Protocol J4H-MC-FVAA (b)

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3972406 in Adults With Moderate-to-Severe Plaque Psoriasis

NCT06176768

Approval Date: 19-Jul-2024

Title Page

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Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3972406 in Adults with Moderate-to-Severe Plaque Psoriasis

Protocol Number: J4H-MC-FVAA

Amendment Number: b

Compound: LY3972406

Brief Title: A Study of LY3972406 in Adults with Moderate-to-Severe Plaque Psoriasis

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number:

IND: 165890

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

Document ID: VV-CLIN-075822

Medical monitor name and contact information will be provided separately.

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	*31-Oct-2023*
Original Protocol	*28-Mar-2023*

Overall Rationale for the Amendment:

The primary purpose of this amendment is to allow WOCBP to participate in the study and streamline study activities.

These and other changes and a brief rationale are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
1.3.1. Schedule of Activities for Screening and Treatment Periods of Study J4H-MC-FVAA	Removed rows "Clinical photography, trunk of the body" and "Clinical photography, target lesions"	To streamline study activities
	Added serum pregnancy at V1	To allow WOCBP to participate in the study
	Added urine pregnancy (local) at V2, V5, V7, V9 and added comments	To allow WOCBP to participate in the study
	In comments of follicle stimulating hormone (FSH) row, changed "postmenopausal" to "menopausal"	To align with latest contraception guidance in Section 10.4
	Added "Optional" in the comments of skin biopsy	To streamline study activities
1.3.2. Schedule of Activities for ED, Unscheduled Visits, and Post-Treatment Follow-up of Study J4H-MC-FVAA	Added urine pregnancy (local) at ED, V802 and added comments	To allow WOCBP to participate in the study
	Updated Abbreviations list in the footnote	Editorial consistency
2.2. Background	Updated subsection "Preclinical safety" to include data relevant to repeat dose toxicity studies in CCI and CCI and embryo fetal developmental studies in CCI and CCI	To align with the latest Investigator's Brochure
5.1. Inclusion Criteria	Updated criterion #2 to read "Are men, women of childbearing potential (WOCBP) who agree to adhere to contraceptive requirements for the study or women not of childbearing potential (WNOCBP)"	To allow WOCBP to participate in the study
	In criterion #7,	To streamline study activities

Section # and Name	Description of Change	Brief Rationale
	• Changed skin biopsy from required to optional • Removed the 4th bullet on the lesion being distinct from the one being photographed	
	Removed criterion #8 on photography	To streamline study activities
5.2. Exclusion Criteria	Removed criterion #46 on photography of participants having identifiable skin findings	To streamline study activities
CCI		
8.2.7. Pregnancy Testing	Added details on pregnancy testing for participants who become pregnant	To allow WOCBP to participate in the study
10.2. Appendix 2: Clinical Laboratory Tests	In notes of low-density lipoprotein cholesterol, revised triglycerides level from ">400 mg/dL" to "≥400 mg/dL"	Editorial correction
	Added serum pregnancy and urine pregnancy under "Hormones (female)" and added notes	To allow WOCBP to participate in the study
10.4. Appendix 4: Contraceptive and Barrier Guidance	Added contraception guidance for female participants	To allow WOCBP to participate in the study
	Revised the contraception guidance for male participants	To align with the findings from embryo fetal developmental studies
10.9. Appendix 9: Photography	Removed the appendix	To streamline study activities
10.10. Appendix 10: Noninvasive Skin Sampling and Skin Punch Biopsy	• Updated the section to clarify that agreement to participate in skin punch biopsy procedure is optional • Removed the statement on the lesion selected for biopsy being distinct from the one selected for clinical photography • Renamed subsection "skin punch biopsy" to "skin punch biopsy (optional)" and added "As stated in the SoA, lesional and nonlesional biopsy samples will be collected at the randomization visit (baseline;	To streamline study activities

Section # and Name	Description of Change	Brief Rationale
	Visit 2) <u>for all participants who consent to this procedure</u>"	
10.11.1 Permitted Concomitant Medications	In topical steroids and emollients, revised the 2nd bullet in comments column as: "Emollients may be used on nontarget lesions (that is, plaque psoriasis lesions that have not been or will not be sampled via CCI or skin biopsy ~~or photographed~~, if applicable) only if applied using a stable regimen beginning at least 14 days prior to baseline (Visit 2/randomization) and maintained throughout the study"	To align with removal of photography
10.15. Appendix 15: Protocol Amendment History	Added amendment (a) summary of changes table	To update the amendment history
Throughout the protocol	Minor editorial changes	For consistency

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3972406 in Adults with Moderate-to-Severe Plaque Psoriasis

Brief Title: A Study of LY3972406 in Adults with Moderate-to-Severe Plaque Psoriasis

Regulatory Agency Identifier Number:

IND: 165890

Rationale:

This study will evaluate the efficacy and safety of LY3972406 in adults with moderate-to-severe plaque psoriasis. This is the first Phase 2 study for this compound, and data from this study will inform decisions for the clinical development of LY3972406.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To compare the efficacy of LY3972406 versus placebo in the treatment of participants with moderate-to-severe plaque psoriasis	• Proportion of participants achieving PASI 75 at Week 12
Secondary	

• To compare the efficacy of LY3972406 versus placebo, as measured by improvement in clinical signs and symptoms	• Proportion of participants achieving the following at Week 12
	  ○ PASI 90
	  ○ PASI 100
	  ○ sPGA 0 (clear), or
	  ○ sPGA 0/1 (clear or almost clear).
	• PASI percent change from baseline to Week 12
	• BSA mean change from baseline to Week 12
	• Proportion of participants who achieve PSSI score of 0[a] at Week 12
	• PSSI mean change from baseline to Week 12[a]

• To compare patient-reported outcomes from participants who received LY3972406 to those who received placebo	• Mean change from baseline to Week 12 for quality-of-life measures
	  ○ DLQI
	  ○ PatGA Psoriasis, and

Objectives	Endpoints
	○ PSS.
• To characterize the PK of LY3972406	• Observed trough LY3972406 plasma concentration at Week 12
• To describe the safety of LY3972406 in participants with psoriasis	Summary of safety data, including number and incidence of • SAEs • TEAEs • Discontinuations due to AE

Abbreviations: AE = adverse event; BSA = body surface area; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; PatGA Psoriasis = Patient's Global Assessment of Psoriasis; PK = pharmacokinetics; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; SAE = serious adverse event; sPGA = Static Physician's Global Assessment; TEAE = treatment-emergent adverse event.

[a] Only for participants with baseline scalp psoriasis involvement, defined as baseline PSSI >0.

Estimands

The primary clinical question of interest is:

> What is the difference between each dosing regimen of LY3972406 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 an adverse event (AE)?

The efficacy estimands are described by the following attributes:

- Estimand strategy
  - Binary endpoints: hybrid of composite variable and treatment policy estimands
  - Continuous endpoints: hypothetical
- Population: Adults with moderate-to-severe plaque psoriasis
- Endpoints
  - Binary: PASI 75, PASI 90, PASI 100, sPGA 0 (clear), sPGA 0/1 (clear or almost clear), and PSSI 0
  - Continuous: PASI, BSA, DLQI, PatGA Psoriasis, PSSI, and PSS
- Timepoints: Week 12 for all endpoints

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- How to account for intercurrent events (ICEs):
  - ICEs related to study intervention include the use of prohibited concomitant medication and early discontinuation from the study or study intervention due to lack of efficacy or an AE. Participants with ICEs related to study intervention will be considered as a treatment failure (binary endpoints) or missing at random (continuous endpoints) from the time of the ICE.
  - 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:
  - Binary endpoints: Difference in proportion of participants achieving response between each dosing regimen of LY3972406 and placebo
  - Continuous endpoints: Mean difference between each dosing regimen of LY3972406 and placebo
- 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 an AE, the participant experienced a burden of the study intervention that outweighed its benefits.
  - All remaining ICEs are considered unrelated to the study intervention.

The safety estimand will be evaluated on each dosing regimen of LY3972406 and placebo on the safety analysis set. The estimand is described with the following attributes:

- Population: Adults with moderate-to-severe plaque psoriasis who had at least 1 dose of the study intervention
- Endpoints: SAEs, TEAEs, and discontinuations due to AE
- Timepoints: All aggregated timepoints
- Population-level summary: Proportion of participants experiencing the safety endpoint

The occurrence of ICEs is irrelevant.

Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of LY3972406 in adults with moderate-to-severe plaque psoriasis. This is a 12-week study with follow-up visits up to 12 weeks after the last dose of intervention. The design will have 2 stages:

- In Stage 1, the participants will be randomly assigned to receive LY3972406 CCI or placebo CCI
- If Stage 2 is implemented, the participants will be randomly assigned to receive either

  LY3972406 CCI LY3972406 CCI or placebo CCI

  OR

  LY3972406 CCI or placebo CCI

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Brief Summary:

The purpose of this study is to measure how LY3972406 compares with placebo in improving the signs and symptoms of plaque psoriasis.

Study details include:

- The study duration will be up to 29 weeks.
- The treatment duration will be up to 12 weeks.
- The treatment period will be double-blind, which means neither the participants nor the researchers will know which study intervention participants are receiving until the study is over.
- During the treatment period, the visit frequency will be every 2 weeks starting at Week 2. During the post-treatment follow-up, the visit frequency will be every 2 weeks for the first 2 visits and then every 4 weeks for the last 2 visits.
    - The last 2 visits will not be performed for participants with a PASI score at or after Week 16 that is greater than or equal to the baseline PASI score.

Study Population:

Adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

Number of Participants:

Approximately CCI participants will be randomly assigned.

Intervention Groups and Duration:

In Stage 1, approximately CCI study participants will be treated with LY3972406 CCI or placebo CCI The results of one or more interim analyses with Stage 1 participant data will be used to determine whether Stage 2 will be implemented.

Stage 2 may be initiated at the sponsor's discretion post review of the interim analysis data from Stage 1, to collect additional safety and efficacy data at the CCI dose level. If Stage 2 is implemented, approximately an additional CCI participants will be enrolled and will be treated with LY3972406 CCI placebo, and potentially CCI

As indicated in the "Brief Summary" section of this Synopsis, the treatment duration in this study will be up to 12 weeks.

Ethical Considerations of Benefit/Risk:

Study J4H-MC-FVAA (FVAA) is the first clinical study evaluating LY3972406 in psoriasis patients, so there are no clinical efficacy data to support the benefit of LY3972406. Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

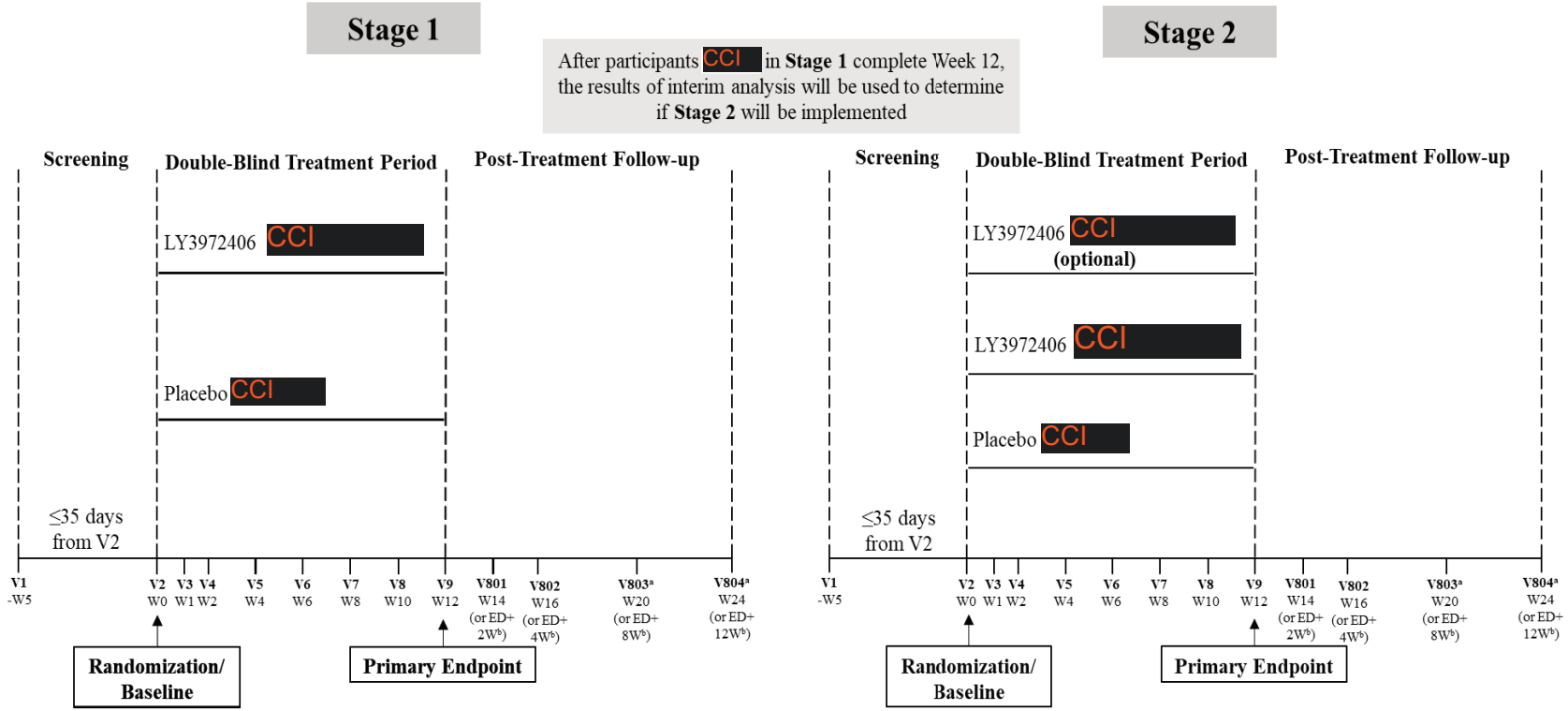
The safety profile of LY3972406 has been characterized thus far in nonclinical toxicology studies and in a Phase 1 study of healthy adult participants. The safety profile thus far is appropriate to test LY3972406 in Study FVAA to characterize the benefit/risk profile in patients

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 will review the interim efficacy, safety, and PK/PD data in an unblinded fashion.

1.2. Schema



Abbreviations: ED = early discontinuation; n = number of participants; CCI ; V = visit; W = week.

For randomization ratios, see Section 4.1.

[a] Visits 803 and 804 are not required for all participants (see Section 7.2 for details).

[b] For the follow-up visits, the weeks in parentheses indicate weeks after the last dose.

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities for the Screening and Treatment Periods of Study J4H-MC-FVAA

Study J4H-MC-FVAA	Screening	Double-Blind Treatment Period								Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	≤5	—	1	2	4	6	8	10	12	
Visit interval tolerance (days)	≤35	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		X							X	Participants should not eat or drink anything except water for 12 hours before the visit.
Informed consent	X									The informed consent form must be signed before any protocol-specific tests/procedures are performed.
Inclusion and exclusion criteria, review and confirm	X	X								
Demographics	X									Includes year of birth, sex, ethnicity (where permissible), and race.
Preexisting conditions and medical history, including relevant surgical history	X									Collect all ongoing conditions and relevant past surgical and medical history.
Prespecified medical history (indication and history of interest)	X									Includes psoriasis diagnosis, onset, and last clinically significant flare. Also includes comorbidities such as diabetes, coronary artery disease, stroke, IBD, and psoriatic arthritis.
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	X	

Study J4H-MC-FVAA	Screening	Double-Blind Treatment Period								Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	≤5	—	1	2	4	6	8	10	12	
Visit interval tolerance (days)	≤35	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		X							X	Participants should not eat or drink anything except water for 12 hours before the visit.
Adverse events (AEs)	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 8.3.1. Additional data will be collected for infection-related AEs (Section 8.3.4).
Physical evaluation										
Height	X									Participant should remove shoes.
Weight	X									
Vital signs	X	X	X	X	X	X	X	X	X	See Section 8.2.1.
Physical examination	X									See Section 8.2.2. The complete physical examination excludes pelvic, rectal, and breast examinations, unless clinically indicated. This physical examination includes assessment of tuberculosis (TB) risk factors and symptoms or signs of TB, including an assessment of peripheral lymph nodes (see Section 8.2.8).
Symptom-directed physical assessment		X	X	X	X	X	X	X	X	As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations. At least every 3 months, assess for TB risk factors, and for signs and symptoms of active TB, including examination of peripheral lymph nodes; see Section 8.2.8.
12-lead ECG (central)	X	X			X		X		X	At Visit 2, a predose and a postdose ECG should be collected. The postdose ECG should be collected prior to the first

Study J4H-MC-FVAA	Screening	Double-Blind Treatment Period								Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	≤5	—	1	2	4	6	8	10	12	
Visit interval tolerance (days)	≤35	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		X							X	Participants should not eat or drink anything except water for 12 hours before the visit.
										postdose PK sample (scheduled between 0.5 and 2 hours after the dose). Collect ECG at least 30 minutes before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. See Section 8.2.4.
Chest x-ray (local)	X									Posterior-anterior (PA) and, if needed, lateral view. Interpreted and reported by a radiologist or pulmonologist. Chest x-ray is not required if one was performed within 3 months prior to Visit 1 and if sufficient documentation exists for the TB evaluation. See Section 8.2.5.
CCI										
Patient-reported outcomes (electronic)										Complete prior to any clinician-administered assessments.
Psoriasis Symptoms Scale (PSS)		X			X		X		X	

Study J4H-MC-FVAA	Screening	Double-Blind Treatment Period								Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	≤5	—	1	2	4	6	8	10	12	
Visit interval tolerance (days)	≤35	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		X							X	Participants should not eat or drink anything except water for 12 hours before the visit.
Patient's Global Assessment of Psoriasis (PatGA Psoriasis)		X			X		X		X	
Dermatology Life Quality Index (DLQI)		X				X			X	
CCI										
Clinician-administered assessments (electronic)										Complete in the order listed here.
Body Surface Area (BSA)	X	X	X	X	X	X	X	X	X	
Psoriasis Activity and Severity Index (PASI)	X	X	X	X	X	X	X	X	X	Emollients and other topical treatments should be avoided approximately 24 hours prior to visits requiring the PASI assessment. See Section 10.11.1.
Psoriasis Scalp Severity Index (PSSI)		X	X	X	X	X	X	X	X	Only for participants with scalp involvement at baseline.
Static Physician's Global Assessment (sPGA)	X	X	X	X	X	X	X	X	X	
Fitzpatrick Scale of Skin Phototypes		X								
Clinician-administered assessments (paper)										
CCI										

Study J4H-MC-FVAA	Screening	Double-Blind Treatment Period								Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	≤5	—	1	2	4	6	8	10	12	
Visit interval tolerance (days)	≤35	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		X							X	Participants should not eat or drink anything except water for 12 hours before the visit.
Laboratory tests and sample collections										
Hematology	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	
Estimated glomerular filtration rate (eGFR)	X	X							X	Will be calculated by the Lilly-designated laboratory using the CKD-EPI creatinine equation (2021).
Lipid panel		X							X	If a participant attends these visits in a nonfasting state, the sample should still be collected. This will not be considered a protocol deviation.
Urinalysis	X	X							X	
Serum pregnancy	X									
Urine pregnancy (local)		X			X		X		X	Urine pregnancy test will be done for all WOCBP. See Sections 8.2.7 and 10.4. Additional urine pregnancy testing can be performed as required during the study or at the investigator's discretion or if required per local regulations.
Follicle stimulating hormone (FSH)	X									Optional; performed as needed to confirm menopausal status. See Section 10.4.1.
Tuberculosis (TB) test	X									See Appendix 2, Section 10.2. Participants who had a tuberculin skin test (TST) must have the test read 48 to 72 hours after placement. The TST test does not need to be read at the site but must be read by a trained professional and results must be presented to the site prior to first dose of

Study J4H-MC-FVAA	Screening	Double-Blind Treatment Period								Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	≤5	—	1	2	4	6	8	10	12	
Visit interval tolerance (days)	≤35	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		X							X	Participants should not eat or drink anything except water for 12 hours before the visit.
										study intervention. See Section 8.2.8 and Appendix 7, Section 10.7.
HIV screening tests	X									
Hepatitis C Virus (HCV) screening tests	X									If HCV antibody test is positive, it must be followed by an HCV RNA test. See Section 8.2.10.
Hepatitis B Virus (HBV) screening tests	X									Includes testing for HBsAg and anti-HBc. See Section 8.2.9.
HBV DNA	X								X	Only for participants who are positive for anti-HBc at screening. See Section 8.2.9.
CCI										
C-reactive protein, high-sensitivity (hsCRP)		X							X	
Pharmacokinetic (PK) samples (predose)		X			X	X	X		X	Starting at Visit 5, for each PK sample collected, record time and date of previous dose administration.
Pharmacokinetic (PK) samples (postdose)		X		X					X	For each PK sample collected, record time and date of previous dose administration. At Visit 2 and Visit 9, collect 2 PK samples: one in the period of 0.5 to 2 hours and one in the period of 3 to 4 hours postdose. At Visit 4 collect at any time postdose. All actual sample dates and times should be recorded.
Stored samples										
Genetics sample		X								Sample can be obtained at or after the specified visit.

Study J4H-MC-FVAA	Screening	Double-Blind Treatment Period								Comments
Visit number	1	2	3	4	5	6	7	8	9	
Weeks from randomization	≤5	—	1	2	4	6	8	10	12	
Visit interval tolerance (days)	≤35	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		X							X	Participants should not eat or drink anything except water for 12 hours before the visit.
CCI										
Skin biopsy		X							X	Optional **Visit 2:** 1 biopsy each of lesional and non-lesional skin. **Visit 9:** 1 biopsy of lesional skin. See Appendix 10, Section 10.10
Randomization and dosing										
Register visit with IWRS	X	X	X	X	X	X	X	X	X	
Randomization via IWRS		X								
Dispense study intervention to participant (for at home dosing)		X			X		X			
Observe participant administer study intervention		X		X	X		X		X	Participants will be instructed to withhold study intervention on study visit days, until after predose laboratory samples have been collected.
Participant brings study intervention			X	X	X	X	X	X	X	
Assess study intervention compliance			X	X	X	X	X	X	X	

1.3.2. Schedule of Activities for ED, Unscheduled Visits, and Post-Treatment Follow-up of Study J4H-MC-FVAA

Study J4H-MC-FVAA			Post-Treatment Follow-up				Comments
Visit number	ED	UV*	801	802	803**	804**	For discontinuations that occur before Visit 802, see the activities listed for ED in this table.
Weeks from randomization	—	—	14 or ED + 2 weeks after last dose	16 or ED + 4 weeks after last dose	20 or ED + 8 weeks after last dose	24 or ED + 12 weeks after last dose	* For unscheduled visits (UV), additional safety laboratory tests and procedures should be performed as needed. ** V803 and V804 will only be performed if the PASI score from the previous visit (V802 and V803, respectively) is less than the baseline PASI score (see Section 7.2).
Visit interval tolerance (days)	—	—	±3	±3	±7	±7	
Fasting visit	X						Participants should not eat or drink anything except water for 12 hours before the visit.
Concomitant medications	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 8.3.1. Additional data will be collected for infection-related AEs (Section 8.3.4).
Physical evaluation							
Weight	X			X			
Vital signs	X	X	X	X	X	X	See Section 8.2.1.
Symptom-directed physical assessment	X	X	X	X	X	X	As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations. At least every 3 months, assess for tuberculosis (TB) risk factors, and for signs and symptoms of active TB, including examination of peripheral lymph nodes; see Section 8.2.8.
12-lead ECG (central)	X						Collect ECG at least 30 minutes before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. See Section 8.2.4.

Study J4H-MC-FVAA			Post-Treatment Follow-up				Comments
Visit number	ED	UV*	801	802	803**	804**	For discontinuations that occur before Visit 802, see the activities listed for ED in this table.
Weeks from randomization	—	—	14 or ED + 2 weeks after last dose	16 or ED + 4 weeks after last dose	20 or ED + 8 weeks after last dose	24 or ED + 12 weeks after last dose	* For unscheduled visits (UV), additional safety laboratory tests and procedures should be performed as needed. ** V803 and V804 will only be performed if the PASI score from the previous visit (V802 and V803, respectively) is less than the baseline PASI score (see Section 7.2).
Visit interval tolerance (days)	—	—	±3	±3	±7	±7	
Fasting visit	X						Participants should not eat or drink anything except water for 12 hours before the visit.
CCI							
Patient-reported outcomes (electronic)							Complete prior to any clinician-administered assessments in the order listed here.
Psoriasis Symptoms Scale (PSS)	X			X		X	
Patient's Global Assessment of Psoriasis (PatGA Psoriasis)	X			X		X	
Dermatology Life Quality Index (DLQI)	X			X		X	
CCI							

Study J4H-MC-FVAA			Post-Treatment Follow-up				Comments
Visit number	ED	UV*	801	802	803**	804**	For discontinuations that occur before Visit 802, see the activities listed for ED in this table.
Weeks from randomization	—	—	14 or ED + 2 weeks after last dose	16 or ED + 4 weeks after last dose	20 or ED + 8 weeks after last dose	24 or ED + 12 weeks after last dose	* For unscheduled visits (UV), additional safety laboratory tests and procedures should be performed as needed. ** V803 and V804 will only be performed if the PASI score from the previous visit (V802 and V803, respectively) is less than the baseline PASI score (see Section 7.2).
Visit interval tolerance (days)	—	—	±3	±3	±7	±7	
Fasting visit	X						Participants should not eat or drink anything except water for 12 hours before the visit.
Clinician-administered assessments (electronic)							
Body Surface Area (BSA)	X		X	X	X	X	
Psoriasis Activity and Severity Index (PASI)	X	X	X	X	X	X	At UV, PASI assessment is optional but recommended if UV is to evaluate an AE or an increase in disease activity. Emollients and other topical treatments should be avoided approximately 24 hours prior to visits requiring the PASI assessment. See Section 10.11.1.
Psoriasis Scalp Severity Index (PSSI)	X		X	X	X	X	Only for participants with scalp involvement at baseline.
Static Physician's Global Assessment (sPGA)	X		X	X	X	X	
Clinician-administered assessments (paper)							
CCI							

Study J4H-MC-FVAA			Post-Treatment Follow-up				Comments
Visit number	ED	UV*	801	802	803**	804**	For discontinuations that occur before Visit 802, see the activities listed for ED in this table.
Weeks from randomization	—	—	14 or ED + 2 weeks after last dose	16 or ED + 4 weeks after last dose	20 or ED + 8 weeks after last dose	24 or ED + 12 weeks after last dose	* For unscheduled visits (UV), additional safety laboratory tests and procedures should be performed as needed. ** V803 and V804 will only be performed if the PASI score from the previous visit (V802 and V803, respectively) is less than the baseline PASI score (see Section 7.2).
Visit interval tolerance (days)	—	—	±3	±3	±7	±7	
Fasting visit	X						Participants should not eat or drink anything except water for 12 hours before the visit.
Laboratory tests and sample collections							
Hematology	X		X	X	X	X	
Clinical chemistry	X		X	X	X	X	
Estimated glomerular filtration rate (eGFR)	X						Will be calculated by the Lilly-designated laboratory using the CKD-EPI creatinine equation (2021).
Lipid panel	X						Lipid panel to be collected at ED *only* if ED is before Week 12. If a participant attends this visit in a nonfasting state, the sample should still be collected. This will not be considered a protocol deviation.
Urine pregnancy (local)	X			X			Urine pregnancy test will be done for all WOCBP. See Sections 8.2.7 and 10.4. Additional urine pregnancy testing can be performed as required during the study or at the investigator's discretion or if required per local regulations.
Urinalysis	X						
HBV DNA	X					X	Only for participants who are positive for anti-HBc at screening. See Section 8.2.9.
CCI							

Study J4H-MC-FVAA			Post-Treatment Follow-up				Comments
Visit number	ED	UV*	801	802	803**	804**	For discontinuations that occur before Visit 802, see the activities listed for ED in this table.
Weeks from randomization	—	—	14 or ED + 2 weeks after last dose	16 or ED + 4 weeks after last dose	20 or ED + 8 weeks after last dose	24 or ED + 12 weeks after last dose	* For unscheduled visits (UV), additional safety laboratory tests and procedures should be performed as needed. ** V803 and V804 will only be performed if the PASI score from the previous visit (V802 and V803, respectively) is less than the baseline PASI score (see Section 7.2).
Visit interval tolerance (days)	—	—	±3	±3	±7	±7	
Fasting visit	X						Participants should not eat or drink anything except water for 12 hours before the visit.
C-reactive protein, high-sensitivity (hsCRP)	X						
Pharmacokinetic (PK) samples	X						For each PK sample collected, record time and date of previous dose administration. Sample can be obtained at any time during the visit.
Stored samples							
CCI [redacted]							
Dosing							
Register visit with IWRS	X		X	X	X	X	
Participant returns study intervention	X						
Assess study intervention compliance	X						

Abbreviations: anti-HBc = antibody to hepatitis B core antigen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration [equation]; ECG = electrocardiogram; ED = early discontinuation; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; IWRS = interactive web-response system; CCI [redacted]; UV = unscheduled visit; V = visit; WOCBP = women of childbearing potential.

2. Introduction

2.1. Study Rationale

Study J4H-MC-FVAA (FVAA) will evaluate the efficacy and safety of LY3972406 in adults with moderate-to-severe plaque psoriasis. This is the first Phase 2 study for this compound, and data from this study will inform decisions for the clinical development of LY3972406.

2.2. Background

Disease state and treatment goals

Psoriasis is a common chronic inflammatory skin disease; it is increasingly being recognized as a systemic inflammatory disorder (Takeshita et al. 2017). This lifelong and life-shortening disease is manifested by prototypic red, thick, and scaly plaques. Plaque psoriasis is the most common form and has been shown to have a significant impact on the overall health of patients. Along with an association with inflammatory arthritis in the form of psoriatic arthritis, plaque psoriasis is associated with increased risk for multiple comorbid conditions, including myocardial infarction and stroke, metabolic syndrome, diabetes mellitus, malignancies, chronic renal insufficiency, gastrointestinal disease, and liver abnormalities (Yeung et al. 2013; Takeshita et al. 2017). The life span of patients with moderate-to-severe plaque psoriasis may be shortened by as many as 5 years (Ryan and Kirby 2015), partly due to association with cardiovascular comorbidities (Gelfand et al. 2006; Ryan and Kirby 2015).

LY3972406 and the role of CCI diseases

LY3972406 CCI is a CCI a member of the CCI effects, including

- controlling the activity of CCI , as well as the CCI and CCI of CCI
- triggering CCI and
- facilitating CCI .

The CCI effect of CCI is mediated by its ability to regulate the CCI dependent CCI involved in CCI and it is expressed at CCI compared to CCI The CCI expression of CCI cells makes it an attractive target to modify disease CCI such as CCI CCI In psoriatic lesions, CCI and targeting these cells has demonstrated benefit in patients with psoriasis CCI In addition, targeting CCI resulted in improved disease CCI and clinical efficacy in psoriasis patients CCI

Nonclinical and clinical data for LY3972406

More detailed information about the nonclinical and clinical data for LY3972406 may be found in the IB.

Preclinical pharmacology

Preclinical *in vitro* pharmacology studies for LY3972406 demonstrate high potency CCI with a IC_{50} of CCI LY3972406 was also shown *in vitro* to have potential CCI effects, as it CCI

The preclinical *in vivo* efficacy of LY3972406 has also been evaluated in a CCI, in which clinical scores and CCI were CCI compared to the vehicle control group. CCI scores were also CCI with LY3972406. Furthermore, in the CCI LY3972406 was shown to improve CCI markers.

Preclinical safety

Toxicology studies of up to CCI in CCI and CCI in CCI were conducted to support Study FVAA(b). There were no adverse changes related to LY3972406 observed in the CCI CCI Fur discoloration manifesting as paleness of brown fur with correlating depigmentation of hair follicles from brown-haired skin, but no degenerative change, was observed in CCI in the 9-month repeat dose study. This observation was initially noted after at least 20 weeks of dosing at 200 mg/kg/day dose in both sexes and during or after Week 23 in females dosed at 30 mg/kg/day. Clinical pathology assessments performed at Weeks 12, 22, 26, and 39 were not suggestive of any health concerns. Additionally, minor corneal opacities observed after 9 months at the highest dose of 200 mg/kg/day did not cause apparent visual deficit, and increased PR and QRS interval durations on Day 3, Day 135, and in Week 39 at 200 mg/kg/day exhibited no correlating functional change.

In the CCI repeated dose study in CCI the CCI of LY3972406 was the CCI administered to CCI LY3972406 was CCI was observed CCI No liver effect was observed in the CCI repeated dose toxicity study in CCI at doses up to 200 mg/kg/day.

LY3972406 did not affect female fertility in CCI or result in embryo fetal toxicity in CCI or CCI at plasma concentrations (AUC-based) at least 28-fold higher than the projected clinical exposures.

Effects in humans

Initial safety and tolerability of LY3972406 have been evaluated in the Phase 1 study CCI which was a SAD (Part 1, CCI) and MAD (Part 2) study in

healthy adult participants. LY3972406 was administered in single doses ranging from CCI in the SAD and multiple doses from CCI in the MAD. There were CCI in the Phase 1 study. All TEAEs were CCI . The most common SOC TEAE reported was CCI occurring CCI of participants administered LY3972406 enrolled in CCI No CCI were recorded in CCI . CCI . There were CCI in laboratory test results, vital signs, ECGs, or physical examinations. All patients recovered and there were no study discontinuations.

The CCI and CCI and mean C_{max} occurred between CCI The mean elimination half-life ($t_{1/2}$) ranged from CCI

From available CCI the estimated margins of safety for CCI LY3972406 are CCI

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3972406 may be found in the IB.

2.3.1. Risk Assessment

Study intervention

Potential risks of LY3972406 are primarily based on nonclinical toxicology studies and the safety data from the Phase 1 study CCI . The target organ in nonclinical toxicology studies was the CCI . In the Phase 1 study, a TEAE of CCI As stated in Section 2.2, in humans, the most common TEAEs related to LY3972406 were CCI

CCI

Study procedures

The procedures in Study FVAA 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

Sections 5.1, 5.2, 7.1, and 8.2 address known potential risks associated with LY3972406.

Participants will be monitored closely in Study FVAA with scheduled visits every 1-2 weeks where safety procedures will be conducted, including AE reporting, vital signs, laboratory tests, physical assessments, and ECGs. Participants with elevated risk, including recent infection and significant liver function abnormalities, are excluded from the trial. Hepatic monitoring with guidance for study intervention interruption/discontinuation is described in Sections 8.2.11 and 7.1.1. In addition, blinded trial level safety reviews will be conducted by the study team on an ongoing basis, and an IAC will evaluate unblinded safety data as described in Sections 9.4 and 10.1.5.

2.3.2. Benefit Assessment

Study FVAA is the first clinical study evaluating LY3972406 in psoriasis patients, so there are no clinical efficacy data to support the benefit of LY3972406. Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

2.3.3. Overall Benefit Risk Conclusion

Study FVAA is the first clinical study to evaluate the efficacy and safety of LY3972406 in patients with psoriasis. The study has 2 stages. If Stage 2 is implemented, approximately an additional 35 participants will be enrolled. The safety profile of LY3972406 has been characterized thus far in nonclinical toxicology studies and in a Phase 1 study of healthy adult participants. The safety profile thus far is appropriate to test LY3972406 in Study FVAA to characterize the benefit/risk profile in patients with psoriasis. Close monitoring will be conducted in the study on both an individual and trial level to ensure participant safety.

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3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To compare the efficacy of LY3972406 versus placebo in the treatment of participants with moderate-to-severe plaque psoriasis	• Proportion of participants achieving PASI 75 at Week 12
Secondary	

• To compare the efficacy of LY3972406 versus placebo, as measured by improvement in clinical signs and symptoms	• Proportion of participants achieving the following at Week 12
	  ○ PASI 90
	  ○ PASI 100
	  ○ sPGA 0 (clear), or
	  ○ sPGA 0/1 (clear or almost clear).
	• PASI percent change from baseline to Week 12
	• BSA mean change from baseline to Week 12
	• Proportion of participants who achieve PSSI score of 0[a] at Week 12
	• PSSI mean change from baseline to Week 12[a]

• To compare patient-reported outcomes from participants who received LY3972406 to those who received placebo	• Mean change from baseline to Week 12 for quality-of-life measures
	  ○ DLQI
	  ○ PatGA Psoriasis, and
	  ○ PSS.

• To characterize the PK of LY3972406	• Observed trough LY3972406 plasma concentration at Week 12
• To describe the safety of LY3972406 in participants with psoriasis	Summary of safety data, including number and incidence of • SAEs • TEAEs • Discontinuations due to AE

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Objectives	Endpoints
Exploratory	
Exploratory objectives and endpoints may include, but are not limited to, evaluations of the following at various study time points in participants with moderate-to-severe plaque psoriasis: CCI Additional details will be provided in the SAP.	

Abbreviations: AE = adverse event; BSA = body surface area; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; PatGA Psoriasis = Patient's Global Assessment of Psoriasis; CCI PK = pharmacokinetics; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; SAE = serious adverse event; SAP = statistical analysis plan; sPGA = Static Physician's Global Assessment; TEAE = treatment-emergent adverse event.

[a] Only for participants with baseline scalp psoriasis involvement, defined as baseline PSSI >0.

Estimands

The primary clinical question of interest is:

> What is the difference between each dosing regimen of LY3972406 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 an AE?

The efficacy estimands are described by the following attributes:

- Estimand strategy
  - Binary endpoints: hybrid of composite variable and treatment policy estimands
  - Continuous endpoints: hypothetical
- Population: Adults with moderate-to-severe plaque psoriasis
- Endpoints
  - Binary: PASI 75, PASI 90, PASI 100, sPGA 0 (clear), sPGA 0/1 (clear or almost clear), and PSSI 0
  - Continuous: PASI, BSA, DLQI, PatGA Psoriasis, PSSI, and PSS
- Timepoints: Week 12 for all endpoints

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- How to account for ICEs:
    - ICEs related to study intervention include the use of prohibited concomitant medication and early discontinuation from the study or study intervention due to lack of efficacy or an AE. Participants with ICEs related to study intervention will be considered as a treatment failure (binary endpoints) or missing at random (continuous endpoints) from the time of the ICE.
    - 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:
    - Binary endpoints: Difference in proportion of participants achieving response between each dosing regimen of LY3972406 and placebo
    - Continuous endpoints: Mean difference between each dosing regimen of LY3972406 and placebo
- 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 an AE, the participant experienced a burden of the study intervention that outweighed its benefits.
    - All remaining ICEs are considered unrelated to the study intervention.

The safety estimand will be evaluated on each dosing regimen of LY3972406 and placebo on the safety analysis set. The estimand is described with the following attributes:

- Population: Adults with moderate-to-severe plaque psoriasis who had at least 1 dose of the study intervention
- Endpoints: SAEs, TEAEs, and discontinuations due to AE
- Timepoints: All aggregated timepoints
- Population-level summary: Proportion of participants experiencing the safety endpoint

The occurrence of ICEs is irrelevant.

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4. Study Design

4.1. Overall Design

Study FVAA is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of LY3972406 in adults with moderate-to-severe plaque psoriasis.

The study duration will be approximately 29 weeks over 3 study periods:

- **Screening**: occurs within 35 days before the planned randomization visit (baseline; Visit 2/Week 0)
- **Double-blind treatment period**: lasts for 12 weeks from baseline
- **Post-treatment follow-up**: lasts for up to 12 weeks after last treatment visit (or last dose for ED) (Visits 801-804)

  Note: Visits 803 and 804 will only be performed if the PASI score from the previous visit (Visits 802 and 803, respectively) is less than the baseline PASI score (see Section 7.2 for details).

See SoA (Section 1.3) for additional details about the study visits and visit specific- assessments. The study schema is presented in Section 1.2.

The study will have 2 stages.

- In Stage 1, approximately CCI participants will be randomly assigned to receive LY3972406 CCI or placebo CCI
- Stage 2 may be initiated at the sponsor's discretion post review of the interim analysis data from Stage 1, to collect additional safety and efficacy data at the CCI dose level (see Section 9.4). If Stage 2 is implemented, approximately an additional CCI participants will be enrolled. The participants will be randomly assigned to receive either

  LY3972406 CCI, LY3972406 CCI or placebo CCI

  OR

  LY3972406 CCI or placebo CCI

For randomization stratification factors, see Section 6.3.

4.2. Scientific Rationale for Study Design

Primary endpoint definition

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).

Duration of the treatment period and post-treatment follow-up

The 12-week duration of the treatment period is appropriate for assessing efficacy based on achieving steady state concentrations after CCI with LY3972406 and allowing sufficient time for pharmacological effects to occur. This duration is also supported by the toxicology data for LY3972406 available at the time this study was designed.

The post-treatment follow-up can be up to 12 weeks and is designed to capture any additional safety signals and assess time to potential relapse.

Choice of control and number of treatment groups

Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the trial conditions. The double-blind (that is, blinded to investigator, participant, and sponsor staff who are involved in the treatment or clinical evaluation of the participants), randomized, placebo-controlled design minimizes bias on safety and tolerability assessments and allows a more robust comparison among LY3972406 doses and placebo.

Demographics collection

In this study, collection of demographic information includes ethnicity (as allowed per local regulations) and race. 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.

4.2.1. Patient Input into Design

Not applicable.

4.3. Justification for Dose

The relationship between dose, exposure, and efficacy for CCI has not been established for psoriasis.

The planned dosing regimens of LY3972406 in Study FVAA are CCI These doses were selected based on CCI

In Study CCI From available CCI (see the IB for more details).

The planned dose levels of CCI will evaluate an exposure range that is anticipated to be CCI . Each dose is targeted to achieve CCI , approximately CCI

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.

5. Study Population

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 the study only if all the following criteria apply:

Age

[1] Participant must be 18 to 75 years of age inclusive, at the time of signing the informed consent.

Sex and contraceptive requirements

[2] Are men, women of childbearing potential (WOCBP) who agree to adhere to contraceptive requirements for the study or women not of childbearing potential (WNOCBP).

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

Definitions and contraception requirements for participants in this study are provided in Appendix 4, Section 10.4.

Type of participant and disease characteristics

[3] Participants who have moderate-to-severe chronic plaque psoriasis for at least 6 months prior to baseline based on investigator-confirmed diagnosis of chronic psoriasis vulgaris, with these criteria

a. Plaque psoriasis involving ≥10% BSA and absolute PASI score ≥12 in affected skin at screening (Visit 1) and randomization/baseline (Visit 2).
b. sPGA score of ≥3 at Visit 1 and Visit 2.

Study procedures

[4] Have venous access sufficient to allow for blood sampling.

[5] Are able to swallow oral medication.

[6] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures, including skin punch biopsies.

[7] For skin biopsy (optional) CCI [redacted] (required); see Appendix 10, Section 10.10: Have at least 1 lesion that

- represents the overall disease severity
- is located in a region that is preferably not exposed to the sun, and
- has a size of approximately 12 cm^2 at baseline or more.

[8] Inclusion Criterion [8] has been deleted

Weight

[9] Have a BMI within the range of 18 to 40 kg/m^2 (inclusive).

Informed consent

[10] Are capable of giving signed informed consent as described in Appendix 1, Section 10.1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Laboratory test results

[11] Have clinical laboratory test results within the ranges listed in this table, other test results within normal reference ranges, or test results with acceptable deviations that are judged to be not clinically significant by the investigator.

Note: one repeat test is allowed during screening for these tests.

5.2. Exclusion Criteria

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

Medical conditions

[12] Have a clinically significant flare of psoriasis during the 12 weeks before baseline.

[13] Have any other skin conditions, excluding plaque psoriasis, that would affect interpretation of data, including, but not limited to, scleroderma, eczema, drug-induced psoriasis, guttate psoriasis, pustular psoriasis, or parapsoriasis, as judged by the investigator.

[14] Have a diagnosis of immune-mediated conditions that are commonly associated with psoriasis for which a participant requires current systemic (oral, subcutaneous, or intravenous) immunosuppressant treatment (including corticosteroids and biologics).

[15] Have manifestations of other autoimmune diseases, such as systemic lupus erythematosus.

Infections and infectious disease

[16] 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.

[17] Have had any of these types of infections within 3 months prior to screening and up to randomization/baseline visit

- Serious: requiring hospitalization, or intravenous or equivalent oral antibiotic treatment
- Opportunistic: as defined in Winthrop et al. 2015 (see Appendix 8, Section 10.8)
- Chronic: duration of symptoms, signs or treatment of 6 weeks or longer
- Recurring: including, but not limited to herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis
    - Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over
    - 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 may be considered for enrollment if other eligibility criteria are met.

[18] Have HIV infection.

[19] Have a current infection with HBV; that is, positive for HBsAg and/or PCR positive for HBV DNA (see Section 8.2.9).

[20] Have a current infection with HCV; that is, positive for HCV RNA (see Section 8.2.10).

[21] Have active TB (see Section 8.2.8).

[22] Have or have had CCI that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization (WHO) or the United States Centers for Disease Control and Prevention (CDC), unless such treatment is underway (see Section 8.2.8).

Other medical conditions

[23] Have clinically significant ECG abnormalities including QTc, Fridericia's correction >450 msec for males and >470 msec for females.

[24] Have a history of additional risk factors for Torsades de Pointes such as, heart failure, hypokalemia, or a family history of long QT syndrome.

[25] Have clinically relevant abnormal blood pressure or heart rate as determined by the investigator.

[26] Have an unstable or uncontrolled illness, including but not limited to a cerebrocardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurologic disease, or abnormal laboratory values at screening, that in the opinion of the investigator would potentially affect participant safety within the study or interfere with the interpretation of data.

[27] Have a diagnosis or history of malignant disease within 5 years prior to baseline, with the following exceptions:

a. Basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
b. Cervical carcinoma in situ, with no evidence of recurrence within 5 years prior to baseline.

[28] Have a history of or current significant psychiatric disorders.

[29] Are, in the judgment of the investigator, actively suicidal and therefore deemed a significant risk for suicide.

CCI

[31] Have a history of major surgery within 12 weeks prior to screening or will require major surgery during the study.

[32] Have a history of significant allergies to lidocaine or other topical anesthetics used during skin biopsy.

Vaccines

[33] Have received any live vaccine (that is, live attenuated) within less than 4 weeks before randomization, or intend to receive a live vaccine during the study, or within 4 weeks after receiving the last 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.

[34] Have received a Bacillus Calmette-Guerin vaccine or treatment within less than 4 weeks before randomization or intend to during the study and within less than 5 half-lives after the last dose of intervention.

Prior/concomitant therapy

[35] Have received any investigational intervention within 4 weeks or 5 half-lives prior to screening, whichever is longer.

[36] Have a history of any disease that required treatment with oral or parenteral corticosteroids for more than 2 weeks within 24 weeks prior to screening.

[37] Have received biologic treatments for immune conditions, such as monoclonal antibodies, including marketed or investigational drugs, within 12 weeks or 5 half-lives prior to baseline, whichever is longer.

[38] Have received systemic nonbiologic treatment for immune conditions within 4 weeks prior to baseline (see Section 10.11.2).

[39] Have received topical psoriasis treatment within 14 days prior to baseline (see Section 10.11.2).

[40] Are unable or unwilling to avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline and during the study.

[41] Are currently using or plan to use medications that prolong the QT/QTc interval.

Prior/concurrent clinical study experience

[42] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other exclusions

[43] Have evidence of current, or history within 1 year prior to screening, of any substance use disorder(s) of any severity as defined by the DSM-V in the opinion of the investigator, excepting disorders of nicotine or caffeine use.

[44] Have donated blood of more than 500 mL within 4 weeks prior to screening.

[45] Have received blood products within 6 months prior to screening.

[46] Exclusion Criterion [46] has been deleted.

[47] Are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.

[48] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[49] Are unsuitable for inclusion in this study in the opinion of the investigator or the sponsor.

5.3. Lifestyle Considerations

Blood donation

Participants should not donate blood during participation in the study.

Sperm donation and contraception

See Appendix 4, Section 10.4.2.

CCI

Prohibited medications and procedures

See Section 10.11.2 for prohibited medications and procedures.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly 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 SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time and require a new identification number. Repeating of laboratory tests during the screening period does not constitute rescreening. See Section 8.2.8 and Appendix 7, Section 10.7 for retesting for TB.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

As stated in the SoA, study intervention will be self-administered by participants at home except for the visits specified in the SoA.

This table lists the interventions used in this clinical study.

Intervention Name	LY3972406	Placebo
Dose Level(s)	CCI	Not applicable
Frequency of Administration	CCI	
Route of Administration	Oral	Oral

Abbreviations: EU = European Union; CCI

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 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. For off-site (at-home) administration, sponsor will provide 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

The IWRS will allocate newly enrolling participants to groups according to the randomization ratios. For randomization ratios, see Section 4.1.

Participants will be stratified at baseline by prior exposure to biologic therapy for psoriasis (biologic naïve vs. biologic experienced).

6.4. Blinding

This is a double-blind study. Blinding will be maintained throughout the conduct of the study, as described in the separate Blinding and Unblinding Plan.

Investigators will remain blinded to each participant's assigned study intervention within each dose group, throughout the course of the study.

Emergency unblinding

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind.

Discontinuation from the study in case of unblinding

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study (Section 7.2). In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor's medical monitor for the participant to continue in the study.

6.5. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each applicable visit during the treatment period by counting returned capsules per bottle.

A participant will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses of study intervention during the study, unless the participant's study intervention is withheld by the investigator for safety reasons. Similarly, a participant will be considered significantly noncompliant if he or she is judged by the investigator to have taken 20% more than the prescribed amount of medication during the study.

Participants will be counseled by study staff on the importance of taking the study intervention as prescribed, as appropriate.

A record of the number of capsules dispensed to and returned by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention interruptions will also be recorded in the CRF.

Participant compliance will be further defined in the SAP.

6.6. Dose Modification

Dose modifications will not be allowed during this study.

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

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

6.8. Treatment of Overdose

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator 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.
- Obtain a plasma sample for PK analysis if requested.

6.9. Prior and Concomitant Therapy

See Appendix 11, Section 10.11 for lists of medications that are permitted or prohibited in this study.

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the participant is receiving at the time of enrollment or receives during the study must be recorded.

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 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.

Participants who require treatment with concomitant medications that are prohibited in this study will be permanently discontinued from the study intervention (Section 7.1.3).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

This section describes reasons for a participant's

- temporary or permanent discontinuation of study intervention (Section 7.1), or
- discontinuation (withdrawal) from the study (Section 7.2).

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7.1. Discontinuation of Study Intervention

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study intervention **based on liver test elevations in participants with normal or near-normal baseline liver tests**

In study participants with normal or near normal baseline liver tests (ALT, AST, ALP <1.5x ULN), the study intervention should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.11) if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA 2009 and other consensus guidelines, with minor modifications	

Interrupting study intervention **based on elevated liver tests in participants with abnormal baseline liver tests**

In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5x ULN), the study intervention should be **interrupted** if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >4x baseline	
ALT or AST >3x baseline for more than 2 weeks	
ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5x baseline, when the source of increased ALP is the liver	
ALP >2x baseline and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA 2009 and other consensus guidelines, with minor modifications	

Resuming or permanently discontinuing study intervention **after elevated liver tests**

Resumption of the study intervention can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non study-drug etiology is identified. Otherwise, the study intervention should be discontinued.

7.1.3. 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 ED visit and post-treatment follow-up as shown in the SoA.

Possible reasons leading to permanent discontinuation of study intervention include, but are not limited to, the following:

Participant decision

- The participant requests to discontinue the study intervention.

Pregnancy

- The participant becomes pregnant during the study.

Infections

A participant should be permanently discontinued from study intervention if the participant

- develops active TB or HIV infection during the study
- has untreated CCI or
- becomes HBV DNA or HCV RNA positive as described in Sections 8.2.9 and 8.2.10.

  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 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.

Suicidal ideation or behavior

A participant may also be discontinued from study intervention if they

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

Malignancy

The participant develops a malignancy (except for successfully treated basal or squamous cell skin carcinoma).

Hepatic event or liver test abnormality (Section 7.1.1)

Concomitant medications

- The participant requires treatment with prohibited medications specified in Section 10.11.2. The permanent discontinuation from the study intervention should occur before introduction of a prohibited medication.

Hematologic test abnormality: CCI [redacted]

[redacted]

Noncompliance: The investigator decides the participant is noncompliant with study drug administration or any other study procedure.

7.1.4. Temporary Discontinuation of Study Intervention

Temporary withholding of study intervention is required if the participant meets any of the criteria described in this table.

Criteria for temporary discontinuation of study intervention	Next steps
Infection criteria	
Serious or opportunistic infections, as defined in Section 5.2	Withhold until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment. If participant is diagnosed with CCI see Section 7.1.3.
HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification	• Contact sponsor's designated medical monitor. • Repeat HBV DNA testing as soon as feasible. • If HBV DNA is confirmed as positive, then intervention should be permanently discontinued, as described in Section 7.1.3.
Any acute infection or illness	At the discretion of the investigator and sponsor or its designee, withhold intervention until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.
Hepatic event or liver test abnormality	See Section 7.1.1.
Hematology laboratory criteria	
Hold study intervention if the following laboratory test results occur:	*Resume study intervention after approval from sponsor (or its designee) if the following laboratory results occur:*
[redacted]	

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

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, legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- 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
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

In addition, discontinuation from the study will occur for the following reasons:

- At or after Visit 802, if the PASI score is greater than or equal to the baseline (Visit 2) PASI score.
- If an investigator, site personnel performing assessments, or participant is unblinded. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor or designee for the participant to continue in the study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit and post-treatment follow-up, as shown in the SoA. 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. Participants who discontinue the study at Week 16 onward due to a PASI score greater than or equal to the baseline PASI score are not required to complete an ED visit or additional post-treatment follow-up.

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 he or she repeatedly fails to return for scheduled visits and is 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.

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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

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 Efficacy Assessments

Some of these assessments may support both secondary and exploratory endpoints. See Section 3 and the SAP for details.

8.1.2.1. Patient-Reported Outcome Instruments

Psoriasis Symptoms Scale (PSS)

The Psoriasis Symptoms Scale (PSS) is a patient-reported, 8-item scale. It is based on the assessment of

- 4 symptoms: itch, pain, stinging, and burning
- 3 signs: redness, scaling, and cracking, and
- 1 item on the discomfort related to symptoms/signs (Armstrong et al. 2020).

Respondents are asked to answer the questions based on their psoriasis symptoms in the past 24 hours.

Symptoms domain scores range from 0 (no symptoms) to 40 (worst imaginable symptoms).

Signs domain scores range from 0 (no signs) to 30 (worst imaginable signs).

Each of the 8 individual items is scored from 0 to 10, where 0 indicates no symptom/sign and 10 indicates worst imaginable symptom/sign.

The overall severity for each individual symptom or sign ranges from 0 to 10.

Patient's Global Assessment of Psoriasis (PatGA Psoriasis)

The PatGA Psoriasis is a patient-reported, single-item scale. Patient global assessments allow for an overall evaluation of disease severity or global impact of the disease from the patient's perspective (Perez-Chada et al. 2020). Participants are asked to rank the severity of their psoriasis "today" by selecting a number on a 0 to 5 numeric rating scale, with 0 indicating clear/no psoriasis and 5 indicating severe psoriasis.

Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (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.

A DLQI total score of 0 to 1 is considered as having no effect on a participant's health-related quality of life (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

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8.1.2.2. Clinician-Administered Assessments

Body Surface Area (BSA)

The percent BSA is an investigator-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 90 and PASI 100

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

Psoriasis Scalp Severity Index (PSSI)

The PSSI is an investigator-administered, multi-item scale. It measures the affected scalp area and the severity of clinical symptoms.

The PSSI is a composite score derived from the sum of scores for erythema, induration, and desquamation multiplied by a score for the extent of scalp area involved (range, 0 to 72). The higher scores indicate worse severity (Thaçi et al. 2015).

Static Physician's Global Assessment (sPGA)

The sPGA is an investigator-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) (Cappelleri et al. 2013).

Noninvasive skin sampling CCI and skin punch biopsy

See Appendix 10, Section 10.10.

8.2. Safety Assessments

Planned time points for all safety assessments are provided CCI

8.2.1. Vital Signs

Blood pressure, body temperature, and pulse rate will be measured when specified in the SoA and as clinically indicated. Additional vital signs may be measured during study visits if warranted, as determined by the investigator.

Vital signs should be measured after participant has been sitting at least 5 minutes, before obtaining an ECG tracing, and before collection of blood samples for laboratory testing.

8.2.2. Physical Examinations

Physical examination at screening

The complete physical examination will include assessments of these areas and body systems

- Skin
  - Head
  - Abdomen
  - Extremities
- Ears, eyes, nose, throat
- Lymph nodes

- Cardiovascular
- Respiratory
- Gastrointestinal, and
- Neurologic.

Height and weight will also be measured and recorded.

The complete physical examination includes assessment of TB risk factors and symptoms or signs of TB, including an assessment of peripheral lymph nodes (Section 8.2.8).

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

Symptom-directed physical examination after screening

These assessments are performed based on participant status and standard of care. These examinations should also include an assessment of TB risk factors and symptoms or signs of TB, including an assessment of peripheral lymph nodes, at least every 3 months during the study (Section 8.2.8).

8.2.3. 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.

8.2.4. Electrocardiograms

ECG collection

For each participant, 12-lead digital ECGs in triplicate will be collected according to the SoA. ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs (triplicate) will be obtained at approximately 1-minute intervals. ECGs may be obtained at additional times, when deemed clinically necessary.

ECG interpretation

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

Participant assessment after ECGs

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the participant for symptoms (for example, palpitations, near syncope, syncope) to determine whether the participant can continue in the study (Section 7.1.2). The investigator or qualified designee is responsible for determining if any

change in participant management is needed and must document his/her review of one of the replicate ECGs printed at the time of collection.

Responsibilities of the central ECG laboratory

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by the sponsor. A cardiologist at the central ECG laboratory will then conduct a full overread on 1 of the replicate ECGs (including all intervals). A report based on data from this overread will be issued to the investigative site. For each set of replicates, the RR and QT intervals and heart rate will also be determined by the central ECG laboratory on the ECGs that were not fully overread. These data are not routinely reported back to the investigative site. All data from all the overreads will be placed in the sponsor's database for analytical and study report purposes. Any clinically significant finding that was not present on the fully overread single ECG, but was present in the other replicate ECGs, will be reported to the investigator and to the sponsor.
If there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate participant management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the final overread ECG report issued by the central ECG laboratory, and any alert reports.

8.2.5. Chest Imaging

A high-quality, locally performed chest x-ray (posterior–anterior view and, if needed, a lateral view), interpreted and reported by a radiologist or pulmonologist, will be obtained as specified in the SoA.

For each participant, the chest x-ray films, images, or a radiology report must be available to the investigator for review before the participant is randomized to a treatment in this study.

Conditions for using a previous chest x-ray at screening

Participants do not need to have a chest x-ray at screening if, in the opinion of the investigator, both of these 2 conditions are met:

- the chest x-ray was performed within 3 months before the initial screening, and
- documentation of the chest x-ray, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

  Note: In some jurisdictions, the interval between x-rays must be greater than 3 months. If so, a chest x-ray performed within 6 months before Visit 1 can be used.

Alternatives to chest x-ray

In consultation with the sponsor's medical monitor, results of a chest CT scan or other imaging study similar to a chest x-ray, if performed within the same time window, may be used instead of a chest x-ray for the TB evaluation.

8.2.6. Clinical Safety Laboratory Tests

See Appendix 2, Section 10.2 for the list of clinical laboratory tests to be performed and the SoA 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 Appendix 2, 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.

8.2.7. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA.

Participants who become pregnant during the study should be permanently discontinued from the study (Section 7.1.3). Participants who become pregnant will complete procedures for an ED visit and safety 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.

8.2.8. 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
- Signs of previous or active TB by means of

- Thorough physical examination for signs of active TB, including measurement of body temperature (Section 8.2.1) and assessment of peripheral lymph nodes (Section 8.2.2), and
- A high-quality chest x-ray (posterior-anterior view, including a lateral view if needed) interpreted and reported by a radiologist or pulmonologist (Section 8.2.5).

All participants with no history of CCI 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.*

For details about these tests, see Appendix 7, Section 10.7.

Diagnosed CCI

Participants diagnosed with CCI are excluded (Section 5.2) unless they are candidates for CCI treatment, are treated for CCI and the following criteria are met:

- After receiving at least 4 weeks of appropriate CCI therapy (as per WHO or the United States CDC guidelines), there is no evidence of hepatotoxicity CCI [redacted] or other treatment intolerance.
- The participant must continue and complete appropriate CCI therapy to remain eligible to continue to receive study intervention (Section 7.1.4).

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 8.2.2).

8.2.9. Hepatitis B Testing and Monitoring

CCI [redacted] 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 7.1.3, and the participant should receive appropriate follow-up medical care from a hepatologist or other specialty physician with expertise in evaluation and management of viral hepatitis.

8.2.10. Hepatitis C Testing and Monitoring

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 (see 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, and the participant should receive appropriate follow-up medical care from a hepatologist or other specialty physician with expertise in evaluation and management of viral hepatitis (Section 7.1.3).

8.2.11. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 6, Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, GGT, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥2x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant

medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥2x ULN with hepatic signs/symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-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, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

8.2.11.1. Additional Hepatic Data Collection (Hepatic Safety CRF) in Study Participants Who Have Abnormal Liver Tests During the Study

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)

- In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥2x baseline on 2 or more consecutive tests

2. Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
   - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

Note: the interval between the 2 consecutive blood tests should be at least 2 days.

8.2.12. Suicidal Ideation and Behavior Risk Monitoring

Screening for suicidal ideation or behavior

CCI , screening for suicidal ideation or behavior includes the CCI

Monitoring for suicidal ideation and behavior

Throughout the study, participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study intervention.

Discontinuation of participants with signs of suicidal ideation or behavior

Participants who have signs of suicidal ideation or behavior should be considered for discontinuation of study intervention, following a risk assessment (see Section 7.1.3).

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

The definitions of the following events can be found in Appendix 3, Section 10.3:

- AEs
- SAEs
- 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 (see 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/contacts. All SAEs 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 and/or causality. Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

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	Signing of the ICF	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 CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	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 female participants and female partners of male participants	After the start of study intervention	At least 5 terminal half-lives after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint 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	Product Complaint 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. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

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

- obtain a consent to release information from the pregnant female 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 female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor 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 protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will 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.

8.4. Pharmacokinetics

Pharmacokinetic sample visits and times

At the visits and times specified in the SoA, venous blood samples will be collected to determine the plasma concentrations of LY3972406. The actual date and time (24-hour clock time) of the

PK sample collection, as well as the date and time of the dose administered immediately preceding the PK sampling must be recorded accurately on the appropriate forms.

Collection, handling, and analysis of pharmacokinetic samples

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 LY3972406 will be assayed using a validated bioanalytical assay. Analyses of samples collected from participants while receiving placebo are not planned.

Additional and unused pharmacokinetic samples

Samples may be collected at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. 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.

Blinding pharmacokinetic data

Drug concentration information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data (Appendix 2, Section 10.2).

Pharmacokinetic sample retention

Samples will be retained at a facility selected by the sponsor or its designee. The maximum duration of retention is described in Section 10.1.12.

8.5. Pharmacodynamics

See Appendix 2, Section 10.2 and the SoA for CCI sample collection information. Sample retention is described in Section 10.1.12.

8.6. Genetics

Where local regulations and IRBs or IECs allow, a whole blood sample will be collected from consenting participants, as specified in the SoA.

Genetic sample use

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to

- genetic determinants that impact drug absorption, distribution, metabolism, and excretion
- mechanism of action of the drug
- disease etiology, and/or
- molecular subtype of the disease being treated.

Samples may be used for research related to LY3972406 and its mechanism of action, the drug target, genetic variants thought to play a role in psoriasis, on the disease process, and pathways

associated with psoriasis and related diseases. The samples may also be used to develop tests or assays or diagnostic tools related to LY3972406 and/or interventions of this drug class and psoriasis. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate). The samples may also be used to investigate variable exposure or response to LY3972406. The assessment of variable response may include evaluation of AEs or differences in efficacy.

Molecular technologies are expected to improve during the storage period and therefore cannot be specifically named. However, existing genetic research approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this protocol. The samples may be analyzed as part of single or multi-study assessment of CCI involved in the response to LY3972406 or to study interventions of this class to improve understanding of the disease or related conditions, and additional analyses may be conducted, if necessary, to further understand the clinical data of this study.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

Genetic 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. The sponsor will store the DNA samples in a secure storage facility with adequate measures to protect confidentiality.

Genetic sample retention

Samples will be retained at a facility selected by the sponsor or its designee. Samples will be retained as long as research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified in Section 10.1.12.

8.7. Biomarkers

Samples will be collected for exploratory non-pharmacogenetic biomarker research. These samples are listed in Appendix 2, Section 10.2.

Collection visits and times

See the SoA.

Sample use

Samples may be used for research on the

- drug target
- disease process
- variable response to treatment with LY3972406
- pathways associated with psoriasis
- mechanism of action of LY3972406, and/or
- research methods in validating diagnostic tools or assays related to psoriasis or to LY3972406.

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

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Not applicable to this study.

8.9. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

The SAP will be finalized prior to the first unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypothesis

The primary objective is to demonstrate that LY3972406 is superior to placebo in achieving PASI 75 at Week 12. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows: LY3972406 is not different from placebo in achieving PASI 75 at Week 12.

9.1.1. Multiplicity Adjustment

Adjustment for multiple comparisons will not be employed in the analysis for this study.

9.2. Analyses Sets

For purposes of analysis, the following populations are defined:

Population	Description
Modified intent-to-treat (mITT)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention to which they were assigned.
Per-protocol	All randomized participants who do not commit an Important Protocol Deviation (IPD) that could potentially compromise efficacy results. Participants will be analyzed according to the study intervention to which they were assigned.
Safety	All randomized participants who received at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they received.
Pharmacokinetic (PK)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and have PK data available.
Follow-up	All mITT participants who have entered the post-treatment follow-up period. Participants will be analyzed according to the study intervention to which they were assigned.

Note: In the context of this table and throughout the protocol, the terms “study intervention” and “treatment” may be used interchangeably.

Additional analysis populations will be described in the SAP as deemed appropriate.

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9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Changes to the data analysis methods

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate. Complete details of the planned analyses will be documented in the SAP.

Continuous and categorical data analyses

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages. Comparisons between each LY3972406 dose and placebo will be performed for all analyses in the treatment period with no adjustment for multiple comparisons.

Baseline definitions

For the treatment period efficacy, health outcomes, quality-of-life, and safety analyses, baseline is defined as the last available value before the first drug administration, which in most cases will be the measure recorded at Week 0 (Visit 2). Change from baseline will be calculated as the visit value of interest minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first dosing.

Data analysis methods

Treatment comparisons of categorical efficacy, patient-reported outcomes, and quality-of-life variables will be made using a CMH test stratified by prior exposure to biologic therapy for psoriasis (biologic naïve vs. experienced). The 95% confidence intervals associated with the treatment response rate and treatment difference will be reported.

Treatment comparisons of continuous efficacy, patient-reported outcomes, and quality-of-life variables will be made using MMRM. The model will include the following as fixed factors: treatment, baseline value, visit, prior exposure to biologic therapy for psoriasis (biologic naïve vs. experienced), and the interaction of treatment-by-visit. Type III sums of squares for the least squares means will be used for the statistical comparison; the 95% confidence interval will also be reported.

Fisher’s exact test will be used for categorical safety data including AE, baseline, and discontinuations. Continuous vital sign, ECGs, and laboratory values will be analyzed by analysis of covariance with treatment and baseline value in the model.

Additional details will be provided in the SAP.

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Handling of missing, unused, and spurious data

Handling of missing, unused, and spurious data are 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.

9.3.1.1. Missing Data Imputation

Missing data imputation is not to be confused with estimand strategy, as described in Section 3. Missing data of categorical efficacy, patient-reported outcomes, and quality-of-life variables will be imputed using an NRI method. For continuous variables, missing data will not be imputed.

9.3.2. Primary Endpoint/Estimand Analysis

Treatment comparisons between each LY3972406 dose and placebo in the proportion of participants achieving PASI 75 at Week 12 will be analyzed using the CMH test stratified by prior exposure to biologic therapy for psoriasis (biologic naïve vs. experienced) with NRI, as described in Section 9.3.1. Participants who fail to complete the 12-week treatment period due to an ICE related to study intervention or violate the concomitant medications rules will be treated as nonresponders, as described in Section 3. The 95% confidence intervals associated with the treatment response rate, and treatment difference will be provided by treatment. The primary analysis will be conducted on the mITT analysis set when all participants reach Week 12 or have discontinued during the treatment period.

9.3.3. Secondary Endpoints/Estimands Analysis

Proportions of participants achieving the following scores will be analyzed using the CMH test stratified by prior exposure to biologic therapy for psoriasis (biologic naïve vs. experienced) with NRI, as described in Sections 3 and 9.3.1:

- PASI 90
- PASI 100
- sPGA 0 (clear)
- sPGA 0/1 (clear or almost clear)
- PSSI 0

Participants who fail to complete the 12-week treatment period due to an ICE related to study intervention or violate the concomitant medications rules will be treated as nonresponders, as described in Section 3. The 95% confidence intervals associated with the treatment response rate and treatment difference will be provided by treatment.

Treatment comparisons between each LY3972406 dose and placebo in the PASI percent change, BSA mean change from baseline, PSSI mean change from baseline to Week 12, and patient reported outcomes will be analyzed using the MMRM model, as described in Section 9.3.1. No missing data imputation will be performed. The least squares mean and 95% confidence interval will be summarized by treatment.

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9.3.4. Exploratory Endpoints/Estimands Analysis

Exploratory objectives and endpoints will include, but will not be limited to, those listed in Section 3. Details about exploratory analyses will be included in the SAP.

9.3.5. Safety Analyses

Safety will be assessed by evaluating AEs, laboratory analytes, vital signs, ECGs, and CCI

The treatment period safety analyses will compare LY3972406 to placebo; treatment group comparisons will be analyzed using the methods described in Section 9.3.1. Summaries of safety data collected during the follow-up period will be presented separately. Safety analyses will be conducted on the safety analysis set.

Adverse events analyses

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities. A TEAE is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the treatment period. A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after Week 12 (Visit 9) or the ED. For events that are gender specific, the denominator and computation of the percentage will include participants only from the given gender.

An overall summary of AEs will be provided for the treatment period, including the number and percentage of participants who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, and AEs leading to discontinuation of study intervention.

Follow-up emergent AEs, SAEs including deaths, and AEs leading to study discontinuation will be summarized for the post-treatment follow-up period.

CCI

Laboratory analytes and vital signs

Laboratory analytes and vital signs will be summarized at each visit. For continuous data, change from baseline will also be summarized. Additional details will be included in the SAP.

9.3.6. Pharmacokinetic Analyses

LY3972406 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.

Exploratory PK/PD analyses using both graphical approaches and model-based approaches may be conducted to evaluate the relationship between LY3972406 plasma exposure and select

measures of response (for example, PASI scores or CCI). Additional analyses may be conducted if they are deemed appropriate. Further details on PK and analyses will be provided in the PK/PD analysis plan.

9.3.7. Other Analyses

Additional analyses, including subgroup analyses, may be performed as deemed appropriate and will be detailed in the SAP.

9.4. Interim Analyses

Analyses for the primary database lock will be conducted as described in Section 9.3. If Stage 2 is not initiated, the primary outcome database lock will occur when all the participants from Stage 1 have completed the Week 12 visit or have discontinued the study intervention. If Stage 2 is initiated, the primary outcome database lock will occur when all the participants from Stage 2 have completed the Week 12 visit or have discontinued the study intervention.

Two interim analyses may be conducted during Stage 1 prior to the primary database lock at the sponsor's discretion. One interim may occur when approximately CCI of participants from Stage 1 have completed the CCI visit or have discontinued the study intervention. Another interim analysis may be conducted when approximately CCI of participants from Stage 1 have completed the CCI visit or have discontinued the study intervention. The results of either interim analysis can be used by the sponsor's IAC to recommend if Stage 2 should be initiated.

The interim analyses may include safety, PK, PD, and efficacy data. Additional analyses may be performed as outlined in a separate document. The data may be used for internal decision making and/or development of PK/PD modeling. An assessment of unblinded interim data will be conducted by an IAC with a limited number of individuals who do not have direct site contact or data entry or validation responsibilities (see Section 10.1.5). Study sites will receive information about interim results only if they need to know for the safety of their participants.

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

The SAP will describe interim analyses in greater detail.

At the discretion of the sponsor, prespecified interim analyses may not be conducted.

9.5. Sample Size Determination

For the primary outcome database lock at the end of Stage 1, approximately CCI participants will be randomly assigned to receive LY3972406 CCI or placebo CCI. With approximately CCI participants CCI this study will have more than CCI power to detect a difference between LY3972406 and placebo of CCI in PASI 75 response rates at Week 12. The sample size was determined CCI PASI 75 placebo response rate. If Stage 2 is initiated (with or without the CCI arm), this study will have more than CCI power to detect a difference between each LY3972406 arm and placebo of CCI in PASI 75 response rates at Week 12 under the same assumptions.

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, protocol addenda, 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 Code of Federal Regulations (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

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

10.1.2. Financial Disclosure

Investigators and subinvestigators 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.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

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 Regulation (GDPR).

10.1.5. Committees Structure

Internal Assessment Committee (IAC)

An IAC will review the interim efficacy, safety, and PK and/or PK/PD data in an unblinded fashion. The IAC will determine if Stage 2 will be initiated, pending results of the interim analysis.

The IAC will be fully independent from the study team and will include, at a minimum, a Lilly physician and a statistician. Details about IAC membership, purpose, responsibilities, and operations will be described in an IAC charter, which will be approved prior to the first unblinding.

The IAC will evaluate unblinded safety data if

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 data set 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 or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US 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, CSR, 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 might include 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 access to source documents.

Data monitoring and management

QTLs will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined 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 (CTA) 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, and/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.

Electronic data capture system

An EDC system 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. See the SoA for scales administered via paper.
- eCOA 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 eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data. See the SoA for scales administered electronically.

Data storage and access

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. 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 PC 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 Section 10.1.7.

10.1.9. Study and Site Start and Closure

First act of recruitment

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

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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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
- 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 LY3972406 or after LY3972406 become(s) commercially available.

Sample Type	Custodian	Maximum Retention Period After Last Participant Visit
CCI	Sponsor or Designee	CCI
	Sponsor or Designee	
	Sponsor or Designee	
Skin biopsy CCI	Sponsor or Designee	

Any samples remaining after the retention period will be destroyed.

The sample retention facility will be selected by the sponsor or its designee.

10.2. Appendix 2: Clinical Laboratory Tests

Use of central or local laboratories

The tests detailed in the table below will be performed by the central laboratory or by the local laboratory as specified in the tables in this appendix.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Laboratory tests for inclusion/exclusion of potential study participants

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Allowance for additional laboratory testing

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

Investigator responsibilities

Investigators must document their review of the laboratory safety results.

Provision of laboratory test results

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

	Notes
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (red blood cells [RBC])	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Absolute neutrophil count (ANC) (segmented and bands; calculated)	
Leukocytes (white blood cells [WBC])	
Platelets	
Hematology differential	
Percent and absolute count of:	
Neutrophils, segmented	
Neutrophils, bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Cell morphology (RBC and WBC)	Performed only if abnormalities are detected.

	Notes
Clinical chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	

	Notes
Lipid Panel	
High-density lipoprotein (HDL)	Assayed by Lilly-designated laboratory.
Low-density lipoprotein cholesterol (LDL-C)	If triglycerides are ≥400 mg/dL, direct LDL will be measured. Generated by Lilly-designated laboratory.
Very Low-density lipoprotein cholesterol (VLDL-C)	Generated by Lilly-designated laboratory.
Total cholesterol	Assayed by Lilly-designated laboratory.
Triglycerides	

	Notes
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	

	Notes
Hormones (female)	
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory.
Serum pregnancy	Assayed by Lilly-designated laboratory.
Urine pregnancy	Evaluated locally

	Notes
Calculations	Generated by Lilly-designated laboratory.
Estimated glomerular filtration rate (eGFR)	Calculated using the CKD-EPI creatinine equation (2021).

	Notes
TB, HIV, and Hepatitis Serology	
Tuberculosis (TB) testing:	See Appendix 7, Section 10.7 for more information about TB testing.

CCI	Assayed by Lilly-designated laboratory. May be tested and evaluated locally. Local laboratory must be qualified by local regulations.
Tuberculin skin test (TST)	Tested and evaluated locally. Local staff must be qualified to administer and interpret the test.
HIV testing	Assayed by Lilly-designated laboratory.
Hepatitis C virus (HCV) testing:	Assayed by Lilly-designated laboratory.
HCV antibody (anti-HCV)	
HCV RNA	Performed only for participants who test positive for anti-HCV.
Hepatitis B virus (HBV) testing:	Assayed by Lilly-designated laboratory.
Hepatitis B virus (HBV) DNA	Performed only for participants who test positive for anti-HBc.
Hepatitis B core antibody (anti-HBc)	
Hepatitis B surface antigen (HBsAg)	

	Notes
PK samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3972406 concentration	

	Notes
CCI	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

	Notes
Chemistry	Assayed by Lilly-designated laboratory.
C-reactive protein, high-sensitivity (hsCRP)	

	Notes
Other	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
CCI	

	Notes
Genetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

	Notes
	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
	See Appendix 10, Section 10.10.
Skin biopsy	See Appendix 10, Section 10.10.

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

AE definition

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, whether or not related to the medicinal (investigational) 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, 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 <u>NOT</u> meeting the AE definition

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

10.3.2. 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, 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 PC 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 PCs:
  - deficiencies in labeling information, and
  - use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs 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.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

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

AE, SAE, and PC recording

- When an AE/SAE/PC 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/PC 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 PC information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by 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 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 one 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.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 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.

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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 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 sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the sponsor or designee by telephone.
- Contacts for SAE reporting can be found in the Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

SAE reporting via paper form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee.
- 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 the Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and 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 has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, 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
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • 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	The menopausal state is defined as a woman: • 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[a], 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. [a] Women 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. Women 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.

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10.4.2. Contraception Guidance

Contraception guidance for Females

WOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in a same-sex relationship 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 same-sex relationship, 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

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in same-sex relationship as their preferred and usual lifestyle, must follow the rules in this table.

Must..
Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These methods of contraception must be used for the duration of the study.

Contraception guidance for all male participants

For males, no contraception is required except in compliance with specific local government study requirements.

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 WNOCBP definition above. • combination oral contraceptive pill

Methods	Examples
	• progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy - for males in clinical trials and for female partner (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • vaginal ring containing combination hormone medication, or • intrauterine devices
Effective contraception	• penile condom with spermicide • vaginal condom with 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 forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • post coital douche, or • lactational amenorrhea

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CCI

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic evaluation testing

See Section 8.2.11 for guidance on appropriate test selection.

The Lilly-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.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
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, segmented	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 antibody
Platelets	HCV RNA[b]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	HDV IgM antibody
Direct bilirubin	**Hepatitis E virus (HEV) testing:**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine aminotransferase (ALT)	HEV IgM antibody
Aspartate aminotransferase (AST)	HEV RNA[b]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)**[a]
Hepatic Coagulation Panel	**Anti-actin antibody**[c]
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (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] Not required if anti-actin antibody is tested.

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

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

10.7. Appendix 7: 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 or more mm 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 or more mm 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 *M tuberculosis*	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).

Abbreviations: CXR = chest x-ray; IGRA = interferon gamma release assay; PPD = purified protein derivative; TNF = tumor necrosis factor; TST = tuberculin skin test.

10.8. Appendix 8: Examples of Infections That May Be Considered Opportunistic

For this study, infections are defined as opportunistic according to a consensus recommendation for clinical and postmarketing settings (Winthrop et al. 2015) with the following modifications:

- **Candidiasis infections** involving only the oral cavity or pharynx are not considered opportunistic. For an infection involving the oral cavity or pharynx to meet criteria for classification as an opportunistic infection, diagnostic evidence must confirm infection of the esophagus or gastrointestinal tract below the esophagus.
- **Localized herpes zoster infections** are not considered opportunistic. Only multidermatomal infections, disseminated infections, or a combination of these are considered opportunistic.
    - Localized or nonmultidermatomal are defined as involvement of the primary and/or adjacent dermatomes only. These may be complicated or uncomplicated:
        - Complicated: documented ocular (cornea or deeper structure; for example, iritis, keratitis, retinitis, and so on) or motor nerve involvement (for example, palsy). Postherpetic neuralgia does not meet criteria for motor nerve involvement.
        - Uncomplicated: localized or nonmultidermatomal cases that are not complicated.
    - Multidermatomal is defined as involvement beyond primary and adjacent dermatomes (that is, 4 or more contiguous dermatomes) or involvement of 2 or more noncontiguous dermatomes. These may be complicated or uncomplicated.
        - Complicated: documented ocular (cornea or deeper structure; for example, iritis, keratitis, retinitis, and so on) or motor nerve involvement.
        - Uncomplicated: multidermatomal cases.
    - Disseminated: systemic infection, visceral, or widespread cutaneous (for example, 5 or more dermatomes or from 3 to 4 dermatomes including at least 1 noncontiguous [nonadjacent]).
- **Treatment-emergent, active tuberculosis infection** is an opportunistic infection.

The tables in this appendix list examples of infections that may be considered opportunistic. These tables are intended to aid the investigator in recognizing infections which may be considered opportunistic. The lists are not exhaustive. For data analysis, infections will be categorized by Lilly as opportunistic according to the article by Winthrop et al. (2015).

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Examples of Infections That May Be Considered Opportunistic

Bacterial	
	Bartonellosis (disseminated disease only)
	Campylobacteriosis (invasive disease only)
	Legionellosis
	Listeriosis (invasive disease only)
	Nocardiosis
	Tuberculosis
	Non-tuberculous mycobacterial disease
	Salmonellosis (invasive disease only)
	Shigellosis (invasive disease only)
	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral	
	BK virus disease including polyomavirus-associated nephropathy
	Cytomegalovirus disease
	Hepatitis B virus reactivation
	Hepatitis C virus progression
	Herpes simplex (invasive disease only)
	Herpes zoster (any form)
	Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
	Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus
Fungal	
	Aspergillosis (invasive disease only)
	Blastomycosis
	Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual)
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
	Paracoccidioides infections
	Penicilliosis
	Pneumocystosis
	Sporotrichosis
	Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Parasitic	
	Leishmaniasis (visceral only)
	Strongyloidiasis (hyperinfection syndrome or disseminated disease)
	Microsporidiosis
	Toxoplasmosis
	Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
	Cryptosporidiosis (chronic disease only)

Source: Based on Winthrop et al. (2015).

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10.10. Appendix 10: Noninvasive Skin Sampling and Skin Punch Biopsy

Study participants will have skin samples taken by 2 methods:

- noninvasive skin sampling CCI and
- invasive skin sampling (punch biopsy).

Agreement to participate in noninvasive skin sampling CCI is a requirement for study entry whereas participation in invasive skin sampling (punch biopsy) is optional.

These skin samples should be taken from different areas of the same lesion (see below for details). The lesion chosen should meet Inclusion Criterion [7].

Purpose and sample use

See Section 8.7.

Collection visits

The skin samples will be taken at the visits specified in the SoA (Section 1.3).

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Skin punch biopsy (optional)

As stated in the SoA, lesional and nonlesional biopsy samples will be collected at the randomization visit (baseline; Visit 2) for all participants who consent to this procedure. Only a lesional sample will be collected at Visit 9.

A local anesthetic will be applied, and one 4-mm skin-punch biopsy per visit will be obtained from lesional or non-lesional skin, as applicable. The table below describes the specifications for lesional biopsies.

Timing of lesional biopsy	Specifications
Visit 2 (baseline) and Visit 9	Take the lesional biopsy sample from • the same target lesion that was sampled using CCI • at least 1 cm apart from CCI from a non-overlapping section of the lesion • near (approximately 1 cm) the active border of the target plaque. The biopsy site should still be located completely inside the lesion.
Visit 9	In addition to the specifications above, • ideally the biopsy site should be at least 2 cm away from the (original) Visit 2 biopsy site.

	• if the target lesion has resolved completely by Visit 9, take the biopsy sample from an area of skin that was covered by the target plaque and at least 2 cm away from the Visit 2 biopsy site.

Use of emollients

Emollients should not be used on the lesion selected for skin sampling (see Section 10.11.1).

Potential risks

CCI

Invasive skin sampling (punch biopsy): This procedure may cause bleeding, bruising, infection, pain, or discomfort in the area from which the skin sample is taken.

Sample handling

Instructions on the collection and handling of the skin samples (punch biopsy CCI will be provided by the sponsor.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Section 10.1.12.

10.11. Appendix 11: Permitted and Prohibited Concomitant Medications

10.11.1. Permitted Concomitant Medications

This section describes concomitant medications and vaccinations allowed in this study.

Other medications may be allowed if they are approved by the sponsor or its designee.

Permitted Concomitant Medications (Study FVAA)

Drug Class	Comments
Concomitant treatments for psoriasis	
Topical steroids and emollients	• Class 6 (mild) or 7 (least potent) topical steroids will be permitted for use limited to the face, axilla, and/or genitalia as needed. • Emollients may be used on nontarget lesions (that is, plaque psoriasis lesions that have not been or will not be sampled via CCI or skin biopsy if applicable) only if applied using a stable regimen beginning at least 14 days prior to baseline (Visit 2/randomization) and maintained throughout the study. These topical treatments should be avoided approximately 24 hours prior to visits requiring the PASI assessment.
Additional topical treatments	The following will be allowed, as needed, throughout the study on non-target lesions: • Nonmedicated shampoos • Bath oils, oatmeal bath preparations, and <3% salicylic acid preparations These topical treatments should not be used within approximately 24 hours prior to visits requiring the PASI assessment.
Other concomitant treatments	
Cannabinoid products	May be allowed for medical reasons during this study at the investigator's discretion.
Vaccinations	• Use of live or live attenuated vaccines is permitted up to 4 weeks before screening. • A non-live or inactivated vaccine is allowed if it is received at least 2 weeks before randomization in the study or after the last visit. • Inactivated influenza ("Flu"), pneumococcal, and SARS-CoV-2 vaccines are allowed during the study. **Note:** It is recommended that study intervention not be administered on the same day as a SARS-CoV-2 vaccination.

Abbreviations: PASI = Psoriasis Area and Severity Index; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

10.11.2. Prohibited Concomitant Medications and Procedures

This section describes medications prohibited in the study. If a prohibited treatment listed here is required, the study intervention should be permanently discontinued (Section 7.1.3).

Prohibited Concomitant Medications and Procedures (Study FVAA)

Drug Class/Procedure	Comments
Systemic nonbiologic therapies for immune conditions, including, but not limited to: • cyclosporine • corticosteroids • deucravacitinib • methotrexate • oral retinoids • mycophenolate mofetil • thioguanine • hydroxyurea • sirolimus • azathioprine • fumaric acid derivatives • apremilast • 1, 25-dihydroxyvitamin D3 and analogs, or • phototherapy including either ○ oral and topical PUVA light therapy ○ ultraviolet B, or ○ self-treatment with tanning beds or therapeutic sunbathing.	Prohibited within 4 weeks prior to baseline and during the study.
Topical psoriasis treatments, including but not limited to: • moderate/high potency corticosteroids • anthralin • calcipotriene • topical vitamin D derivatives • retinoids • tazarotene • pimecrolimus • tacrolimus • topical JAK inhibitors • topical PDE-4 inhibitors • topical AHR inhibitors, or • other nonprescription topical products containing ○ urea ○ >3% salicylic acid ○ alpha- or beta-hydroxyl acids, or ○ medicated shampoos, for example, those that contain - >3% salicylic acid - corticosteroids - coal tar, or - vitamin D3 analogs	Prohibited within 14 days prior to baseline and during the study, with the exception of the topical medications described in Section 10.11.1.
Biologics for treatment of immune conditions	Prohibited within 12 weeks prior to baseline or 5 half-lives prior to baseline or during the study.
Any investigational study intervention other than LY3972406	Prohibited within 4 weeks or 5 half-lives (whichever is longer) before screening and during the study.

Abbreviations: AHR = aryl hydrocarbon receptor; JAK = Janus Kinase; PDE-4 = phosphodiesterase-4; PUVA = psoralen plus ultraviolet A.

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10.12. Appendix 12: Country-specific Requirements

For sites in EU Member States

This attachment is not applicable at this time.

For Sites Outside of EU Member States

Country-specific requirements, if any, will be described in a separate protocol addendum.

10.13. Appendix 13: 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.

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 GCP, 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
- CCI (Since Last Assessed, as applicable)
- PC (if applicable)

Assessments that are not approved to be done via a telemedicine visit that may need to be delayed until the next on-site visit or missed, depending on the length of time that sites or participants are impacted and depending on when on-site visits are due, include, but are not limited to, the following:

- PASI/BSA
- sPGA
- PSSI
- Weight
- Vital signs
- Symptom-directed physical assessment
- Laboratory tests and sample collections (if local laboratory cannot be used)

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 PCs 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.

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Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for the following samples:

- PK
- CCI, and
- Genetics

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

Study intervention and ancillary supplies

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, and
- arranging delivery of study supplies.

These 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 35 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 35 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 35 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.

    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 35 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.

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/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.

10.14. Appendix 14: Abbreviations and Definitions

Term	Definition
Abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AHR	aryl hydrocarbon receptor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
anti-HCV	hepatitis C virus antibody
AUC	area under the curve
blinding/masking	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
C_{max}	maximum observed concentration
$C_{min,ss}$	minimum drug concentration at steady state
CCI	[redacted]
CIOMS	Council for International Organizations of Medical Sciences
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessments
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.

Term	Definition
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
CXR	chest x-ray
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee. A data monitoring committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCOA	electronic clinical outcome assessments
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
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
GCP	good clinical practice
GGT	gamma-glutamyl transferase
CCI	[redacted]
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Term	Definition
IAC	Internal Assessment Committee
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IGRA	interferon gamma release assay
CCI	[redacted]
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.
INR	international normalized ratio
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."
IRB	Institutional Review Board
ITT	intent 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.
IWRS	interactive web-response system
CCI	[redacted]
LDH	lactate dehydrogenase

Term	Definition
CCI	[redacted]
MAD	multiple ascending dose
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 one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five 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
mITT	modified intent to treat
MMRM	mixed-effects for repeated measures
NRI	nonresponder imputation
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
PatGA Psoriasis	Patient's Global Assessment of Psoriasis
PC	product complaint
PCR	polymerase chain reaction
PDE-4	phosphodiesterase-4
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
CCI	[redacted]
PSS	Psoriasis Symptoms Scale

Term	Definition
PSSI	Psoriasis Scalp Severity Index
CCI	[redacted]
QTc	corrected QT interval
SAD	sequential single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCID	severe combined immunodeficiency disease
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.
SERMs	selective estrogen receptor modulators
SoA	schedule of activities
SOC	system organ class
sPGA	Static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
ULN	upper limit of normal
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.
Th	T helper
TST	tuberculin skin test
WBC	white blood cells
WNOCBP	women of childbearing potential
WOCBP	women not of childbearing potential

10.15. Appendix 15: 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]: 31-Oct-2023

Overall Rationale for the Amendment:

The primary purpose of this amendment is to modify the study to a staged design that enables the evaluation of a high dose of LY3972406 initially in Stage 1. Depending on the results of this evaluation, a lower dose potentially may then be evaluated in Stage 2.

Section # and Name	Description of Change	Brief Rationale
Title Page 1.1. Synopsis	Updated the brief title.	To shorten the existing brief title.
Title Page 1.1. Synopsis	Deleted EU Trial number.	Not required, since the study will run only in the US.
1.1. Synopsis	• Added the details of modified study design including Stage 1 and 2 in Overall design. • Updated the number of participants. • Updated the intervention groups as per the modified study design including Stage 1 and 2.	To modify the study to a staged design that enables evaluation of a high dose of LY3972406 initially in Stage 1 and depending on the interim analysis results, a lower dose later at Stage 2.
1.2. Schema	Added new data schema to include both Stage 1 and Stage 2 of the modified study design.	To align with the modified study design.
1.3.1. Schedule of Activities for the Screening and Treatment Periods of Study J4H-MC-FVAA 1.3.2. Schedule of Activities for ED, Unscheduled Visits, and Post-Treatment Follow-up of Study J4H-MC-FVAA	Updated the comment in Patient-reported outcomes to include "clinician-administered" assessments.	For clarification.
2.2. Background	In Preclinical safety, added information for toxicological findings in CCI	To update the toxicological findings in the study preclinical safety information.
2.3.3. Overall Benefit Risk Conclusion	Added text regarding that study has 2 stages and approximately an additional CCI participants will be enrolled in Stage 2.	To align with the modified study design.
4.1. Overall Design	Added the details of modified study design including Stage 1 and 2.	To modify the study to a staged design that enables evaluation of a high dose of LY3972406 initially in Stage 1 and depending on the interim

Section # and Name	Description of Change	Brief Rationale
		analysis results, a lower dose later at Stage 2.
6.1. Study Intervention(s) Administered	For LY3972406 CCI added that it is used only in Stage 2.	For clarification.
6.1. Study Intervention(s) Administered	In table listing the study interventions, deleted the last row for EU authorization.	Not required, since the study will run only in the US.
9.4. Interim Analyses	Added the details of database lock and interim analysis for Stage 1 and Stage 2.	To align with the modified study design.
9.5. Sample Size Determination	Updated the sample size calculation based on the updated number of participants.	To align with the modified study design.
10.1.5. Committees Structure	Added that the IAC will determine if Stage 2 will be initiated, pending results of the interim analysis.	For clarification.
10.1.6. Dissemination of Clinical Study Data	Deleted "EU" from the Data section.	Not required, since the study will run only in the US.
10.4.2. Contraception Guidance	Added the heading for the table describing different forms of contraception in male and female participants.	For clarification.
10.9. Appendix 9: Photography	Deleted the statement mentioning that the study sites may include sites in EU Member States and other regions.	Not required, since the study will run only in the US.
10.13. Appendix 13: Country-specific Requirements	Deleted the Germany-specific protocol requirements.	For clarification, since the study will run only in the US.
10.15. Appendix 15: Abbreviations and Definitions	Deleted the abbreviation of EU.	Not required, since the study will run only in the US.
Throughout the protocol	Minor formatting and editorial changes.	Minor, therefore, not detailed.

Approved on 19 Jul 2024 GMT

11. References

Armstrong AW, Edson-Heredia E, Naegeli AN, et al. Development of the Psoriasis Symptoms Scale (PSS) in patients with moderate-to-severe psoriasis: qualitative and quantitative analyses. *J Dermatolog Treat*. 2020;31(5):452-459. https://doi.org/10.1080/09546634.2019.1623370

Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology*. 2015;230(1):27-33. https://doi.org/10.1159/000365390

CCI [redacted]

Cappelleri JC, Bushmakin AG, Harness J, Mamolo C. Psychometric validation of the physician global assessment scale for assessing severity of psoriasis disease activity. *Qual Life Res*. 2013;22(9):2489–2499. https://doi.org/10.1007/s11136-013-0384-y

CCI [redacted]

[redacted]

[EMA] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. November 2004. Accessed December 2, 2022. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf.

[FDA] Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Accessed March 21, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244. https://doi.org/10.1159/000250839

CCI [redacted]

Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741. https://doi.org/10.1001/jama.296.14.1735

CCI [redacted]

High, WA, Tomasini CF, Argenziano G, Zalaudek I. Basic principles of dermatology. In: Bolognia JL, Jorizzo JL, Schaffer JV, editors. *Dermatology (3rd ed.)*. Elsevier; 2012:p 8.

Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol*. 2005;125(4):659-664. https://doi.org/10.1111/j.0022-202X.2005.23621.x

Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. *Br J Dermatol*. 2002;147(suppl 62):25-54.

CCI [redacted]

Leonardi CL, Kimball AB, Papp KA, et al., for the PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet.* 2008;371(9625):1665-1674. https://doi.org/10.1016/S0140-6736(08)60725-4

Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58(1):106-115.https://doi.org/10.1016/j.jaad.2007.09.010

CCI [redacted]

National Psoriasis Foundation. The psoriasis and psoriatic arthritis pocket guide – treatment algorithms and management options (4th ed.). 2016. Accessed December 2, 2022. https://www.psoriasis.org/pocket-guide.

CCI [redacted]

Papp KA, Tyring S, Lahfa M, et al., for the Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152(6):1304-1312. https://doi.org/10.1111/j.1365-2133.2005.06688.x

Perez-Chada LM, Salame NF, Ford AR, et al. Investigator and Patient Global Assessment Measures for psoriasis clinical trials: a systematic review on measurement properties from the International Dermatology Outcome Measures (IDEOM) Initiative. *Am J Clin Dermatol*. 2020;21(3):323-338. https://doi.org/10.1007/s40257-019-00496-w

CCI [redacted]

Reich K, Nestle FO, Papp K, et al., for the EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366(9494):1367-1374. https://doi.org/10.1016/S0140-6736(05)67566-6

Ryan C, Kirby B. Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities. *Dermatol Clin*. 2015;33(1):41-55. https://doi.org/10.1016/j.det.2014.09.004

CCI [redacted]

Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases. Epidemiology. *J Am Acad Dermatol.* 2017;76(3):377-390. https://doi.org/10.1016/j.jaad.2016.07.064

CCI [redacted]

Thaçi D, Unnebrink K, Sundaram M, Sood S, Yamaguchi Y. Adalimumab for the treatment of moderate to severe psoriasis: subanalysis of effects on scalp and nails in the BELIEVE study. *J Eur Acad Dermatol Venerol*. 2015;29(2):353-360. https://doi.org/10.1111/jdv.12553

CCI [redacted]

CCI [redacted]

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74(12):2107–2116. https://doi.org/10.1136/annrheumdis-2015-207841

CCI [redacted]

Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol*. 2013;149(10):1173-1179. https://doi.org/10.1001/jamadermatol.2013.5015

CCI [redacted]

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