28 days from first screening
 - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay. The site should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is interrupted for more than 28 days from screening to randomization visit, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual

SoA should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 1 through 2	up to 28 days prior to Day 1
Visit 3 through 6	within 4 days before or after the intended date per the SoA
Visit 7 through 9	within 6 days before or after the intended date per the SoA
Visit 801	up to 6 days after the intended date
Visit 802	up to 14 days after the intended date

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing or shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AFAB	assigned female at birth
ALT	alanine aminotransferase
AMAB	assigned male at birth
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
AUC	area under the concentration versus time curve
blinding	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BSA	body surface area
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index

Term	Definition
ECG	electrocardiogram
EDC	electronic data capture system
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HBsAg	Hepatitis B surface antigen
IAC	Internal Assessment Committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
LTBI	latent tuberculosis infection
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IL	interleukin
IMP	Investigational Medicinal Product (see also " investigational product ") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INOCBP	individuals not of childbearing potential
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also " IMP ."
IGRA	Interferon-Gamma Release Assay
IOCBP	individuals of childbearing potential
IRB	Institutional Review Board

Term	Definition
IRT	interactive response technology
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication’s labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMRM	mixed-model repeated measures
NRS	Numeric rating scale
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PASI	Psoriasis Area and Severity Index
PC	product complaint
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
QD	once daily
QFT-G	QuantiFERON®-TB Gold Plus panel
QTc	corrected QT interval
QTL	quality tolerance limit

Term	Definition
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
sPGA	Static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reactions Refers to an AE that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TB	tuberculosis
TBL	total bilirubin
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TYK2	tyrosine kinase 2

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment [Summary of Changes](#) Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [a]: (12-Dec-2024)

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment

The main purpose of this amendment is to address regulatory feedback as provided in this table.

Section # and Name	Description of Change	Brief Rationale
10.4. Appendix 4: Contraceptive and Barrier Guidance	Updated the list of highly effective and effective contraception methods	To address EMA regulatory feedback and align with the Clinical Trials Coordination Group (CTCG) “Recommendations related to contraception and pregnancy testing in clinical trials” Version 1.2
10.6.1. European Union	Updated appendix to include protocol changes as follows Updated Exclusion Criterion #25 to read as “History of a suicide attempt within the 5 years prior to the screening visit. Participants with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare professional in line with local law (for example, locally licensed psychiatrist, psychologist, or master’s level therapist) before enrolling into the study”	To address EMA regulatory feedback, the investigator must comply with local laws when selecting the appropriate mental health professional for participant assessment.
	Updated Exclusion Criterion #20 to include history of any clinically significant conditions associated with immunosuppression. Revised Exclusion Criterion #16, sixth bullet to read “have or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and the United States CDC”	To address EMA regulatory feedback
	Added a bullet to Section 7.1.1 to clarify participants with a diagnosis of LTBI or a positive or indeterminate result in the TB testing during the study will be permanently discontinued from the study intervention	
	Updated second bullet in Section 7.1.4 to include that an infectious diseases specialist or hepatologist must be consulted by the investigator in cases where HBV DNA results are reported positive, or as detecting	

Section # and Name	Description of Change	Brief Rationale
	HBV DNA, but HBV DNA is below the level of quantification	
	In Section 8.2.6, Added “Participants with active TB will be excluded. Participants with a prior history of active or latent TB with documented completion of a full course of anti-TB therapy may be eligible, provided that written approval by a TB specialist or an infectious disease specialist is obtained prior to starting study treatment. Participants with LTBI who have not initiated treatment or are currently receiving treatment for LTBI will be excluded” Removed “Participants with latent or active TB will be excluded. No ongoing treatment for LTBI is allowed. If LTBI is determined and treatment is required, participant will be discontinued from study intervention” Removed “Participants diagnosed with LTBI are excluded (Section 5.2)”	Clarification to address EMA regulatory feedback
	Added • Archiving of the clinical trial master file • Reporting of serious breaches • Submission of clinical trial results	To address EMA regulatory feedback
	Updated retesting requirements for IGRA for <i>M. Tuberculosis</i> QFT-G test in Section 10.8 to include “Participants with an indeterminate test followed by a negative result upon retest may be eligible, provided that written approval by a TB or infectious disease specialist is obtained prior to starting study intervention”	To address EMA regulatory feedback

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Signature Page for VV-CLIN-136751 v3.0

Approval	PPD Medical Director 18-Mar-2025 14:58:48 GMT+0000
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Approval	PPD Statistician 18-Mar-2025 20:31:54 GMT+0000
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