Protocol: J4L-MC-KMAA

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3872386 in Healthy Participants, a Multiple-Ascending Dose Study of LY3872386 in Patients with Atopic Dermatitis, and an Open-Label Multiple-Dose Evaluation of the Safety and Tolerability of Prednisone in Healthy Participants.

NCT06119529

Approval Date: 10-Nov-2023

Title Page

Protocol Title:

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3872386 in Healthy Participants, a Multiple-Ascending Dose Study of LY3872386 in Patients with Atopic Dermatitis, and an Open-Label Multiple-Dose Evaluation of the Safety and Tolerability of Prednisone in Healthy Participants.

Protocol Number: J4L-MC-KMAA

Amendment Number: b

Compound: LY3872386

Brief Title:

A Single-Ascending Dose Study of LY3872386 in Healthy Participants, a Multiple-Ascending Dose Study of LY3872386 in Patients with Atopic Dermatitis, and an Open-Label Multiple-Dose Evaluation of Prednisone in Healthy Participants.

Study Phase: 1

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Number(s)

IND: 166698

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

Document ID: VV-CLIN-091227

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	*16-October 2023*
Original Protocol	*01-September-2023*

Amendment: b

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This protocol has been amended to primarily address the FDA clinical non-hold comments regarding ophthalmological examinations, blood glucose monitoring, and treatment stopping criteria.

Minor editorial changes have also been made and are not presented in the summary of changes table.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1: Part A: Single-Ascending Dose of LY3872386 in Healthy Participants	Added line item for bedside glucose monitoring to include time points on Day -1, Day 1, Day 2, and Day 7.	Updated to address FDA comments.
	Added line item for hemoglobin A1c to include time points at screening, Day -1, Day 29 ± 1d, Day 85 ± 3d, and ED.	Updated to address FDA comments and support additional treatment discontinuation and interruption criteria.
	Added an ocular pressure, visual acuity, and cataract evaluation time point to Day 15 ± 1d and 43 ± 1d. Provided additional to indicate that for follow-up Visit 802 and Visit 805, an ocular pressure assessment is required; additional visual acuity assessment may be conducted.	Updated to address FDA comments.
Section 1.3.2: Part B: Multiple-Ascending Dose of LY3872386 in Patients with Atopic Dermatitis	CCI [redacted] **Dosing Schedule:** Added line item for hemoglobin A1c to include time points at screening, Day 1, Day 29 ± 1d, Day 85 ± 1d, Day 183 ± 3d, and ED.	Updated to address FDA comments and support additional treatment discontinuation and interruption criteria.

Section # and Name	Description of Change	Brief Rationale
	Added an ocular pressure, visual acuity, and cataract evaluation time point to Day 29 ± 1d, Day 57 ± 1d, and Day 88 ± 1d. Provided additional notes to state that for Visit 4, Visit 6, and follow-up Visit 801, an ocular pressure assessment is required; additional visual acuity and cataract assessment may be conducted.	Updated to address FDA comments.
	CCI Dosing Schedule: Added line item for hemoglobin A1c to include time points at screening, Day 1, Day 29 ± 1d, Day 85 ± 1d, Day 183 ± 3d, and ED.	Updated to address FDA comments and support additional treatment discontinuation and interruption criteria.
	Added an ocular pressure, visual acuity, and cataract evaluation time point to Day 29 ± 1d, Day 57 ± 1d, and Day 88 ± 1d. Provided additional notes to state that for Visit 4, Visit 6, and follow-up Visit 801, an ocular pressure assessment is required; additional visual acuity and cataract assessments may be conducted.	Updated to address FDA comments.
Section 1.3.3: Part C: Open-Label Multiple Dose of Prednisone in Healthy Participants	**Prednisone CCI mg and CCI mg Dosing Schedule:** Added line item for hemoglobin A1c to include a time point at screening.	Updated to address FDA comments and support additional screening criteria.
	Prednisone CCI mg Dosing Schedule: Added line item for hemoglobin A1c to include a time point at screening.	Updated to address FDA comments and support additional screening criteria.
Section 5.2: Exclusion Criteria	Added Criterion #50 to exclude participants with a known history of diabetes.	Updated given that participants could have a higher risk to develop serious glucocorticoid related effects.
	Added Criterion #51 to exclude participants with a fasting glucose level of ≥126 mg/dL and glycated hemoglobin ≥6.5% and/or taking antidiabetes medications at screening.	

Section # and Name	Description of Change	Brief Rationale
	Added Criterion #52 to exclude participants with a known history of osteoporosis.	
Section 6.9: Prior and Concomitant Therapy	Updated the text to state that acetaminophen may be administered at the discretion of the investigator for the treatment of headache and so on. Updated the text to state that antihistamine may be administered as a premedication for infusion at the discretion of the investigator. Updated the text to state that if a need for concomitant medication arises, the inclusion or continuation of the participant may be at the discretion of the investigator after consultation with the sponsor.	Corrections to clarify the role of the investigator as opposed to the medical monitor.
Section 7.1: Discontinuation of Study Intervention	Updated the section to include additional cardiovascular stopping criteria, ocular pressure interruption criteria, additional serious and opportunistic infections discontinuation and interruption criteria, abnormal laboratory parameters of special interest, including adrenal insufficiency criteria.	Updated to address FDA comments.
Section 8.2.4: Ophthalmological Examinations	Added text to state that all ophthalmological examinations may be completed within a 2-week window. Clarified that postdose evaluations in Parts A and B can be conducted anytime within 1 week of each time point as indicated in the SoA.	Updated to address FDA comments.
Section 10.2: Appendix 2: Clinical Laboratory Tests	Added a line item for hemoglobin A1c.	Updated to address FDA comments and support additional screening and/or treatment discontinuation and interruption criteria.

Section # and Name	Description of Change	Brief Rationale
	Added a line item for bedside glucose monitoring (fasting) with footnote f to indicate that bedside glucose monitoring is performed using standard glucose monitors and capillary blood taken from fingerstick. Fasting should be approximately 2 hours, at a minimum.	Updated to address FDA comments.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3872386 in Healthy Participants, a Multiple-Ascending Dose Study of LY3872386 in Patients with Atopic Dermatitis, and an Open-Label Multiple-Dose Evaluation of the Safety and Tolerability of Prednisone in Healthy Participants.

Brief Title:

A Single-Ascending Dose Study of LY3872386 in Healthy Participants, a Multiple-Ascending Dose Study of LY3872386 in Patients with Atopic Dermatitis, and an Open-Label Multiple-Dose Evaluation of Prednisone in Healthy Participants.

Regulatory Agency Identifier Number(s): IND: 166698

Rationale:

LY3872386 is an ADC consisting of an anti-IL-4R antagonist mAb covalently conjugated via a linker to a small molecule GC (payload or LY3558533, also known as LSN3558533). Study J4L-MC-KMAA (KMAA) is a first-in-human study to characterize the safety, tolerability, and pharmacokinetics (PK) of single doses of LY3872386 in healthy participants and repeat doses in patients with atopic dermatitis (AD). Additionally, this study will assess the safety, tolerability, and PK of multiple dose levels of prednisone in healthy participants who will receive prednisone by mouth (PO) once daily (QD). The data generated in this study will guide the design of subsequent clinical trials.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To characterize the safety of LY3872386 after single dose administration in healthy participants and after repeat dose administration in patients with atopic dermatitis. • To assess the safety of prednisone in healthy participants receiving multiple PO QD doses in various dosing groups.	• Number and incidence of AEs, TEAEs, and SAEs • Number and incidence of AEs, TEAEs, and SAEs
Secondary	
• To characterize the PK of LY3872386, total antibody, and LY3558533 (free payload) following single dose administration in healthy participants and after repeat dosing in patients with atopic dermatitis. • To characterize the PK of prednisone in healthy participants receiving multiple PO QD doses in various dosing groups.	• C_{max} and AUC of LY3872386, total antibody, and LY3558533 (free payload) • C_{max} and AUC of prednisone and prednisolone

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; PO = oral administration; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Statistical Considerations:

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) for each IP will be listed and, if the frequency of events allows, descriptive statistics will summarize the safety data per race and ethnicity. Symptoms, their incidence, severity, and association with investigational product, as perceived by the investigator, will be reported separately for each treatment and IP. All TEAEs will be summarized across each part of the study by system organ class and by decreasing frequency according to the Medical Dictionary for Regulatory Activities.

Overall Design:

Study KMAA is a first-in-human trial designed to characterize the safety and tolerability of LY3872386 as well as the PK of LY3872386, total antibody, and LY3558533 (free payload) in healthy participants and in patients with AD. Additionally, this study will assess the safety, tolerability, PK, and pharmacodynamics (PD) of various dose levels of prednisone in healthy participants. The study will enroll participants of any ethnicity. CCI [redacted] The study will be conducted following 3 parts:

- Part A (single-ascending dose [SAD] of LY3872386) will characterize the safety, tolerability, PK, and PD after single intravenous (IV) and subcutaneous (SC) dose administration of LY3872386 in healthy participants.
- Part B (multiple-ascending dose [MAD] of LY3872386) will characterize the safety, tolerability, PK, and PD after multiple SC and/or IV dose administrations of LY3872386 in patients with AD.
- Part C CCI [redacted] will assess the safety, tolerability, PK, and PD after repeat PO administration of prednisone in healthy participants.

Brief Summary:

Part A is a randomized, placebo-controlled, sponsor-unblinded, investigator- and participant-blinded SAD study in healthy participants for LY3872386. Part B is a randomized, placebo-controlled, sponsor-unblinded, investigator- and participant-blinded, repeat, MAD study in patients with AD for LY3872386. Part C is an open-label study in healthy participants who will receive multiple doses PO QD of prednisone.

Study details include:

Treatment Arms, Duration, and Visit Frequency:

Part A: SAD of LY3872386 in Healthy Participants

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1. Participants will receive a single-dose administration on Day 1 and will remain inpatient for approximately 7 days followed by visits at regular intervals.

A total of CCI IV dose cohorts (CCI [redacted] mg) and CCI SC dose cohorts CCI mg and CCI mg) are planned. Cohort 4 will include Japanese participants and Cohorts 6, 7,

and 8 will include Japanese and Chinese participants. The study intervention will be administered as a single dose on Day 1, followed by a 12-week follow-up period (Section 1.2).

Within each dose cohort, treatment-matched placebo will be given using the same time, frequency, and route as LY3872386, as applicable.

Part B: MAD of LY3872386 in Patients with Atopic Dermatitis

Eligible patients with AD will receive multiple doses of LY3872386 within a 12-week treatment period, with administration at an interval of at most CCI and/or at least CCI. Each dosing and discharge are at the discretion of the investigator, with visits in between the doses and at regular intervals following the last dose of the study drug.

At least 2 IV and/or SC dose cohorts (CCI mg and CCI mg) are planned. The study intervention is planned to be administered on Day 1, followed by dose administration CCI and/or CCI for up to 12 weeks in patients with AD. The route and frequency of administration are planned to be the same for all participants within a cohort. The dose, route, and frequency of administration will be confirmed based on emerging data from the safety and PK data of previous SAD and MAD cohorts. Participants will be followed up for 14 weeks after the last dose (Section 1.2).

Within each dose cohort, treatment-matched placebo will be given using the same time, frequency, and route as LY3872386, as applicable.

Part C: Open-label Multiple Doses of Prednisone in Healthy Participants

Eligible participants will be admitted to the CRU on Day -2. Participants will receive multiple doses of either CCI mg of prednisone during 1 treatment period.

One cohort with 3 dose levels (CCI mg) is planned. A prednisone tablet is planned to be administered to healthy participants and taken PO on Day 1, followed by QD PO dose administration. The CCI mg and CCI mg prednisone groups' safety and PD data will be reviewed to determine if the 1 mg prednisone group will be conducted and/or if the dose may be altered. Participants in the CCI mg and the CCI mg (if conducted) groups will receive prednisone for a total of 30 days. Participants in the CCI mg group will receive prednisone for a total of 7 days. Participants in all groups will be followed up for 2 weeks after the last dose of prednisone (Section 1.2). The CCI mg and CCI mg prednisone dose groups may occur in parallel with each other as well as in parallel to Part A SAD or Part B MAD.

- CCI mg or CCI mg dose levels
  - PO QD dosing in healthy participants for a total of 30 days, then a 2-week follow-up period after each dose level
  - Inpatient for approximately 30 days with follow-up period following the last dose of each dose level.
- CCI mg dose level
  - PO QD dosing in healthy participants for a total of 7 days, then a 2-week follow-up period
  - Inpatient for approximately 7 days with follow-up period following the last dose.

Number of Participants:

CCI participants (healthy participants and patients with AD) may be enrolled to ensure that CCI evaluable participants (CCI healthy participants and up to CCI patients with AD) complete the study. Participants will include:

- CCI healthy participants enrolled in Part A (SAD cohorts) on LY3872386
  - CCI evaluable healthy participants
  - CCI replacements
- Up to CCI patients with AD enrolled in Part B (MAD cohorts) on LY3872386
  - Up to CCI evaluable patients with AD)
  - CCI replacements
  - Japanese patients are not intended to exceed more than approximately CCI% of the total evaluable patients with AD (for example up to approximately CCI patients with AD)
- CCI healthy participants enrolled in Part C (multiple dose cohort) on prednisone
  - CCI evaluable participants
  - CCI replacements

Ethical Considerations of Benefit/Risk: Not applicable

Data Monitoring Committee: No

1.2. Schema

1.3. Schedule of Activities (SoA)

1.3.1. Part A: Single-Ascending Dose of LY3872386 in Healthy Participants

Part A: Single-Ascending Dose of LY3872386 in Healthy Participants																			
Procedures / Assessments	**Screening**		**Treatment Period**							**Follow-up**								**ED**	**Comments**
Visit Number	**V1**	**V2**								**V 801**	**V 802**	**V 803**	**V 804**	**V 805**	**V 806**	**V 807**	**V 808**		
Study Day	CCI																		
Informed consent	X																		
Review/confirm I/E criteria	X	X																	CCI
Admission to CRU		X																	
Randomization			P																
Discharge from CRU									X										
Outpatient visit										X	X	X	X	X	X	X	X	X	
Clinical Assessments																			
Complete medical history	X																		
Review AEs	X	X	P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Substance use (alcohol and tobacco use)	X	X											X				X	X	CCI
Physical examination	X	X											X		X		X	X	

Part A: Single-Ascending Dose of LY3872386 in Healthy Participants																		
Procedures / Assessments	**Screening**		**Treatment Period**							**Follow-up**							**ED**	**Comments**
Visit Number	**V1**	**V2**								**V 801**	**V 802**	**V 803**	**V 804**	**V 805**	**V 806**	**V 807**	**V 808**	
Study Day	CCI																	
Weight	X	X															X	X
Height	X																	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECGs	X		P	X	X		X		X		X		X		X		X	X
Chest x-ray, if indicated (posterior-anterior view)	X																	
QuantiFERON®-TB Gold test or TST	X																	
IP administration			X															
Laboratory Assessments																		
Serologies, syphilis, and FSH	X																	
Thyroid-stimulating hormone, including T3/T4 tests		X															X	X
Serum immunoglobulins	X		P						X		X		X		X		X	X

Part A: Single-Ascending Dose of LY3872386 in Healthy Participants																		
Procedures / Assessments	**Screening**		**Treatment Period**						**Follow-up**								**ED**	**Comments**
Visit Number	**V1**	**V2**							**V 801**	**V 802**	**V 803**	**V 804**	**V 805**	**V 806**	**V 807**	**V 808**		
Study Day	CCI [redacted]																	
CCI [redacted]			<1-, 15-, 120-, and 240-min post injection	24 hr	X	X			X		X		X					CCI [redacted]
Urinary drug screen (including ethanol breath test)	X	X																
Pregnancy test	X	X														X	X	
Clinical chemistry	X	X	P	X	X		X		X	X	X	X	X	X	X	X	X	X
Bedside glucose monitoring		X	P and 12 hr	24 hr and 36 hr					X									
Fasting lipid panel			P										X					X
Hematology	X	X		X	X		X		X		X	X	X	X	X	X	X	X
Hemoglobin A1c	X	X											X				X	X
Urinalysis	X	X		X	X		X		X		X		X	X			X	X

Part A: Single-Ascending Dose of LY3872386 in Healthy Participants																		
Procedures / Assessments	**Screening**		**Treatment Period**							**Follow-up**							**ED**	**Comments**
Visit Number	**V1**	**V2**							**V 801**	**V 802**	**V 803**	**V 804**	**V 805**	**V 806**	**V 807**	**V 808**		
Study Day	CCI																	
Pharmacogenetics			P															CCI
Immunogenicity			P								X		X		X		X	X
LY3872386, total antibody, and LY3558533 (free payload) concentration (PK)			P, EOI, 3 hr, 6 hr, and 12 hr	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI			P	X		X			X		X	X	X	X	X	X	X	X
			P	X		X			X		X	X	X	X	X	X	X	X
			P	X					X		X						X	X
			P	X		X			X		X		X		X		X	X
			P			X			X		X		X		X		X	X
		X							X		X	X	X		X		X	X

Part A: Single-Ascending Dose of LY3872386 in Healthy Participants																	
Procedures / Assessments	**Screening**	**Treatment Period**						**Follow-up**								**ED**	**Comments**
Visit Number	**V1**	**V2**						**V 801**	**V 802**	**V 803**	**V 804**	**V 805**	**V 806**	**V 807**	**V 808**		
Study Day	CCI																
Cortisol		X	P and 12 hr	X	X	X	X	X		X			X				CCI
CCI			X	X	X	X	X	X									
CCI		X						X		X		X		X		X	X

Part A: Single-Ascending Dose of LY3872386 in Healthy Participants																			
Procedures / Assessments	**Screening**	**Treatment Period**							**Follow-up**								**ED**	**Comments**
Visit Number	**V1**	**V2**							**V 801**	**V 802**	**V 803**	**V 804**	**V 805**	**V 806**	**V 807**	**V 808**		
Study Day	CCI																	
Ocular pressure, visual acuity, and cataract evaluation	X									X			X			X	X	CCI

Abbreviations: AE = adverse event; CRU = clinical research unit; CCI CXR = chest x-ray; d = day(s); ECG = electrocardiogram; ED = early discontinuation; EOI = end of IV infusion or subcutaneous dose administration; FSH = follicle-stimulating hormone; hr = hours; I/E = inclusion/exclusion; IP = investigational product; min = minutes; P = predose before IP administration; CCI PK = pharmacokinetic; SAD = single-ascending dose; TB = tuberculosis; TST = tuberculin skin test; V = visit.

1.3.2. Part B: Multiple-Ascending Dose of LY3872386 in Patients with Atopic Dermatitis

1.3.2.1. Part B: LY3872386 CCI Dosing Schedule

Part B: LY3872386 CCI Dosing Schedule														
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**				**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**		
Study Day(s)	CCI													
Informed consent	X													
Review/confirm I/E criteria	X	P												
IWRS randomization		P												
Clinical Assessments														
Complete medical history	X													
Review preexisting conditions/AEs	X	P	P	P	P	P	P	P	X	X	X	X	X	
Concomitant medications	X	P	P	P	P	P	P	P	X	X	X	X	X	
Previous and current AD treatments	X													
Substance use (alcohol and tobacco use)	X													CCI
Physical examination	X			X		X		X	X	X	X	X	X	
Weight	X											X	X	
Height	X													
Vital signs	X	P	P	P	P	P	P	P	X	X	X	X	X	
ECGs	X	P	P	P	P	P	P	P				X	X	

Part B: LY3872386 CCI Dosing Schedule														
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**				**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**		
Study Day(s)	CCI													
Chest x-ray, if indicated (posterior-anterior view)	X													CCI
IP administration		X	X	X	X	X	X	X						
QuantiFERON®-TB Gold test or TST	X													
vIGA-AD	X	X	X	X	X	X	X	X		X	X	X	X	
EASI	X	X	X	X	X	X	X	X		X	X	X	X	
SCORAD	X	X	X	X	X	X	X	X		X	X	X	X	
POEM	X	X		X		X		X		X	X	X	X	
DLQI	X	X		X		X		X		X	X	X	X	
Itch numeric rating scale	X	X	X	X	X	X	X	X		X	X	X	X	
Laboratory Assessments														
Beta-D-glucan	X													CCI
Serologies, syphilis, and FSH	X													
Thyroid-stimulating hormone, including T3/T4 tests		P						X				X	X	
Serum immunoglobulins		X		X		X		X					X	

Part B: LY3872386 CCI Dosing Schedule														
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**				**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**		
Study Day(s)	CCI													
Subcutaneous local injection-site assessment		P	X	X	X	X	X	X		X	X	X	X	CCI
Urinary drug screen (including ethanol breath test)	X	X	X	X	X	X	X	X						
Pregnancy test	X	P	P	P	P	P	P	P				X	X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting lipid panel		P		P		P			X				X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hemoglobin A1c	X	X		X				X				X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacogenetics		P												
Immunogenicity		P	P	P		P		P				X	X	
LY3872386, total antibody, and LY3558533 (free payload) concentration (PK)		P, EOI, 1 hr, and 3 hr	P and EOI	P and EOI	P and EOI	P and EOI	P and EOI	P, EOI, 1 hr, and 3 hr	X	X	X	X	X	
CCI		P and 3 hr	P	P	P	P	P	P		X	X	X	X	
		P	P	P	P	P	P	P				X	X	
		P		P		P		P					X	

Part B: LY3872386 CCI Dosing Schedule														
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**				**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**		
Study Day(s)	CCI													
CCI		P	P	P		P		P		X	X	X	X	CCI
		P	X	X	X	X	X	X		X	X	X	X	
		X						X					X	
		P		P				X					X	
		P		P			P			X		X	X	
		P	P	P	P	P	P	P		X	X	X	X	
Ocular pressure, visual acuity, and cataract evaluation	X			X		X			X			X	X	

Abbreviations: AE = adverse event; AD = atopic dermatitis; CCI [redacted] d = day(s); DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ED = early discontinuation; EOI = end of IV infusion or subcutaneous dose administration; FSH = follicle-stimulating hormone; I/E = inclusion/exclusion; IL-13 = interleukin 13; IP = investigational product; IWRS = Interactive Web Response System; MDC = Macrophage-derived chemokine; P = predose before IP administration; P1NP = Procollagen 1; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; TARC = Thymus- and activation-regulated chemokine; TB = tuberculosis; TST = tuberculin skin test; V = visit; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis.

1.3.2.2. Part B: LY3872386 CCI Dosing Schedule

Part B: LY3872386 CCI Dosing Schedule															
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**					**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**	**V 805**		
Study Day(s)	CCI														
Informed consent	X														
Review/confirm I/E criteria	X	P													
IWRS randomization		P													
Clinical Assessments															
Complete medical history	X														
Review preexisting conditions/AEs	X	P	X	P	X	P	X	P		X	X	X	X	X	
Concomitant medications	X	P	X	P	X	P	X	P		X	X	X	X	X	
Previous and current AD treatments	X														
Substance use (alcohol and tobacco use)	X														CCI
Physical examination	X			X		X		X			X		X	X	
Weight	X												X	X	
Height	X														
Vital signs	X	P	X	P	X	P	X	P		X	X	X	X	X	
ECGs	X	P		P		P		P					X	X	

Part B: LY3872386 CCI Dosing Schedule														
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**					**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**	**V 805**		
Study Day(s)	CCI														
Chest x-ray, if indicated (posterior-anterior view)	X														CCI
IP administration		X		X		X		X							
QuantiFERON®-TB Gold test or TST	X														
vIGA-AD	X	X	X	X	X	X	X	X		X	X	X	X	X	
EASI	X	X	X	X	X	X	X	X		X	X	X	X	X	
SCORAD	X	X	X	X	X	X	X	X		X	X	X	X	X	
POEM	X	X		X		X		X			X	X	X	X	
DLQI	X	X		X		X		X			X	X	X	X	
Itch numeric rating scale	X	X	X	X	X	X	X	X		X	X	X	X	X	
Laboratory Assessments															
Beta-D-glucan	X														CCI
Serologies, syphilis, and FSH	X														
Thyroid-stimulating hormone, including T3/T4 tests		P						X					X	X	
Serum immunoglobulins		X		X		X		X							

Part B: LY3872386 CCI Dosing Schedule														
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**					**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**	**V 805**		
Study Day(s)	CCI														
Subcutaneous local injection-site assessment		P	X	X	X	X	X	X		X	X	X	X	X	See Section 8.2.6.
Urinary drug screen (including ethanol breath test)	X	X		X		X		X							CCI
Pregnancy test	X	P		P		P		P					X	X	
Clinical chemistry	X	X	X	X		X	X	X			X	X	X	X	
Fasting lipid panel		P		P		P		P						X	
Hematology	X	X	X	X		X		X			X	X	X	X	
Hemoglobin A1c	X	X		X				X					X	X	
Urinalysis	X	X	X	X		X		X			X	X	X	X	
Pharmacogenetics		P													
Immunogenicity		P	X	P	X	P	X	P		X	X	X	X	X	
LY3872386, total antibody, and LY3558533 (free payload) concentration (PK)		P, EOI, 1 hr, and 3 hr	X	P and EOI	X	P and EOI	X	P, EOI, 1 hr, and 3 hr	X	X	X	X	X	X	
CCI		P and 3 hr	X	P	X	P	X	P		X	X	X	X	X	
		P	X	P	X	P	X	P					X	X	
		X		X		X		X						X	

Part B: LY3872386 CCI Dosing Schedule														
Procedures/ Assessments	**Screening**	**Treatment Period**							**Follow-up**					**ED**	**Comments**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V 801**	**V 802**	**V 803**	**V 804**	**V 805**		
Study Day(s)	CCI														
CCI		P	X	P		P		P		X	X	X	X	X	CCI
		P	X	X	X	X	X	X		X	X	X	X	X	
		X						X						X	
		P		P				X						X	
		P		P			X				X		X	X	
		P		P		P		P			X		X	X	
Ocular pressure, visual acuity, and cataract evaluation	X			X		X			X				X	X	

Abbreviations: AE = adverse event; AD = atopic dermatitis; CCI [redacted] d = day(s); DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ED = early discontinuation; EOI = end of IV infusion or subcutaneous dose administration; FSH = follicle-stimulating hormone; I/E = inclusion/exclusion; IL-13 = interleukin 13; IP = investigational product; IWRS = Interactive Web Response System; MDC = Macrophage-derived chemokine; P = predose before IP administration; P1NP = Procollagen 1; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; TARC = Thymus- and activation-regulated chemokine; TB = tuberculosis; TST = tuberculin skin test; V = visit; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis.

1.3.3. Part C: Open-Label Multiple Dose of Prednisone in Healthy Participants

1.3.3.1. Part C: Prednisone CCI mg and CCI mg Dosing Schedule

Part C: Prednisone CCI mg and CCI mg Dosing Schedule												
Procedures/ Assessments	**Screening**			**Dosing Period**					**Follow-up**		**ED**	**Comments**
Visit Number	**V1**		**V2**							**V801**		
Study Day	CCI											
Informed consent	X											
Review/confirm I/E criteria	X		X									
Admission to CRU		X										CCI
Discharge from CRU									X			
Outpatient visit										X	X	
Clinical Assessments												
Complete medical history	X											
Review AEs	X	X	X	P	P	P	P	P	X	X	X	
Concomitant medications	X	X	X	P	P	P	P	P	X	X	X	
Substance use (alcohol and tobacco use)	X		X								X	CCI
Physical examination	X		X						X	X	X	
Weight	X		X						X	X	X	
Height	X											
Vital signs	X	X	X	P	P	P	P	P	X	X	X	
ECGs	X		X						X	X	X	

Chest x-ray, if indicated (posterior-anterior view)	X											CCI
QuantiFERON®-TB Gold test or TST	X											
IP administration				X	X	X	X	X				
Laboratory Assessments												
Serologies, syphilis, and FSH	X											CCI
Thyroid-stimulating hormone, including T3/T4 tests			X							X	X	
Serum immunoglobulins	X			P		P		P		X	X	
Urinary drug screen (including ethanol breath test)	X		X									
Pregnancy test	X		X							X		
Clinical chemistry	X		X		Day 2 and Day 7 (P)	P	Day 21 (P)	P		X	X	
Fasting lipid panel				P				P			X	
Hematology	X		X		Day 2 and Day 7 (P)	P	Day 21 (P)	P		X	X	
Hemoglobin A1c	X											
Urinalysis	X		X		Day 2 and Day 7 (P)	P	Day 21 (P)	P		X	X	
Pharmacogenetics				P								
Prednisone and prednisolone concentrations (PK)				P, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr	X	X	X	P, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr	X		X	
CCI				P		X		X			X	
				P		X		X			X	
				P		X		X			X	

CCI				P	Day 7 (P)	P	Day 21 (P)	P		X	X
			X	P and 12 hr	P		P		X		
				P	P	P	P	P			
			X		Day 7 (P)	P		P		X	X

Abbreviations: AE = adverse event; CRU = clinical research unit; CT = computed tomography; CCI d = day(s); ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; hr = hour(s); I/E = inclusion/exclusion; IP = investigational product; P = predose before IP administration; CCI PK = pharmacokinetic; PO = oral administration; TB = tuberculosis; TST = tuberculin skin test; V = visit.

1.3.3.2. Part C: Prednisone CCI mg Dosing Schedule

Part C: Prednisone CCI mg Dosing Schedule															
Procedures/Assessments	**Screening**			**Dosing Period**							**Follow-up**			**ED**	**Comments**
Visit Number	**V1**			**V2**							**V801**	**V802**	**V803**		
Study Day	CCI														
Informed consent	X														
Review/confirm I/E criteria	X		X												
Admission to CRU		X													CCI
Discharge from CRU										X					
Outpatient visit											X	X	X	X	
Clinical Assessments															
Complete medical history	X														
Review AEs	X	X	X	P	P	P	P	P	P	P	X	X	X	X	
Concomitant medications	X	X	X	P	P	P	P	P	P	X	X	X	X	X	
Substance use (alcohol and tobacco use)	X		X											X	CCI
Physical examination	X		X										X	X	
Weight	X		X					X					X	X	
Height	X														
Vital signs	X	X	X	P	P	P	P	P	P	P	X	X	X	X	
ECGs	X		X							X			X	X	
Chest x-ray, if indicated (posterior-anterior view)	X														
QuantiFERON®-TB Gold test or TST	X														
IP administration				X	X	X	X	X	X	X					

															CCI [redacted]
Laboratory Assessments															
Serologies, syphilis, and FSH	X														See Section 10.2.
Thyroid-stimulating hormone, including T3/T4 tests			X										X	X	
Serum immunoglobulins	X			P						P		P	P	P	CCI [redacted]
Urinary drug screen (including ethanol breath test)	X		X												
Pregnancy test	X		X											X	
Clinical chemistry	X		X		P	P		P		P		X	X	X	
Hematology	X		X		P	P		P		P		X	X	X	
Hemoglobin A1c	X														
Urinalysis	X		X		P	P		P		P		X		X	
Pharmacogenetics				P											
Prednisone and prednisolone concentration (PK)				P, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr	P	P	P	P	P	P, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr	X	X	X	X	
CCI [redacted]				P	X		X			X			X	X	
				P	X					X			X	X	
				P	X		X			X			X	X	
				P			X			X			X	X	
				P						P		X	X	X	
			X	P and 12 hr	P	P	P	P	P						

CCI															CCI
				P					P						
			X							P			X	X	

Abbreviations: AE = adverse event; CRU = clinical research unit; CT = computed tomography; CCI d = day(s); ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; hr = hour(s); I/E = inclusion/exclusion; IP = investigational product; P = predose before IP administration; P1NP = Procollagen 1; PD = pharmacodynamic; PK = pharmacokinetic; PO = oral administration; TB = tuberculosis; TST = tuberculin skin test; V = visit.

2. Introduction

LY3872386 is an ADC consisting of an anti-IL-4R antagonist mAb covalently conjugated via a linker to a small molecule GC (payload or LY3558533, also known as LSN3558533). Once LY3872386 is internalized by cells, cleavage of the linker is expected to release the GC payload, which can activate the GR. The mAb component (LY3842708) of the ADC is a fully human IgG4 that specifically recognizes human IL-4Rα subunit (IL-4Rα) with high affinity and antagonizes type 1 and type 2 IL-4R activity from both IL-4 and IL-13 cytokines. The payload is a novel and potent GR agonist with selectivity over other nuclear hormone receptors.

The IL-4R pathway is clinically validated in several Type 2 inflammatory diseases, such as AD, asthma, and nasal polyposis (Bachert et al. 2019). In addition, GCs are known to be potent anti-inflammatory agents and are used in a number of inflammatory diseases, including AD. However, the pleiotropic effects of GCs lead to multiple undesired effects that limit their use (Rhen and Cidlowski 2005). LY3872386 has the potential to provide anti-inflammatory effects from both the activation of the GR pathway and the inhibition of the IL-4R pathway, while targeting the delivery of the GC payload to IL-4R-expressing cells which are pathogenic in various inflammatory disorders, including AD.

2.1. Study Rationale

Study J4L-MC-KMAA (KMAA) is the first-in-human study that will investigate the safety, tolerability, and PK of single doses of LY3872386 in healthy participants and repeat doses in patients with AD. An exploratory evaluation of target engagement through IL-4R RO will be conducted following single doses of LY3872386 in healthy participants and repeat dose in patients with AD. Exploratory assessments of clinical PD and efficacy in patients with AD are also included. Additionally, this study will assess the safety, tolerability, and PK CCI of prednisone in healthy participants CCI

The prednisone treatment will not be blinded with a placebo. CCI

2.2. Background

IL-4 and IL-13 cytokines play a key role in the initiation, amplification, and downstream tissue effects that result in Type 2 inflammatory disease. The IL-4R pathway is a clinically validated pathway in several Type 2 inflammatory diseases (for example, AD, asthma, and nasal polyposis). The two types of receptors formed with the IL-4Rα subunit are type 1 IL-4R and type 2 IL-4R. Type 1 IL-4R is composed of IL-4Rα and common γ chain, whereas type 2 IL-4R is composed of IL-4Rα and the IL-13R α1 chain (IL-13Rα1). Hematopoietic or immune cells mainly express type 1 IL-4R, whereas type 2 IL-4R/IL-13R is more widely expressed on non-hematopoietic/immune cells or tissue-resident cells. The IL-4/IL-13/IL-4R axis has been evaluated with antagonist antibody therapies such as dupilumab and tralokinumab which are approved for the treatment of various inflammatory disorders. GCs have pleiotropic effects, including involvement in the metabolism of various macromolecules, including carbohydrates, fats, and proteins. GCs are also widely known for their anti-inflammatory properties and are

commonly used for the treatment and management of various immunological diseases. While GCs can be highly effective anti-inflammatory mediators, they are known to have various undesirable short- and long-term effects, such as adrenal insufficiency, osteoporosis, and diabetes, which limit their use. By targeting these 2 mechanisms of action through an IL-4R antagonist mAb conjugated to a GC, the ADC inhibits IL-4R signaling and potentially delivers GCs to IL-4R expressing cells. Therefore, the ADC provides additional anti-inflammatory effects above the inhibition of the IL-4R pathway while potentially reducing undesired GC-related effects.

The key characteristics of LY3872386 are listed below.

Nonclinical Biology/Pharmacology Data

- LY3872386 has high affinity (in vitro binding) for human IL-4R (K_D = CCI pM) and cynomolgus monkey IL-4R (K_D=CCI pM) and blocks IL-4 and IL-13 mediated IL-4R signaling in cells.
- LY3872386 inhibits IL-4R signaling and induces GC responses in myeloid cells, demonstrating dual activity of LY3872386 within the same cells.
- LY3872386 inhibits IL-5 and IL-13 cytokine secretion and induces GC/GR-mediated gene expression in Th2 differentiated T cells, which are key mediators of type 2 inflammation.
- LY3872386 inhibits IL-4R-dependent and IL-4R-independent cytokine secretion from human peripheral blood mononuclear cells, indicating added anti-inflammatory effects of the ADC above the inhibition of the IL-4R pathway alone.
- LY3872386 more robustly reduces antigen-challenged-induced inflammation compared to the IL-4R mAb in a humanized mouse model of inflammation. This supports the dual activity of LY3872386, resulting in superior efficacy compared to the antagonist IL-4R mAb alone in vivo.
- LY3558533 (payload) is a highly potent novel activator of the GR. In a cell-based in vitro assay, the payload (LY3558533) EC_{50} were CCI nM CCI for CD4+ T cells, CCI nM CCI for CD19+ B cells, and CCI nM CCI for CD33+ myeloid cells (geometric mean ± standard error of the mean).
- LY3558533 (payload) has higher selectivity towards the GR compared to the progesterone, androgen, estrogen, and mineralocorticoid receptors:
    - The IC_{50} for competition displacement of the radioligand from the receptor was CCI nM for the GR, CCI µM for the progesterone receptor, and over CCI µM for the androgen and estrogen receptors.
    - The EC_{50} in the cell-based translocation assay was CCI nM for the GR and CCI µM for the progesterone and mineralocorticoid receptors.

Nonclinical Toxicology Data

In support of Phase 1 clinical development, the following nonclinical toxicity studies were conducted with LY3872386 (ADC) or with LY3558533 (payload):

LY3872386 (ADC)

A 3-month repeat-dose study in monkeys, including an evaluation of safety pharmacology, was conducted. The key findings in the monkey study were dose-dependent decreases in circulating lymphocytes, and decreases in lymphocytes or lymphoid follicle centers, in thymus, spleen, and lymph nodes. Other important findings were atrophy of skin hair follicles, especially near injection sites, and effects suggestive of suppression of the HPA axis. These effects were generally consistent with the intended pharmacology of the ADC. The immunosuppressive effects on lymphocytes were considered contributory to a severe *Staphylococcus aureus* ulcerative dermatitis, leading to clinical decline and euthanasia in 1 monkey administered the highest dose of LY3872386.

A cross-reactivity study of LY3872386 in tissues from humans and non-human primates demonstrated binding consistent with the reported expression of IL-4R in mononuclear cell populations and generally consistent with the findings in the toxicology study.

LY3558533 (Payload)

General toxicity

One-month repeat-dose toxicology studies with LY3558533 were conducted in rats and monkeys. There were no adverse findings in either study, up to the highest dose tested. Observed effects were generally consistent with known effects of GC in animal species.

Safety pharmacology

In an in vitro hERG assay, the IC_{50} for the inhibitory effect of LY3558533 on hERG potassium current was estimated to be greater than [redacted] µM, an unbound plasma concentration that would not be achievable in humans.

Genotoxicity

LY3558533 was evaluated for mutagenicity in an Ames assay, and for effects on chromosomes in human TK6 cells and in rats. There were no effects observed in any study, up to the highest concentration or dose tested.

Nonclinical Drug Disposition and Pharmacokinetics

LY3872386 (ADC)

- The PK of LY3872386 (fully intact DAR4) and total antibody (includes unconjugated Ab and Ab conjugated to at least 1 payload) were evaluated in PK study in monkeys after IV and SC doses of LY3872386. The plasma clearance of LY3872386 or total antibody was low in monkeys based on comparison to hepatic blood flow. The relative SC bioavailability of LY3872386 was approximately [redacted]%.
- The TK of LY3872386, total antibody, and LY3558533 (unconjugated payload) were evaluated in the 3-month GLP toxicology study. The exposure to LY3872386 and total antibody increased with increasing dose in an approximately dose-proportional manner on Day 1 and in a greater than dose-proportional manner on Day 85. The exposure to LY3558533 increased in an approximately dose-proportional manner. Based on mean exposures including all animals, no to minimal accumulation of LY3872386, total

antibody, or LY3558533 (unconjugated payload) was observed following repeat SC or IV administration of LY3872386. ADA positive response was detected in multiple animals after repeat SC dosing and contributed to the decrease in exposure of LY3872386 and total antibody on Day 85. The presence of ADA had no impact on the exposure to LY3558533 (unconjugated payload).

- The stability of fully intact LY3872386 (DAR4, containing all 4 GC payloads) was evaluated in vivo using PK plasma samples and by in vitro incubations with plasma and serum. The percent remaining of intact LY3872386 in vivo in monkey plasma remained ≥90% for IV and SC by 168 hours and CCI % IV and CCI % SC by 336 hours postdose, demonstrating adequate stability of LY3872386 in vivo. The in vitro stability in human plasma or serum was generally comparable to that in preclinical species.

LY3558533 (Payload)

- The PK of LY3558533 were evaluated in rats and monkeys after IV or SC doses of LY3558533. The plasma clearance of LY3558533 was high in rat and moderate in monkey based on comparison to hepatic blood flow. The SC bioavailability of LY3558533 was approximately CCI % with half-life ranging from CCI to CCI hours across species after SC dose.
- The TK of LY3558533 were evaluated in rats and monkeys in GLP toxicology studies after IV or SC doses of LY3558533. The exposure to LY3558533 increased with dose, but the increase was not always dose-proportional. No gender difference was observed. After repeated daily, there was no or minimal accumulation of LY3558533 in rats and monkeys.
- The in vitro plasma protein binding of LY3558533 ranged from CCI % to CCI % in mouse, rat, dog, monkey, and humans.
- Based on preliminary metabolite identification and qualitative profiling, LY3558533 was the most prominent component circulating in rat and monkey plasma. The metabolic pathways include oxidations, direct or secondary glucuronidation and N-acetylation. The in vitro metabolite profile was generally similar between nonclinical species and human.
- Excretion data from rats and monkeys suggest that LY3558533 is cleared via hepatic metabolism with minimal contribution of biliary excretion.

CCI

Additional information regarding the in vitro and in vivo mechanism of action, toxicological, and drug disposition assessments of LY3872386 or LY3558533 are available in the IB.

2.3. Benefit/Risk Assessment

The toxicology data for LY3872386 demonstrate an acceptable nonclinical safety profile and margin of safety to support the transition from preclinical status to a clinical single-dose study in healthy participants and a multiple-dose study in patients with AD.

The nonclinical safety profile of LY3872386 is generally consistent with its intended pharmacology. Primary safety concerns predicted from studies with the ADC and the payload are bacterial and other infections, secondary to decreases in lymphoid tissue lymphocytes and circulating blood lymphocytes. Other potential risks identified for LY3872386 in toxicology studies and consistent with GC pharmacology are

- atrophy of skin hair follicles, especially near SC injection sites, potentially leading to thinning hair or hair loss
- suppression of the HPA axis
- increased serum triglycerides, and
- increased serum glucose.

The safety and efficacy associated with modulation of the IL-4/IL-13/IL-4R axis have been evaluated with approved drugs such as dupilumab and tralokinumab, and the safety and efficacy of GCs as a class are well-established. The key safety concerns and PD effects of LY3872386, including infection, conjunctivitis, hypersensitivity reactions, local injection site reactions, and systemic GC exposure from LY3558533 (free payload), will be closely monitored during the clinical study.

CCI

As with other immunomodulatory therapies, LY3872386 and prednisone may increase the risk of developing infections, increase the risk of an infection becoming more serious, and/or change the effectiveness of vaccines administered. LY3872386 may also increase the risk of opportunistic infections and the reactivation of latent infections. Participants will therefore be screened for hepatitis B, hepatitis C, HIV, and TB. In addition, all participants should be monitored for symptoms and signs of infection after administration of LY3872386 or prednisone.

Infusion reactions and hypersensitivity reactions are potential risks for all biologics. These risks will be carefully monitored during the dosing period in Parts A and B (the LY3872386 portions of the study), with close observation after infusion and stopping rules that prevent re-challenge of patients/participants with significant hypersensitivity reactions.

There is no anticipated therapeutic benefit for the healthy participants in this trial. However, healthy participants may benefit from the screening procedures (through detection of unknown health issues) even if they receive no therapeutic benefit from the study. In addition, patients with AD may derive therapeutic benefit from the trial.

LY3872386 has not been administered to humans previously. Therefore, this study has been designed in accordance with the Guideline on Strategies to Identify and Mitigate Risks for First-in-human Clinical Trials with Investigational Medicinal Products (EMA 2017). More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3872386 is to be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety of LY3872386 after single dose administration in healthy participants and after repeat dose administration in patients with AD. • To characterize the safety of prednisone in healthy participants receiving multiple PO QD doses in various dosing groups.	• Number and incidence of AEs, TEAEs, and SAEs • Number and incidence of AEs, TEAEs, and SAEs
Secondary	
• To characterize the PK of LY3872386, total antibody, and the LY3558533 (free payload) following single dose administration in healthy participants and after repeat dosing in patients with AD. • To characterize the PK of prednisone in healthy participants receiving multiple PO QD doses in various dosing groups.	• C_{max} and AUC of LY3872386, total antibody, and LY3558533 (free payload) • C_{max} and AUC of prednisone and prednisolone

CCI

Objectives	Endpoints
CCI	

Abbreviations: AE = adverse event; AD = atopic dermatitis; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; CCI PK = pharmacokinetics; PO = oral administration; CCI QD = once daily; SAE = serious adverse event; SC = subcutaneous; CCI

Primary Endpoint Analysis

TEAEs, SAEs, and AEs for each IP will be listed, and if the frequency of events allows, descriptive statistics will summarize the safety data per race and ethnicity. Symptoms, their incidence, severity, and association with the IP, as perceived by the investigator, will be reported separately for each treatment and IP. All TEAEs will be summarized across each part of the study by system organ class and by decreasing frequency according to the Medical Dictionary for Regulatory Activities.

4. Study Design

4.1. Overall Design

Study KMAA is a first-in-human trial designed to characterize the safety and tolerability of LY3872386 as well as the PK of LY3872386, total antibody, and LY3558533 (free payload) in healthy participants and in patients with AD. Additionally, this study will assess the safety, PK, tolerability, and PD of various dose levels of prednisone in healthy participants. The study will enroll participants of any ethnicity. The inclusion of healthy Japanese and Chinese participants in Part A, the LY3872386 SAD portion of this study, will facilitate the inclusion of Japanese and Chinese participants in subsequent clinical trials. The study will be conducted in 3 parts as follows:

- Part A (SAD of LY3872386) will characterize the safety, tolerability, PK, and PD after single IV and SC dose administration of LY3872386 in healthy participants.
- Part B (MAD of LY3872386) will characterize the safety, tolerability, PK, and PD after multiple SC and/or IV dose administrations of LY3872386 in patients with AD.
- Part C CCI will assess the safety, tolerability, PK, and PD after repeat PO administration of prednisone in healthy participants.

Section 1.2 illustrates the study schema and demonstrates the relationship among Parts A, B, and C. Section 1.2 also provides details on dosing and the inclusion of healthy Chinese and Japanese participants. Part A will begin first and will inform and thereby trigger the initiation of Parts B and C.

Screening Period

Screening may occur up to 35 days prior to Day 1 of the study. After obtaining informed consent, participants will be screened for eligibility as detailed in Section 5. Screening procedures will be performed as outlined in the SoA (Section 1.3).

Participants who are not enrolled within 35 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. The assessments will be repeated at the discretion of the investigator.

Treatment Period and Visit Frequency

Part A: SAD of LY3872386 in Healthy Participants

Part A will be a SAD study of LY3872386 in healthy participants and will be comprised of 8 cohorts. SAD Cohorts 1 to 5 will consist of CCI healthy participants each who will be randomly assigned to receive LY3872386:placebo in a CCI manner. SAD Cohorts 6 to 8 will consist of CCI participants who will be randomly assigned to receive LY3872386:placebo in a CCI manner. See Table KMAA.1 for further details.

The planned doses are CCI mg IV (Cohort 1), CCI mg IV (Cohort 2), CCI mg IV (Cohort 3), CCI mg IV (Cohort 4), CCI mg SC (Cohort 5), CCI mg IV (Cohort 6), CCI mg SC (Cohort 7), and CCI mg IV (Cohort 8). The study intervention will be administered as a single dose on Day 1, followed by a 12-week follow-up period. Dose escalation will be based on the review of available data from the ongoing cohorts. Refer to Section 6.6.1 for further details on dose escalation.

CCI [redacted] he maximal concentration of LY3872386 following IV administration is expected to occur immediately following the single dose, while the maximal concentration of LY3872386 following SC administration is uncertain and is projected to occur approximately 1 to 4 days after the dose following single administration, which is similar to reports for mAb therapies (Ryman and Meibohm 2017). However, the maximal concentration of LY3558533 (free payload) following administration is uncertain and is projected to occur approximately CCI to CCI days after dose following a single SC administration. CCI [redacted]

Refer to Sections 6.1.1 and 6.6.1.1 for details on administration and data review prior to dosing.

Participants will be inpatient CCI [redacted], followed by visits at regular intervals. Participants will be monitored for safety, CCI [redacted] and samples will be collected as outlined in Section 1.3.1. Participants will be discharged from the CRU CCI [redacted] after all the study assessments have been completed during the treatment period and in agreement with the investigator.

Part B: MAD of LY3872386 in Patients with Atopic Dermatitis

Part B will be a MAD study in patients with AD and will be comprised of 2 cohorts. Each cohort will consist of at least CCI [redacted] randomized participants.

The planned doses are CCI [redacted] mg IV or SC (Cohort 1) and CCI [redacted] mg IV or SC (Cohort 2). The study intervention will be administered CCI [redacted] for up to 12 weeks. See Table KMAA.1 for further details.

Participants will be followed on an outpatient basis by visits at regular intervals.

Refer to Sections 6.1.1 and 6.6.1.2 for details on administration, commencement of Part B, and data review prior to dosing.

Part C: Open-label Multiple Dose of Prednisone in Healthy Participants

Part C will be an open-label multiple dose study of prednisone in 1 cohort of healthy participants. Participants will receive either CCI [redacted] mg of prednisone (Table KMAA.2).

- CCI [redacted] mg or CCI [redacted] mg prednisone PO QD for a total of CCI [redacted] doses
  CCI [redacted]
- CCI [redacted] mg prednisone PO QD for a total of CCI [redacted] doses
  CCI [redacted]

Refer to Sections 6.1.1and 6.6.1.3 for details on administration and the commencement of Part C.

For all study parts

The timings and procedures are outlined in Section 1.3. If the investigator deems it necessary, participants may remain in the CRU for a longer duration. Any changes to the planned discharge day will be made in consultation with the sponsor.

Follow-up Period

Participants will be required to return to the CRU for clinical assessments and blood samples on an outpatient basis (Section 1.3). The final follow-up visit will be approximately 12 weeks after the single dose of the study intervention in Part A, 14 weeks after the last dose of the study intervention in Part B, and 2 weeks after the last dose of prednisone in Part C.

Table KMAA.1. Summary of Participants in Cohorts Dosed with LY3872386

Part A: SAD of LY3872386 in Healthy Participants[a]								
Cohort #	**Planned Dose / Administration Route**	**Number of Planned Non-Japanese / Non-Chinese Participants**		**Number of Planned Japanese Participants**		**Number of Planned Chinese Participants**		**Total Number of Planned Completers**
		LY	**PBO**	**LY**	**PBO**	**LY**	**PBO**	
Cohort 1 **Cohort 2** **Cohort 3** **Cohort 5**	CCI mg IV CCI mg IV CCI mg IV CCI mg SC	CCI LY: CCI PBO						CCI per cohort
Cohort 4[b]	CCI mg IV	CCI						
Cohort 6[c] **Cohort 7[c]** **Cohort 8[c]**	CCI mg IV CCI mg SC CCI mg IV	CCI						CCI per cohort
Part B: MAD of LY3872386 in Patients with AD								
Cohort #	**Planned Dose/ Administration Route**	**Number of Planned Patients**						**Total Number of Planned Randomized Patients**
Cohort 1	CCI mg IV or SC	CCI LY: CCI PBO						CCI
Cohort 2	CCI mg IV or SC	CCI LY: CCI PBO						CCI

Abbreviations: AD = atopic dermatitis; IV = intravenous; LY = LY3872386; MAD = multiple-ascending dose, PBO = placebo; SAD = single-ascending dose; SC = subcutaneous.

[a] Sentinel dosing will be used.

[b] Sentinel pair must be non-Japanese and non-Chinese participants OR Sentinel pair must be mixed ethnicities (CCI non-Japanese/non-Chinese participant and CCI Japanese participant).

[c] Sentinel pair must be non-Japanese and non-Chinese participants.

Table KMAA.2. Summary of Participants Dosed with Prednisone

Part C: Multiple Doses of Prednisone in Healthy Participants		
Dosing Group	**Planned Dose/Administration Route**	**Total Number of Planned Completers**
Group 1	CCI mg PO	CCI
Group 2	CCI mg PO	CCI
Group 3	CCI mg PO	CCI

Abbreviation: PO = oral administration.

4.2. Scientific Rationale for Study Design

Study KMAA is the first-in-human dose study that will characterize the safety, tolerability, and PK of single doses of LY3872386 in healthy participants, multiple doses of LY3872386 in patients with AD, and multiple dose levels of prednisone in healthy participants. Participants receiving prednisone PO QD will not be blinded with a placebo. Blinding of subjects to prednisone was not deemed necessary as only objective safety and PD biomarker results following prednisone or LY3872386 administration will be compared. A lack of blinding would not be expected to affect these results. The data generated in this study will guide the design of the subsequent clinical trials.

4.3. Justification for Dose

Dose ranges from CCI mg IV to CCI mg IV and from CCI mg SC to CCI mg SC LY3872386 was selected to evaluate in the SAD and MAD portions of the study, respectively, based on current nonclinical pharmacology and toxicology data.

Human Pharmacokinetics and Dose Prediction

CCI

Human PK parameters were determined using allometric scaling (Deng et al. 2011).

CCI

According to the model, the projected desired efficacious dose range to meet expected outcome measures on EASI disease score percent change from baseline ranged from CCI mg to CCI mg CCI SC. Based on the emerging safety, PK, and PD from SAD Part A, CCI SC and/or IV dosing may be investigated to evaluate clinical effects in the MAD. The MAD Part B dosing paradigm will be confirmed based on emerging SAD data.

The investigational dose range of CCI mg LY3872386 is intended to assess the dose-response relationship and fully characterize safety and tolerability in humans for subsequent studies. This range is supported by a 3-month study in monkeys, CCI

CCI

These effects are monitorable in humans and would be expected to be reversible with the cessation of dosing. The adverse clinical decline from infection, observed at the highest dose in a single monkey, was considered secondary to decreased lymphocytes and would be expected to be avoidable with clinical monitoring and intervention. Therefore, clinical doses approaching the NOAEL in monkeys would be considered safe.

SAD Starting Dose

The proposed SAD starting dose is CCI mg IV, which is supported by

- a CCI -fold dose multiple to the NOAEL in the 3-month repeat-dose toxicology study in monkeys
- a predicted CCI -fold exposure multiple to the NOAEL in the 3-month repeat-dose toxicology study in monkeys, and
- the expectation that this dose is below a minimum anticipated biological effect level.

SAD Maximum Dose

The proposed SAD maximum dose is CCI mg IV (Table KMAA.3), which is supported by

- a CCI -fold dose multiple to the NOAEL in the 3-month repeat-dose toxicology study in monkeys
- a predicted CCI -fold exposure multiple to the NOAEL in the 3-month repeat-dose toxicology study in monkeys, and
- the monitorability of the effects of LY3872386 pharmacology.

MAD Dosing

The dose for MAD Cohort 1 is planned to be CCI mg with dose and route to be confirmed based on emerging SAD data. The dose for MAD Cohort 2 is planned to be CCI mg with dose and route to be confirmed based on SAD data and data from MAD cohort 1.

The planned dose of CCI mg for MAD Cohort 1 (Table KMAA.4) is supported by

- a CCI -fold dose multiple to the NOAEL in the 3-month repeat-dose toxicology study in monkeys
- predicted CCI fold exposure multiples (depending on dosing route and frequency) to the NOAEL in the 3-month repeat-dose toxicology study in monkeys, and
- the monitorability of the effects of LY3872386 pharmacology.

The maximum planned dose of CCI mg for MAD Cohort 2 is supported by

- a CCI -fold dose multiple to the NOAEL in the 3-month repeat-dose toxicology study in monkeys
- predicted CCI fold exposure multiples (depending on dosing route and frequency) to the NOAEL in the 3-month repeat-dose toxicology study in monkeys, and
- the monitorability of the effects of LY3872386 pharmacology.

Table KMAA.3. NOAEL-Based Dose and Model-Predicted Exposure Multiples for Proposed Single Administrations of LY3872386 to Human Participants

	Dose (mg)	Dose[a] (mg/kg)	Dose Multiple[b]	$AUC_{0\text{-inf}}$ (µg·hr/mL)	Exposure Multiple[b]
Human Starting Dose	CCI				
Human Maximum Dose					
Monkey NOAEL[c]					

Abbreviations: AUC = area under the plasma concentration versus time curve; $AUC_{0\text{-}168hr,ss}$ = area under the plasma concentration versus time curve from time 0 to 168 hour, at steady state; $AUC_{0\text{-inf}}$ = area under the plasma concentration versus time curve from time 0 to infinity; CL = clearance; IB = Investigator's Brochure; IV = intravenous; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetic; SAD = single-ascending dose; SC = subcutaneous.

a Calculations based on CCI kg patient.

b Dose multiple is the dose in animals divided by the dose in humans based on mg/kg. Exposure multiple is the calculated AUC in animals/predicted AUC in humans (The mean human dose projection PK parameter of linear CL = CCI L/h and SC bioavailability = CCI % was used to calculate the human predicted AUC.) (Note: The route of administration if different between species). For single-dose administration in the SAD portion of the first-in-human study, monkey $AUC_{0\text{-}168hr,ss}$ /predicted human $AUC_{0\text{-inf}}$ is used to calculate a conservative estimate of exposure multiple.

c NOAEL determined in a 3-month repeat-dose toxicity study (Study 20341655).

d Mean AUC value is inclusive of all animals, including 2 in which exposure was impacted by the presence of anti-drug antibodies (see Section 4 of the IB). This value results in a more conservative estimate of exposure at the NOAEL.

Table KMAA.4. NOAEL-Based Dose and Model-Predicted Exposure Multiples for Proposed Repeat Administrations of LY3872386 to Human Participants

	Dose (mg) and Frequency	Dose[a] (mg/kg)	Dose Multiple[b]	$AUC_{0-336hr}$ (ug*h/mL)	$AUC_{0-672hr}$ (ug*h/mL)	$C_{av,ss}$[c] (ug/mL)	Exposure Multiple[d]
Human Multiple Dose	CCI						
Monkey NOAEL[e]							

Abbreviations: AUC = area under the plasma concentration versus time curve; $AUC_{0-336hr}$ = area under the plasma concentration versus time curve from time 0 to 336 hour (2 weeks); $AUC_{0-672hr}$ = area under the plasma concentration versus time curve from time 0 to 672 hour (4 weeks); IV = intravenous; $C_{av,ss}$ = average plasma concentration over the dosing interval, at steady state; N/A = not applicable; NOAEL = no-observed-adverse-effect level; CCI SC = subcutaneous.

a Calculations based on CCI kg patient.

b Dose multiple is the dose in animals divided by the dose in humans based on mg/kg.

c AUC value is expressed as average plasma concentration ($C_{av,ss}$) to normalize for differences in the dosing interval between studies in humans and monkeys, and is calculated by dividing the AUC value by the number of hours in the dosing interval.

d Monkey $C_{av,ss}$/predicted human $C_{av,ss}$ is used to calculate a conservative estimate of exposure multiple.

e NOAEL determined in a 3-month repeat-dose toxicity study (Study 20341655). $C_{av,ss}$ is calculated from the AUC of CCI ng*hr/mL.

Prednisone Dose Justification:

Doses of CCI mg and sometimes up to CCI mg of prednisone are common in inflammatory diseases to treat acute flares for short durations (≤3 months). 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 or the last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial globally.

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

5. Study Population

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

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply at screening and/or enrollment:

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Characteristics

2. Overtly healthy for Part A and Part C as determined by medical evaluation, including medical history, physical examination, laboratory tests, and cardiac monitoring (including ECGs).
   a. To qualify as Japanese for the purpose of this study, the participant must be first-generation Japanese, defined as the participant's biological parents and all of the participant's biological grandparents must be of exclusive Japanese descent, and must have been born in Japan.
   b. To qualify as Chinese for the purpose of this study, the participant must be, at a minimum, third-generation Chinese, defined as all 4 of the participant's biological grandparents must be of exclusive Chinese descent and born in China.
3. Have clinical laboratory test results within the normal reference range for the population or investigative site or results with acceptable abnormalities that are judged to be not clinically significant by the investigator.
4. Have venous access sufficient to allow for blood sampling and administration of IP for IV administration as per the protocol.
5. Are reliable, willing to make themselves available for the duration of the study, and willing to follow study procedures.

Body Mass Index and Weight

6. Have a body mass index of 18.0 to 32.0 kg/m^2, inclusive, for Parts A and C, and 18.0 to 38.0 kg/m^2, inclusive, for Part B.

Sex and Contraceptive/Barrier Requirements

7. Male or Female
   a. Male participants:

i. Refer to Appendix 4 (Section 10.4) for definitions and additional guidance related to contraception.

b. Female participants:

ii. WNOCBP may participate in this trial. Refer to Section 10.4 for definitions and additional guidance related to contraception.

Informed Consent

8. Are capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.1.1. Additional Inclusion Criteria for Part B (Patients with Atopic Dermatitis)

9. Female Participants
    a. WNOCBP and WOCBP may participate in Part B of this study. Please refer to Appendix 4 (Section 10.4) for definitions and additional guidance related to contraception.
10. Have a diagnosis of AD at least 12 months prior to screening as defined by the American Academy of Dermatology (Eichenfield et al. 2014).
11. Have AD, including all of the following:
    a. EASI score ≥12 at screening (Visit 1) and at randomization (Visit 2)
    b. vIGA-AD score of ≥3 at screening (Visit 1) and at randomization (Visit 2)
    c. ≥7% of body surface area involvement at screening (Visit 1) and at randomization (Visit 2)
12. Have a history, documented by a physician and/or investigator, of inadequate response to existing topical medications within 6 months preceding screening, or participants who failed systemic therapies intended to treat AD (such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, within 6 months preceding screening), or a history of intolerance to topical therapy as defined by at least 1 of the following:
    a. Inability to achieve good disease control defined as mild disease or better (for example, vIGA-AD ≤2) after use of at least a medium potency TCS for at least 4 weeks or for the maximum duration recommended by the product prescribing information (for example, 14 days for super-potent TCS), whichever is shorter. TCSs may be used with or without TCNIs.
    b. History of clinically significant adverse reactions with the use of TCS, such as skin atrophy, allergic reactions, or systemic effects that, in the opinion of the investigator, outweigh the benefits of retreatment.
13. Participants who have applied emollients daily for at least 14 days prior to randomization and agree to use emollient daily throughout the treatment period.
14. Participants who are receiving chronic treatments to improve sleep should be on a stable dose for at least 2 weeks prior to screening as determined by the investigator.

5.2. Exclusion Criteria

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

15. women who are pregnant and/or lactating.
16. are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
17. are Lilly employees or are employees of a third-party organization involved with the study.
18. are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study or have received any nonbiologic or biologic agent (such as monoclonal antibodies, including marketed drugs) within 30 days or 5 half-lives (whichever is longer) of randomization.
19. have a current or recent acute, active infection. For at least 30 days before screening and up to the randomization visit, participants must have no symptoms or signs of infection in the absence of any, anti-infective treatment.
20. have had any of the following types of infection within 3 months prior to the screening visit or develops any of these infections before the randomization visit:
    - Serious (requiring hospitalization or IV or equivalent oral antibiotic treatment, or both)
    - Opportunistic (as defined in Winthrop et al. 2015)
      Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
    - Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
    - Recurring (including, but not limited to, herpes simplex, herpes zoster, and recurring cellulitis). Participants with only recurrent, mild, and uncomplicated orolabial herpes and/or genital herpes may be discussed with the sponsor's designated medical monitor and considered for enrollment if other study eligibility requirements are met.
    - Have syphilis, as shown by positive results for both rapid plasma reagin and Treponema pallidum hemagglutination tests.
21. have received live vaccine(s) (including attenuated live vaccines) or Bacillus Calmette-Guérin within 35 days of screening or intend to receive them during the study (non-live or inactivated vaccinations are allowed) or within 14 weeks after receiving the last dose of study intervention.
22. show evidence of active or latent TB, as documented through medical history and examination, chest x-rays (posterior to anterior, read by a radiologist, pulmonologist, or designee; a lateral chest x-ray may be performed if clinically or radiologically indicated), and TB testing, either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guérin or other vaccination history) or a positive QuantiFERON®-TB Gold test. If the QuantiFERON-TB Gold test result is indeterminate, it may be repeated only once, and if the repeat test is indeterminate, the participant will be deemed ineligible. The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local standard of care. Please note that if a chest x-ray has been performed in the past 6

months, found to be normal and the report is available, a further chest x-ray is not required, provided there has been no known TB exposure since the x-ray was performed.

Note: Results of a chest CT scan or other imaging study similar to a chest x-ray may be substituted in place of the chest x-ray as described above, in consultation with the sponsor's medical monitor.

23. have 1 of the following viral infections:
    a. a current infection with HBV (that is, positive for HBsAg and/or polymerase chain reaction positive for HBV DNA; Section 8.2.10).
    b. a current infection with HCV (that is, positive for HCV RNA; Section 8.2.11).
    c. HIV infection.
24. had any surgical procedure (except for minor surgery requiring local or no anesthesia and without any complications or sequelae) within 12 weeks prior to screening or any planned surgical procedure scheduled to occur during the study.
25. have a history or presence of multiple or severe allergies or an anaphylactic reaction to prescription or nonprescription drugs.
26. have a history or presence of allergy or reactions to ADC, mAbs, systemic GCs or have clinically significant multiple or severe drug allergies, intolerance to TCSs (for healthy participants only), or a history of severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
27. had any malignancy within the past 5 years. Exceptions: successfully treated basal cell skin carcinoma or squamous cell skin carcinoma with no evidence of recurrence or metastatic disease within the 3 years prior to baseline.
28. current smoker using >10 cigarettes or other tobacco products per day and are unable/unwilling to stop smoking tobacco products while in the study unit and have a positive cotinine test.
29. are regular users of known drugs of abuse and/or have positive findings on urinary drug tests at screening, OR an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), OR are unwilling to stop alcohol consumption during study visits/time in the research unit (1 unit of alcohol = 12 oz or 360 mL of beer, 5 oz or 150 mL of wine, and 1.5 oz or 45 mL of distilled spirits).
30. are regular users of cannabis (legal or medical).
31. have received blood products within 6 months before screening or donated blood of more than 500 mL within the previous 30 days of study screening.
    a. For Chinese participants:
        i. Have donated blood of more than 400 mL within the previous 30 days of study screening.
32. have known hypogammaglobulinemia or a screening serum immunoglobulin G or immunoglobulin M below the reference range.

33. have a history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the participant to infection that, in the opinion of the sponsor or investigator, poses an unacceptable risk to the participant.
34. have presence of significant uncontrolled cerebro-cardiovascular (for example, myocardial infarction, unstable angina, hypertension, moderate-to-severe [New York Heart Association Class III/IV] heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders, or abnormal laboratory values at screening that, in the opinion of the sponsor or investigator, pose an unacceptable risk to the participant if participating in the study or interfering with the interpretation of data.
35. use or intend to use herbal, over-the-counter, or prescription medication within 14 days prior to dosing and during the study, other than estrogen/progesterone as a form of hormone replacement therapy and/or oral contraceptives. Certain medications (for example, vitamin supplements or prescription medications) may be permitted at the discretion of the investigator and in agreement with the sponsor.
36. Diagnosed with active endoparasitic infections; suspected or at high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
37. History of preexisting glaucoma, severe acne, osteonecrosis, uncontrolled hypertension, or peripheral edema.
38. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
50. Known history of diabetes.
51. Fasting glucose level of ≥126 mg/dL and glycated hemoglobin ≥6.5% and/or taking anti-diabetes medications at screening.
52. Known history of osteoporosis.

5.2.1. Additional Exclusion Criteria for Part B (Patients with Atopic Dermatitis)

39. Are currently experiencing or have a history of other concomitant skin conditions (for example, psoriasis or cutaneous lupus) that would interfere with the evaluation of the effect of the study medication on AD.
40. participants who, in the opinion of the investigator, are currently experiencing or have a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or IV treatment for skin infections that may interfere with their participation in the study.
41. Have a history of eczema herpeticum
    a. within 6 months prior to screening, or
    b. 2 or more episodes during lifetime.
42. participants who are currently experiencing a skin infection that requires treatment or is currently being treated with topical or systemic antibiotics.

Note: Participants may not be rescreened until at least 4 weeks after the date of their previous screen failure and at least 2 weeks after the resolution of the infection.

43. Have a history of TCS use suggestive of a high risk for TCS withdrawal, for example, a history of prolonged or frequent use of moderate- to high-potency TCS, especially on the face (Hajar et al. 2015), such that, in the opinion of the investigator, the participant will be unable to withdraw and abstain from TCS for several weeks during the study.
44. have any serious concomitant illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active, frequent monitoring (for example, unstable chronic asthma requiring hospitalization and/or systemic corticosteroids in the 6 months prior to screening).
45. have been treated with the following therapies:
    a. Other mAb (for example, ustekinumab, omalizumab, dupilumab, tralokinumab, and lebrikizumab (whether approved or investigational) within 5 half-lives prior to randomization (Visit 2).
    b. Received any parenteral corticosteroid administered by intramuscular or IV injection within 2 weeks prior to study entry (Visit 1) or within 6 weeks prior to planned randomization (Visit 2) or are anticipated to require parenteral injection of corticosteroids during the study.
    c. Have had an intra-articular corticosteroid injection within 2 weeks prior to study entry (Visit 1) or within 6 weeks prior to planned randomization (Visit 2).
    d. Have used any of the following topical medications within 1 week prior to randomization (Visit 2):
        - topical corticosteroids or topical immune modulators (for example, tacrolimus or pimecrolimus)

        Note: pimecrolimus may not be available in all regions, including Japan.

        - topical phosphodiesterase type 4 inhibitor, or
        - topical Janus kinase inhibitor.

    Note: Intranasal or inhaled steroid use is allowed during the trial.

46. have received the following excluded medications/treatments within 4 weeks prior to randomization (Visit 2) or plan to use during the study:
    a. oral systemic corticosteroids and leukotriene inhibitors.
    b. systemic immunomodulators, including, but not limited to, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, and Janus kinase inhibitors (such as tofacitinib, ruxolitinib, baricitinib, upadacitinib or abrocitinib).
    c. sedating antihistamines including, but not limited to, alimemazine, chlorphenamine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, ketotifen, and promethazine.

        Note: Participants may use newer, less sedating antihistamines (for example, fexofenadine, loratadine, and cetirizine).

d. any other systemic therapy used to treat AD or symptoms of AD (approved or off-label use).
e. phototherapy, including therapeutic phototherapy (psoralen plus ultraviolet-A and ultraviolet-B), excimer laser, or tanning beds.

47. patients with a positive beta-D-glucan test at screening and a confirmed diagnosis of pneumocystis pneumonia will be excluded.
48. have experienced hypersensitivity to the active substance or to any of the excipients.
49. For Japanese participants only: have evidence of, or a positive test for, HBV infection, defined as:
    a. positive for hepatitis B surface antigen (HBsAg), or
    b. positive for hepatitis B core antibody (HBcAb) and positive HBV DNA, or
    c. positive for hepatitis B surface antibody (HBsAb) and positive for HBV DNA.

    Note: Patients who are positive for HBcAb or HBsAb and negative for HBV DNA may be enrolled in Part B of the study. In this case, repeat testing for HBV DNA is required at least once every month during the study.

5.3. Lifestyle Considerations

Throughout the study, participants must adhere to lifestyle restrictions as outlined by the CRU and in the study procedures. Participants may undergo medical assessments and a review of compliance with requirements before continuing in the study.

5.3.1. Meals and Dietary Restrictions

During the confinement period (where applicable), participants will consume only food and beverages that are provided to them by the CRU staff. Standard meals (for example, breakfast, lunch, dinner, and snack) will be provided to the participants while resident at the CRU.

In Part A (SAD) and Part B (MAD), participants will be required to fast for approximately 4 hours before study intervention administration. Water is permitted. Participants may eat approximately 2 hours postdose. A normal diet may be consumed at all other times during the study.

In Part C (PO QD prednisone), the participants will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1-hour predose until 2-hour postdose, excluding the amount of water consumed at dosing. Food is allowed 4 hours postdose. At all other times during the study, participants may consume water ad libitum.

For all outpatient visits in Parts A, B, and C, participants will be required to fast approximately 10 hours before visits that include clinical chemistry testing. Water is permitted.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

For Parts A, B, and C, consumption of caffeine-containing beverages is permitted during the outpatient portions of the study. For Parts A and C, participants will abstain from ingesting caffeine- or xanthine-containing products (for example, coffee, tea, cola drinks, and chocolate) from check-in and through discharge from the CRU.

For Parts A and C, participants will not consume alcohol from check-in and through discharge from the CRU. For Part B, participants should not consume alcohol for at least 24 hours prior to dosing and at least 2 days postdose. During outpatient periods, all participants should be advised to limit alcohol consumption to no more than 2 units per day.

Participants should be willing and be able to abide by smoking restrictions at the CRU during both the inpatient period and outpatient visits.

Study participants should be instructed not to donate blood, blood products, and/or tissue during the study or for 14 weeks following the final visit of the study.

5.3.3. Activity

Participants will abstain from strenuous exercise for approximately 5 days before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (for example, watching television and reading).

5.4. Screen Failures

A screen failure occurs when a participant consents to participate in the clinical study but is not subsequently assigned to the study intervention or enrolled in the study. A participant who is an alternate in a study group/cohort may be enrolled in the next group/cohort if within the screening window or may screen for a subsequent group, unless the participant was a screen fail.

As Part A and Part C are healthy participant-only studies, individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, although screening tests such as clinical laboratory tests and vital signs or ECGs may be repeated at the discretion of the investigator. If subjects have minor deviations in screening assessments (for example, vital signs), these may be repeated at the investigator's discretion to confirm eligibility.

As Part B participants are patients with AD, individuals who do not meet the eligibility criteria for participation in this study (screen failure) may not be rescreened until at least 4 weeks after the date of their previous screen failure and at least 2 weeks after resolution of a skin infection, unless the rescreening is for administrative reasons (see below). Blood tests may be repeated at the discretion of the investigator during screening without being considered a screen failure. Participants may be rescreened once. When rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

Allowed Rescreening for Administrative Reasons

An individual may be rescreened once for an administrative reason, such as falling out of the screening window because of scheduling conflicts. The sponsor does not need to approve rescreening for administrative reasons. The rescreening can start immediately after the administrative reason has been resolved.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention of a Participant

Not applicable.

6. Study Interventions 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 or used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3872386	Placebo (0.9% sodium chloride solution)	Prednisone
Dosage Level(s)	CCI mg/vial (single administration, CCI for 12 weeks, and CCI for 12 weeks)	N/A	CCI mg CCI x 30 days), CCI mg (CCI x 30 days), and CCI mg (CCI x 7 days)
Route of Administration	IV and SC Approximately CCI min IV infusion	Same as LY3872386 administration	Oral
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized, not used according to authorization	Authorized, not used according to authorization

Abbreviations: EU = European Union; IV = intravenous; SC = subcutaneous; CCI .

Packaging and Labeling

LY3872386 will be supplied by the sponsor in accordance with the current Good Manufacturing Practice. The study interventions will be labeled as appropriate for country requirements.

6.1.1. Administration Details

Part A and Part B: LY3872386 Administration

In IV dosing cohorts, LY3872386 will be administered as a slow IV infusion over approximately CCI to CCI minutes. Resuscitation equipment, emergency drugs, and appropriately trained staff must be available while the participant is staying at the investigation site.

In SC dosing cohorts, all LY3872386 injections will be administered into the SC tissue of the abdominal wall. Injection sites will be alternated between 4 sites (that is, right and left upper quadrants and the right and left lower quadrants) on the abdominal wall (where applicable). Whenever possible, study drug administration should be carried out by the same personnel.

Part C: Prednisone Administration

All doses of prednisone will be administered with approximately CCI mL of room temperature water while in a sitting position.

Prednisone tablets should be swallowed whole. Participants should not break, crush, or chew the study intervention.

On dosing days, participants will adhere to meal restrictions as outlined in Section 5.3.1.

6.1.2. Premedication for Infusions

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator(s). If infusion reactions are observed, but review of the data suggests that dose escalation may continue, administration of acetaminophen 500 to 1000 mg and/or an antihistamine may be administered orally 30 to 60 minutes prior to the start of infusion for subsequent participants.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and the sponsor, and recorded in the study documentation, along with the dose-escalation decision.

Any premedication given will be documented as a concomitant therapy (see Section 6.9).

6.1.3. Management of Infusion Reactions

There is a risk of an infusion reaction with any biological agent. Therefore, all participants should be monitored closely.

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to:

- fever
- chills
- nausea
- headache
- bronchospasm
- hypotension
- angioedema
- throat irritation
- rash
- pruritus
- myalgia, and
- dizziness.

In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The investigational product infusion should be slowed (for example, reduce the infusion rate by 50% [for example, an infusion rate of 12 mL/h becomes 6 mL/h or slower]) or stopped, depending on the symptoms/signs present:

    - if slowed, the infusion should be completed at the slower rate, as tolerated, and
    - if determined by the investigator that the infusion should no longer continue, no further attempts to dose the participant should be made.
- Supportive care should be employed in accordance with the symptoms/signs and consistent with local guidelines.
- If a participant's infusion reaction is sufficiently severe to discontinue the infusion, subsequent infusions may be administered with premedication at the discretion of the investigator, following agreement with the Lilly CRP or clinical pharmacologist
- If a participant's infusion rate is reduced due to an infusion reaction, subsequent infusions may be administered at the discretion of the investigator, following agreement with the Lilly CRP or clinical pharmacologist. If further infusions are administered, the infusion rate must not exceed the slowest rate used to complete the infusion on the occasion when the infusion reaction occurred. Premedication may be administered at the discretion of the investigator.
- If it is determined that the participant should not receive further doses of the investigational product, the participant should complete AE and other follow-up procedures per the SoA (Section 1.3) of this protocol.

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, prepare, or administer study intervention.

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.

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 preparation, handling, storage, and final disposition of unused study interventions are provided in the Pharmacy Manual/Pharmacy Preparation Instructions.

Where applicable, the study intervention will be prepared by an unblinded pharmacy staff or a pharmacist who is not involved in any other study-related procedures.

6.3. Assignment to Study Intervention

For Part A and Part B, this is a double-blinded, randomized study of LY3872386 in healthy participants and in patients with AD. For Part C, this is an open-label study of prednisone in healthy participants.

6.4. Blinding

6.4.1. Part A: Single-Ascending Dose of LY3872386

This is a double-blind study in which participants and investigators are blinded to the study intervention. Emergency codes regarding treatment assignment will be available to the investigator, and in case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment, unless this could delay the emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study interventions and will endeavor to ensure that there are no differences in the time taken to dispense following the randomization.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor CRP for the participant to continue in the study.

6.4.2. Part B: Multiple-Ascending Dose of LY3872386

For MAD Part B only, all participants will be centrally assigned to the randomized study intervention using an IWRS. Before the study is initiated, log-in information and directions for the IWRS will be provided to each site. IWRS will not be used for the dispensing of study intervention and will only be used for randomization.

This is a double-blind study in which participants and investigators are blinded to the study intervention. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if the unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment, unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately within 24 hours of this occurrence. The date and reason that the blind was broken must be recorded.

6.4.3. Part C: Open-Label of Prednisone

This is an open-label study.

6.5. Study Intervention Compliance

The study intervention will be administered under medical supervision by the investigator or designee. The dose of the study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.6. Dose Modification

6.6.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis.

Safety data, in particular AEs, SAEs, and laboratory abnormalities, will be independently assessed by the investigator.

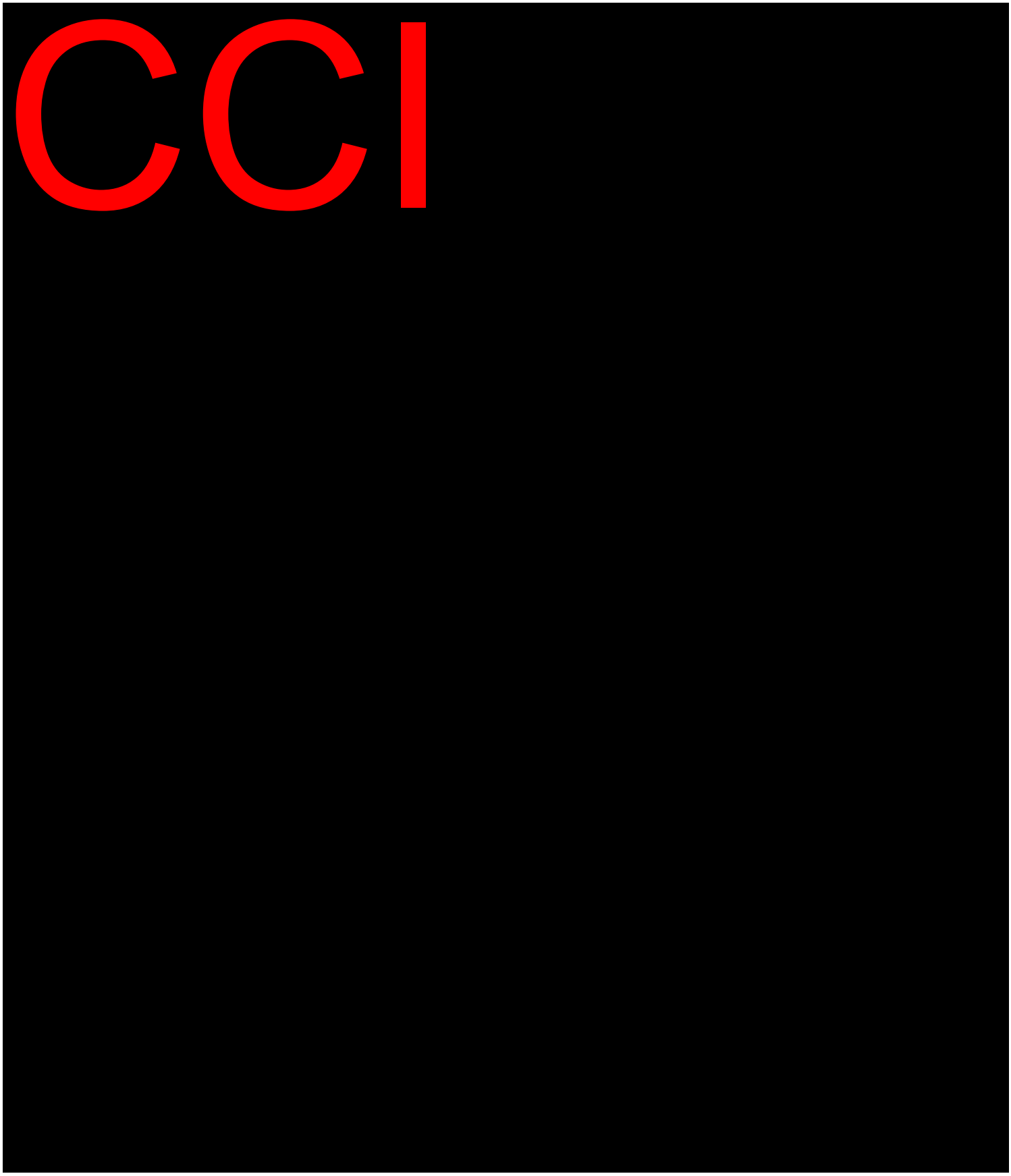
Safety and tolerability data will be the primary criteria for the dose escalation in Part A (SAD of LY3872386) and Part B (MAD of LY3872386) (Section 8.2). CCI

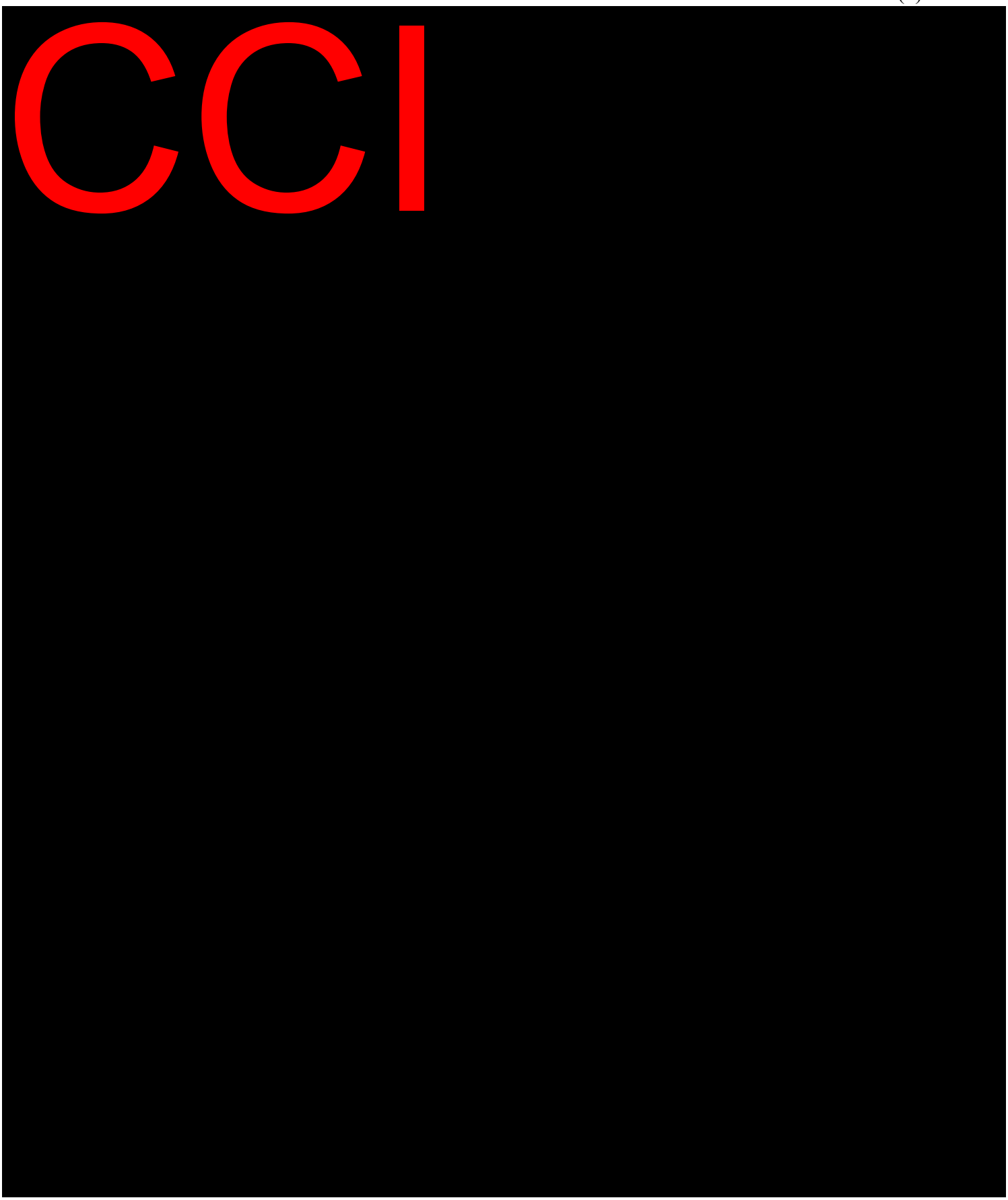
CCI

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for the next cohort/dose level. The magnitude of dose escalations may be reduced following data review, CCI

No dose decision can occur without prior discussion and agreement between the investigators and the sponsor.

CCI


CCI


CCI

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

LY3872386 and prednisone will not be made available to participants after the conclusion of the study.

6.8. Treatment of Overdose

For this study, an overdose of LY3872386 or prednisone is considered any dose higher than the dose assigned through randomization. Treatment for overdose is the best supportive care.

The sponsor does not recommend specific treatment for an overdose.

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

- contact the Lilly Clinical Pharmacologist immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether the study intervention should be interrupted or the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities for approximately 12 weeks or 5 half-lives (whichever is longer)

- obtain a blood sample for PK analysis if requested by the Lilly Clinical Pharmacologist (determined on a case-by-case basis), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.9. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

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

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

In general, concomitant medication should be avoided. The use of chronic, stable doses of thyroid hormone, or hormone replacement therapy is allowed. Acetaminophen (1 g, maximum 4 g/24 hours) may be administered at the discretion of the investigator for the treatment of headache and so on. Antihistamine may be administered as a premedication for infusion at the discretion of the investigator. Other concomitant medications may be considered on a case-by-case basis by the medical monitor in consultation with the Lilly CP/CRP or designee. If the need for concomitant medication (other than acetaminophen) arises, the inclusion or continuation of the participant may be at the discretion of the investigator after consultation with the sponsor. Any medication used during the course of the study must be documented.

For AD therapies permitted as part of rescue therapy see below.

6.9.1. Rescue Medicine

Criteria for rescue therapy initiation

- Investigators should attempt to manage participants with emollients. However, investigators are allowed to rescue participants who are experiencing unacceptable or worsening symptoms of AD after Week 8. Prior to rescue, it is recommended that an increased frequency of emollient use is attempted to at least twice a day or more in an effort to control symptoms. The rationale for rescue will be documented.

Choice of rescue therapy treatment

- Triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment. In the event that providing 1 or both of these topical formulations is not possible, an alternate, equivalent potency TCS cream and/or ointment may be provided.
    - Commercially available triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment may be supplied by the clinical site.

- Investigators may elect to use TCNIs and/or crisaborole where approved, although use of either of them during the study is not encouraged. If TCNIs are prescribed, use should be limited to problem areas only (for example, face, neck, skin folds, and genital areas).
- On the days of study visits, topical therapy should not be applied before the participant has undergone all study procedures and clinical evaluations to allow adequate assessment of skin dryness.
- Participants receiving topical therapy will remain on the study and continue to take IP. The use of rescue therapy will be documented in the eCRF.

In participants who do not improve sufficiently with the provided rescue topical therapy after 7 days, a higher potency TCS may be used, and IP may continue. It is recommended that if a participant achieves “clear” to “almost clear” skin after topical rescue, medium- and/or high-potency TCSs and TCNIs should be stopped, and low-potency TCSs (for example, hydrocortisone 2.5% ointment) should be used once daily for an additional 7 days, then stopped. If lesions return, participants can be retreated with TCSs with or without TCNIs and/or crisaborole as before, at the discretion of the investigator.

If topical rescue therapy as described above fails to sufficiently control AD symptoms, then oral systemic medications may be used as rescue (for example, corticosteroids, cyclosporine, and methotrexate). However, IP will be required to be permanently discontinued for the remainder of the 12-week study duration. If these medications are needed for other medical conditions (for example, asthma flare), they will still be treated as rescue medications.

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit can be used for this purpose if necessary.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants discontinuing from the study intervention prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 of this protocol.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study for additional data collection, consistent with routine safety monitoring. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The following infections lead to study intervention discontinuation: confirmed diagnosis of pneumocystis pneumonia, HIV, and active TB, including hepatitis B and C (as further described in Section 7.1.2).

A participant should be permanently discontinued from the study intervention

- if the participant becomes pregnant during the study
- for safety reasons, in the opinion of the investigator, or
- if the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

7.1.1. Rules for Stopping Dosing and Enrollment in a Cohort

If any of the following scenarios occur, dosing at the current level and further dose escalation will be interrupted and may resume only following written approval from the sponsor medical monitor:

- A single participant experiences an SAE unless obviously unrelated to LY3872386 administration.
- Severe nonserious AEs considered at least possibly related to the study intervention occurring in 2 participants in Parts A or B within the same cohort, independent of whether or not the events are in the same system organ class.
- Two or more participants per cohort in Parts A or B develop TEAEs or clinically significant changes in laboratory safety that are graded as at least moderate, unless there is an obvious explanation other than study intervention or study procedures for the event(s).

- One or more participants present severe AEs related to IV infusion that are related to LY3872386, and the TEAE does not resolve with a reduced IV infusion rate or supportive care.

7.1.2. Hepatic Criteria for Study Drug Interruption or Discontinuation

See Section 8.2.8 for hepatic criteria for study drug interruption or discontinuation.

7.1.3. Cardiovascular Stopping Criteria

7.1.3.1. QTc Stopping Criteria

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

Discontinuation of IP should be considered by the investigator and the sponsor if any of the following occur in a participant:

- QTcF >500 msec
- increase from baseline in QTc >60 msec, from at least 2 consecutive readings

7.1.3.2. Hypertension Stopping Criteria

If 2 consecutive systolic blood pressure $\geq$160 mm Hg or if 2 consecutive diastolic blood pressure $\geq$100 mm Hg; medical intervention indicated.

7.1.4. Ocular Pressure Interruption Criteria

The following criteria will lead to study intervention interruption:

- >10 points over baseline confirmed by an additional, consecutive assessment conducted prior to treatment administration, or
- >25 mmHg confirmed by an additional, consecutive assessment conducted prior to treatment administration, or
- develops signs of glaucoma

Therapy may resume when ocular pressure is within normal limits and/or sign of glaucoma resolve.

7.1.5. Serious and Opportunistic Infections Discontinuation and Interruption Criteria

7.1.5.1. Discontinuation: The Following Infections Lead to Study Intervention Discontinuation

HBV or HCV: The participant tests positive for HBV DNA (see Section 8.2.10) or tests positive for HCV RNA (Section 8.2.11).

Note: The HBV DNA result is to be confirmed if initial test result is positive but below the level of quantification (Section 7.1.5.2). Prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study intervention, the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

Certain AEs:

- The participant develops HIV infection.
- The participant develops active TB or has untreated LTBI.

7.1.5.2. Infection-Related Criteria for Temporary Withholding

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

- Serious or opportunistic infections, as defined in Section 5.2. Study intervention has to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment (exception for LTBI, noted below).
- A participant diagnosed with LTBI during the study has to be permanently discontinued from study intervention unless the participant is a candidate for LTBI treatment, and is treated for LTBI as follows:
    - Study intervention is temporarily withheld for at least the first 4 weeks of LTBI treatment.
    - After receiving at least 4 weeks of appropriate LTBI therapy (as per World Health Organization or US Centers for Disease Control and Prevention guidelines), if there is no evidence of hepatotoxicity (ALT/AST level must remain ≤2 times ULN) or other treatment intolerance, study intervention may be resumed.
    - The participant must complete appropriate LTBI therapy to remain eligible to receive study intervention.
- HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. In this situation, the sponsor's designated medical monitor should be contacted regarding the participant's status. HBV DNA testing is to be repeated as soon as it is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention.

7.1.6. Abnormal Laboratory Parameters of Special Interest

7.1.6.1. Hematological Values for Permanent Discontinuation

Any of these laboratory results with no other obvious cause in the opinion of the investigator:

- hemoglobin level <8 g/dL

- neutrophil count <1 x 10^9 /L
- total lymphocyte count <0.5 x 10^9/L, or
- platelet number <50K/mcL

7.1.6.2. Glucose and HbA1c Values for Permanent Discontinuation

Any of these laboratory results with no other obvious cause in the opinion of the investigator:

- If 2 fasting glucose measures are ≥126 mg/dL
- If 1 fasting glucose measure is ≥126 mg/dL and glycated hemoglobin level is ≥6.5% (48 mmol/mol) (ElSayed et al. 2023)

7.1.6.3. Adrenal Insufficiency Criteria for Permanent Discontinuation in Part B Only

Morning blood cortisol levels of <83 nmol/L, confirmed by a consecutive test conducted within 3 to 5 days of initial value or fail to respond to cosyntropin (or ACTH) assessment within normal limits.

Sponsor should be contacted, and participant may be referred to a health care provider for additional assessments, monitoring and/or management.

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, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an IP or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, and
- 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 the treatment of the study indication. In this case, discontinuation from the study occurs prior to the introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit as shown in the SoA (Section 1.3). If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant

withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist and the investigator to determine if the participant may continue in the study. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled participant to continue in the study, with or without continued treatment with IP.

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.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get the investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

- 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.
- Section 1.3 lists the SoA, detailing the study procedures and their timing (including tolerance limits for timing). The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based on emerging clinical information. The scheduled time points may be subject to minor alterations. However, the actual time must be correctly recorded in the CRF.
- Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.
- Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.
- Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.
- Failures or delays that are outside stipulated time allowances in performing procedures or obtaining samples due to legitimate clinical issues (for example, equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations, but the CRU will still be required to notify the sponsor.

8.1. Efficacy Assessments

In Part B of the trial, the following efficacy assessments will be performed:

Clinician-rated scales

Participant-rated scales

The following assessments should be completed prior to any clinical assessments being performed on days when study visits occur:

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will be completed only at screening, the last scheduled follow-up visit, and at early discontinuation. At admission, a medical assessment is performed, which includes a medical review and a brief physical examination. Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, skin, lymph nodes, and neurological systems. Weight will also be measured and recorded. Height will only be measured and recorded at screening.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to the clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3) and follow the study-specific recommendations included in the Manual of Operations for the study.

On Day 1 in Part A, blood pressure and PR will be assessed at predose, end of infusion (for IV only), and 3-, 6-, and 12-hour postdose. Blood pressure and PR should be measured after resting for at least 5 minutes in a supine position.

Temperature and oxygen saturation will be measured. Temperature and oxygen saturation are required only at screening, baseline, last scheduled visit, and early discontinuation.

In the case of AEs suggestive for orthostatic measurements, participants should be in a supine position for at least 5 minutes and stand for at least 2 minutes.

If the participant is unable to stand, only supine vital signs will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

Additional vital signs may be measured during each study period if warranted and agreed upon between the investigator and sponsor.

On days with concurrent ECG and/or PK sampling, these measurements should occur at approximately the same time. Vital sign measurements should occur prior to the blood draw.

8.2.3. Electrocardiograms

For each participant, ECGs should be collected according to the SoA (Section 1.3).

For Part A, a single ECG will be obtained at screening and at the last scheduled follow-up visit, but not transmitted to the central ECG vendor. At all other time points in Part A, consecutive ECGs are to be obtained in triplicate at approximately 1-min intervals. Additional tracings may be taken at each time point to obtain high quality data, when needed. Times are referenced to the end of dosing. ECGs will be obtained on Day 1 (predose [any time prior to dosing on the day of dosing but within approximately 90 minutes prior to the predose blood draw], end of infusion [approximately 6 hours after the end of infusion for the IV cohort and predose only for the SC cohort], Day 2 [approximately 24 hours after the end of dosing for both the IV and SC cohorts], and at any time on other specified visits [but prior to any blood draws at the same visit]).

For MAD Part B, a single ECG will be collected locally and stored at the investigator's site, unless the ECG values for participants in SAD Part A cohorts show clinically significant changes (for example, an increase in PR or QT interval). In this situation, triplicate 12-lead digital ECGs will be collected for participants in Part B cohorts.

For Part C, a single ECG will be collected prior to dosing locally and stored at the investigator's site unless the ECG values for participants show clinically significant changes (for example, an increase in PR or QT interval). In this situation, triplicate 12-lead digital ECGs will be collected for participants in Part C cohorts.

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

When scheduled at the same time point, ECGs must be recorded before collecting any blood samples. Participants must be in a supine position for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. ECGs may be obtained at additional times when deemed clinically necessary.

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

If a clinically significant quantitative or qualitative change from baseline is identified after the enrollment, the investigator will assess the participant for symptoms (for example, palpitations, near syncope, and syncope) to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document review of the ECG as soon as possible after the time of collection from at least one of the replicate ECGs from each time point.

Triplicate digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes, unless a cardiologist's overread of the ECGs is conducted prior to the completion of the final study report (in which case the overread data would be used).

8.2.5. Clinical Safety Laboratory Tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a source document agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that 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 the follow-up 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 (Section 1.3), standard collection requirements, and laboratory manual.

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

8.2.6. Injection-site Reactions

8.2.6.2. Injection-Site Bleeding Assessment

All injection sites will be observed within 1 minute after each injection by the investigator or designee, and the presence of visible bleeding will be recorded on the eCRF (Injection Procedure Evaluation Form).

A bandage may be placed on the injection site after assessment. In addition, if pain is present, participants will be asked if they can distinguish the cause of the pain (that is, needle insertion or fluid injection).

8.2.6.3. Injection-Site Bruising Assessment

Any spontaneously reported or clinically significant finding of injection-site bruising, as deemed by the Principal Investigator or designee, will be reported as an AE with additional information about the bruise (for example, maximum width).

8.2.7. Safety Monitoring

The sponsor will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures.

The sponsor will periodically review

- trends in safety data,
- laboratory analytes, including hematology and chemistry, and
- AEs.

When appropriate, the sponsor will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research physician.

8.2.7.1. Other Safety Monitoring

8.2.7.1.1. Pregnancy Testing

In this study, a serum pregnancy test will be conducted at screening only. A urine pregnancy test will be used at all other time points. For all female participants, follicle-stimulating hormone should be drawn to confirm status as defined in the Inclusion Criterion [7b] and to be considered exempt for further pregnancy tests during the study.

8.2.7.1.2. Infusion-related Reactions

IRR are systemic events temporally related to infusion (for example, IV or large volume SC) of a therapeutic agent for which an etiology is yet to be identified. IRRs may encompass a wide range of clinical events, including anaphylaxis and other events that may not be directly related to antibody responses, such as cytokine release syndrome.

Signs and symptoms of IRR shall be captured in the eCRF.

8.2.7.1.3. Hypersensitivity

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving the study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

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

In case of systemic hypersensitivity reactions, defined as anaphylaxis or generalized urticaria, additional blood samples should be collected as described in Appendix 2 (Section 10.2). Laboratory results are provided to the sponsor via the central laboratory.

In the event of drug hypersensitivity reactions (immediate or nonimmediate), up to 3 additional samples will be collected each for PK and immunogenicity at the following time points: as close to the onset of the reaction event as possible, at the resolution of the event if possible, and approximately 30 days following the event.

8.2.8. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Drug Interruption or Discontinuation

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

If this laboratory value is observed…	**Then…**		
	Initiate or continue close hepatic monitoring	**Initiate comprehensive evaluation**	**Interrupt or discontinue study drug**
ALT or AST ≥3x ULN	X		
ALP ≥2x ULN	X		
TBL ≥2x ULN[a]	X		
ALT or AST ≥5x ULN	X	X	
ALP ≥2.5x ULN	X	X	
ALT or AST ≥3x ULN with hepatic signs or symptoms[b]	X	X	X
ALT or AST ≥5x ULN for more than 2 weeks	X	X	X
ALT or AST ≥8x ULN	X	X	X
ALT or AST ≥3x ULN and TBL ≥2x ULN[a]	X	X	X
ALP ≥3x ULN	X	X	X
ALP ≥2.5x ULN and TBL ≥2x ULN[a]	X	X	X
ALP ≥2.5x ULN with hepatic signs or symptoms[b]	X	X	X

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

8.2.8.1.1. Close Hepatic Monitoring

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

ALT or AST ≥3x ULN **or**
ALP ≥2x ULN **or**
TBL ≥2x ULN[a]

[a] In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Close hepatic monitoring should include the following actions:

- Laboratory tests described in Appendix 6 (Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, creatine kinase, and complete blood count with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 1-2 times weekly until levels normalize or return to approximate baseline values.
- In addition to lab tests, a basic 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 current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

8.2.8.1.2. Comprehensive Hepatic Monitoring

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

ALT or AST ≥5x ULN **or**
ALP ≥2.5x ULN **or**
ALT or AST ≥3x ULN with hepatic signs or symptoms[a] **or**
ALT or AST ≥5x ULN for more than 2 weeks **or**
ALT or AST ≥8x ULN **or**
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR≥ 1.5

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

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

Comprehensive hepatic evaluation should include the following actions:

- At a minimum, comprehensive hepatic evaluation should include a physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, an ultrasound or CT scan).
- Based on the participant'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, a urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests, including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of approximately 1 to 2 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and test results related to hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.8.1.3. Study Drug Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study-drug and continue close monitoring and comprehensive hepatic evaluation as described in Section 8.2.8.1.1. and 8.2.8.1.2.

ALT or AST ≥3x ULN with hepatic signs/ symptoms[a] **or**
ALT or AST ≥5x ULN for more than 2 weeks **or**
ALT or AST ≥8x ULN **or**
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5 **or**
ALP ≥3x ULN **or**
ALP ≥2.5x ULN and TBL ≥2x ULN[b] **or**
ALP ≥2.5x ULN with hepatic signs or symptoms[a]

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

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

Interruption or discontinuation of study drug should include the following actions:

- While the participant is not receiving the study drug, clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study (that is, data lock), the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, data lock date).
- All the medical information and test results related to close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study drug after interruption for a hepatic reason can be considered only in consultation with the Lilly designated medical monitor, only if the liver test results returned to near baseline, and if a self-limited non-study-drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

8.2.9. Immunological Status Assessments

WBC subpopulations (including, but not limited to, total B cells, total T cells, and NK cells) in blood samples collected at visits and times specified in the SoA (Section 1.3) will be measured using flow cytometry as part of immunophenotyping assessment in Parts A, B, and C. A maximum of 3 samples may be collected at additional time points during the study (as unscheduled samples) if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded. Immunoglobulin samples will also be collected as specified in the SoA (Section 1.3) as part of safety assessment.

8.2.10. Hepatitis B Testing and Monitoring

Testing

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.

Monitoring

If the screening HBV DNA is negative, and proof of HBV vaccination cannot be provided, repeat testing for HBV DNA is required at least every 3 months during the study.

8.2.11. Hepatitis C Testing

Testing for HCV infection includes anti-HCV.

- If anti-HCV is positive, a test for circulating HCV RNA is required.
  - If HCV RNA test is positive, the participant is excluded.

8.2.12. Pregnancy Testing

In this study, pregnancy testing will be carried out at time points indicated in the SoA (Section 1.3). Testing will be performed on all female participants. A serum pregnancy test will be conducted at screening, and a urine pregnancy test will be conducted at all other time points, including discharge.

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, and
- PCs.

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/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 product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations, as indicated, to elucidate the nature or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

Investigators are responsible for monitoring the safety of participants who have entered this study and alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Adverse Events

Investigators must document their review of each laboratory safety report. The investigator remains responsible for following through an appropriate healthcare option, AEs that are serious or otherwise medically important, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention before completing the study. The participant should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator. After the ICF is signed, study-site personnel will record, via eCRF, the occurrence and nature of each participant's preexisting conditions. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to the study treatment or a study procedure, considering the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause-and-effect relationship between the IP, study device and/or study procedure, and the AE.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's study intervention is discontinued due to an AE, study-site personnel must report this to Lilly or its designee via eCRF.

Serious Adverse Events

Study-site personnel must alert the sponsor, or its designee, of any SAE as soon as practically possible.

Additionally, study-site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed up with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the eCRF after signing the informed consent, SAE reporting to the sponsor begins after the participant has signed informed consent and has received the study intervention. However, if an SAE occurs after signing informed consent but prior to receiving study intervention AND is considered reasonably possibly related to a study procedure, then it must be reported.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued from and/or completed the study (the subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant

has been discharged from the study and he/she considers the event reasonably possibly related to the study intervention or study participation, the investigator must promptly notify Lilly.

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 ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	NA
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of ICF	Start of intervention	Within 24 hours of awareness	SAE CRF for mechanism of reporting and for back up SAE paper form	SAE CRF for mechanism of reporting and for back up 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	LSS SAE reporting process	NA
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	NA	Promptly	SAE paper form	NA
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Part A: 12 weeks after last dose. Part B: 14 weeks after last dose. Part C: 2 weeks after last dose.	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	NA
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	NA
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product	NA

				Complaint form with all changes signed and dated by the investigator	
PC (if investigator becomes aware)	Participation in study has ended	NA	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; LSS = Lilly Safety System; NA = not applicable; PC = product complaint; SAE = serious adverse event.

* Serious adverse events 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 the study intervention.

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

- will obtain 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 the 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. Consult the appropriate medically qualified team member if unsure if this section is applicable for a particular protocol.

8.3.3. Adverse Events of Special Interest

Not applicable.

8.4. Pharmacokinetics

For Parts A, B, and C, a maximum of 3 additional blood samples may be collected as additional unscheduled time points during the study, if warranted and agreed upon between both the investigator and sponsor. Refer to Section 10.2.1 for details. Instructions for the collection and handling of blood samples will be provided by the sponsor. Times are referenced at the start of dosing. The actual date and time (24-hour clock time) of each sampling will be recorded. Samples are requested to be taken at the specified time. However, aberrations from the specified sampling times will not be considered protocol deviations as long as the samples are taken, and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms.

Drug concentration information that may unblind the study will not be reported to CRU or blinded personnel until the study has been unblinded.

In the event of the early discontinuation of a participant in any part of the study, a PK sample will be taken at the early discontinuation visit as an unscheduled sample. The actual date and time of the collection must be recorded.

8.4.1. Pharmacokinetics of LY3872386 in Part A and Part B

8.4.2. Pharmacokinetics of Prednisone in Part C

At the visits and times specified in the SoA (Section 1.3), venous blood samples of approximately 3 mL will be collected to determine the concentrations of prednisone and its metabolite, prednisolone.

Predose assessments should be completed before IP administration. All other PK time points should be collected 24 hours post previous day's administration of prednisone. On days where applicable, collection should be prior to receiving prednisone administration.

8.4.3. Bioanalysis

Plasma samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Analyses of samples collected from placebo-treated participants are not planned.

Bioanalytical samples collected to measure IP concentrations for Parts A, B, and C will be retained for a maximum of 1 year following the last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism, protein binding, or bioanalytical development.

For Parts A and B, concentrations of LY3872386 (ADC), total antibody, and LY3558533 (unconjugated payload) will be analyzed using validated LC-MS methods. Analyses of samples collected from the placebo-treated participants are not planned.

Drug concentration information that may unblind the study will not be reported to CRU or blinded personnel until the study has been unblinded.

For Part C, concentrations of prednisone and its metabolite prednisolone will be analyzed using validated LC-MS methods.

8.5. Pharmacodynamics

8.5.1. Pharmacodynamics of LY3872386

At the times specified in the SoA (Section 1.3), venous blood samples will be collected and used to determine both the target engagement effects and the effects on cytokines (IL-4, IL-5, IL-13 [Part B only], and sCD163) and/or immunoglobulins by LY3872386. Blood will be collected to evaluate target engagement, biological activity, and cytokine and/or immunoglobulin levels.

RO supplies required for the collection and shipment of the participants' samples will be supplied by the sponsor. RO sample handling and shipment to the central laboratory will occur per the instructions given to the study site. The actual date and 24-hour clock time of each RO sampling will be recorded. Samples are requested to be taken at the specified time. However, aberrations from the specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms. Samples will be analyzed at a laboratory approved by the sponsor using validated assays. Any unused blood samples will be destroyed in accordance with local regulations. The biological activity of LY3872386 will be assessed using a whole blood ex vivo stimulation assay (TSTIM) using cytokine concentrations as the readout. Changes in selected markers will be assessed by measurement from serum and/or bulk RNA analysis from peripheral blood samples. Instructions for the collection and handling of blood samples will be supplied by the sponsor.

8.5.2. Pharmacodynamics of Prednisone

At the times specified in the SoA (Section 1.3), venous blood samples will be collected to evaluate biological activity and cytokine levels. The biological activity of prednisone will be assessed using a whole blood ex vivo stimulation assay (TSTIM, Lipopolysaccharide) to measure changes in cytokine concentrations as the readout depending on exposure. Changes in selected markers will be assessed by biomarker measurement from serum and/or bulk RNA analysis and slide-based staining protocols from peripheral blood samples. Instructions for the collection and handling of blood samples will be supplied by the sponsor.

8.6. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3), where local regulations allow.

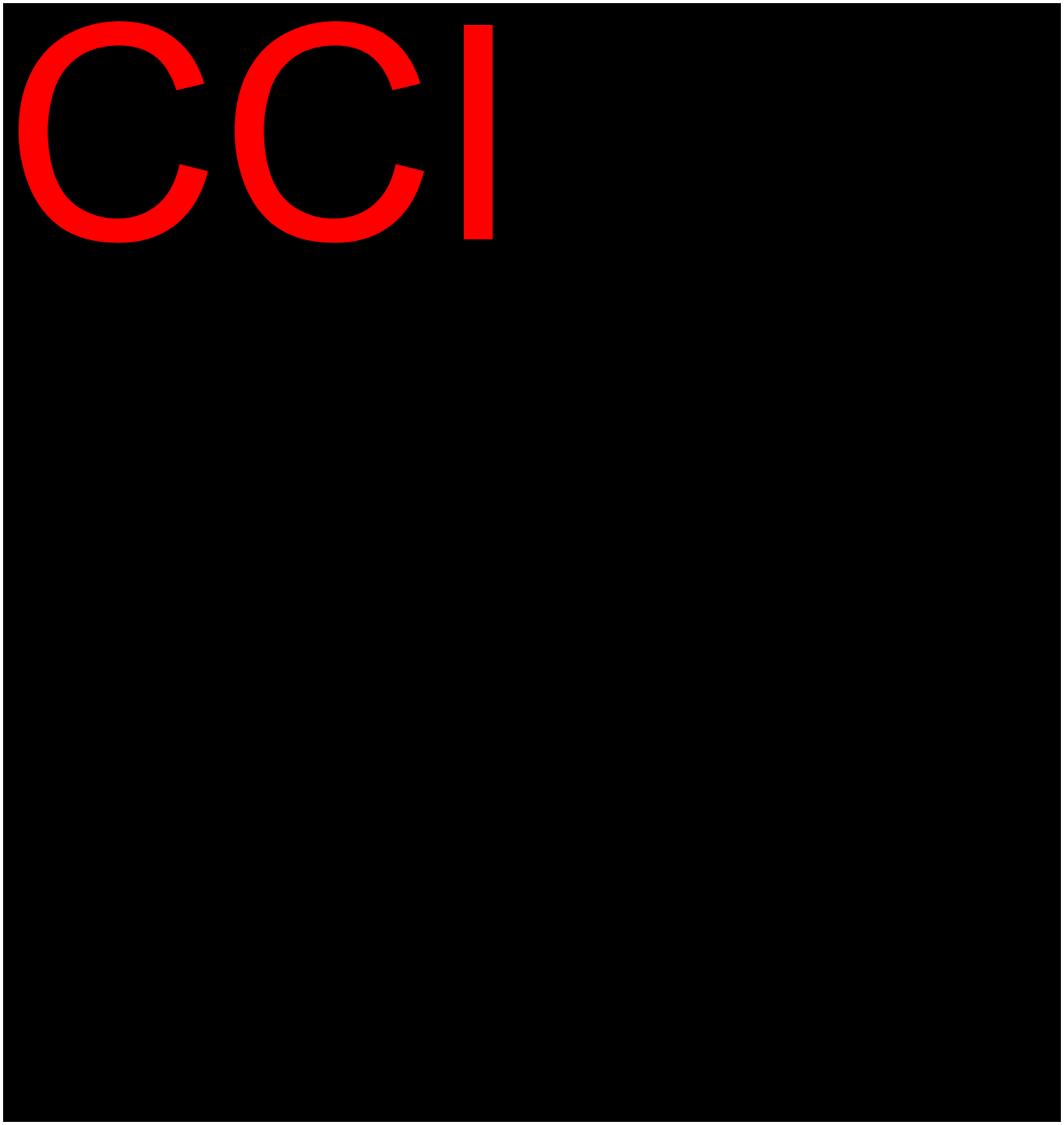
Samples will not be used to conduct unspecified disease or population genetic research, either now or in the future. Samples will be used to investigate variable exposure or response to LY3872386 and/or prednisone and to investigate genetic variants thought to play a role in disease. Assessment of variable responses may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last participant visit for the study at a facility selected by Lilly or its designee. This retention period enables the use of new technologies, response to regulatory questions, and investigation of variable responses that may

not be observed until later in the development of LY3872386 or after it is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of the technology utilized, the data generated will be used only for the specific research scope described in this section.



8.8. Immunogenicity Assessments

For SAD Part A and MAD Part B, at the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected and stored for potential future immunogenicity analyses. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma PK concentrations of LY3872386, total antibody, and LY3558533 (free payload). Samples for immunogenicity should be taken predose when applicable and possible.

TE ADAs are defined in Section 9.3.4.4.

Samples will be retained for a maximum of 15 years after the last participant visit at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY3872386. Any samples remaining after 15 years will be destroyed.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan 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 Hypotheses

No formal hypotheses will be employed.

9.1.1. Multiplicity Adjustment

There will be no formal hypothesis testing, and therefore, no multiplicity adjustment is planned.

9.2. Analyses Sets

For purposes of analysis, the following populations are defined:

Participant Analysis Set	Description
Full analysis set (FAS)	• All randomized participants.
Modified Intent-to-Treat (mITT)	• All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment to which they were assigned (regardless of whether the participant fails to receive the correct treatment, or otherwise fails to follow the protocol).
Safety analysis set	• All randomized patients who receive at least 1 dose of study drug will be included according to the treatment they actually received, regardless of whether they have completed all protocol requirements.
PK analysis set	• All participants who receive at least 1 dose of the study drug and have evaluable PK data

A detailed description of participant disposition will be provided at the end of the study. All participants who discontinue the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

The participant's baseline characteristics and other demographic characteristics will be recorded, listed, and summarized by treatment group and overall.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Statistical analyses of this study will be the responsibility of Lilly or its designee.

PK analyses will be conducted on data from all participants who receive at least 1 dose of the study drug and have evaluable PK data.

Safety analyses will be conducted for all participants who are exposed to study intervention. Summary statistics, data tabulations, and data graphs by population will be provided as appropriate.

Summary statistics, data tabulations, and data graphs may be presented separately by race and ethnicity (for example, Japanese, Chinese, and non-Japanese/non-Chinese), as appropriate.

Continuous variables will be summarized by the number of observations, mean, standard deviation, and median minimum and maximum values. Categorical variables will be summarized by counts and percentages. Summary statistics, data tabulations, and data graphs will be provided and may be separated by population, as appropriate. No tests to assess statistical significance are planned due to the small sample size per treatment group. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The data from placebo groups will be pooled across cohorts as 1 placebo group.

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.

Statistical considerations and methodology for handling missing data will be detailed in the SAP.

9.3.2. Primary Endpoint Analysis

The primary objectives for this study are to assess the safety and tolerability following a single dose of LY3872386 in healthy participants and multiple doses of the same in patients with AD, as well as the safety and tolerability of prednisone in healthy participants receiving multiple PO QD doses at various dose levels. The primary endpoints are the frequency of AEs, TEAEs, and SAEs for LY3872386 and prednisone.

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment and each IP will be presented by severity and by association with the study drug as perceived by the investigator. Symptoms reported to have occurred prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified according to the Medical Dictionary for Regulatory Activities.

The number of participants who experience a TEAE and/or SAE will be summarized by both study treatment and IP, both for all causalities and TEAEs/SAEs related to the study drug. All TEAEs will be summarized by system organ class and by decreasing frequency within system organ class.

The number of drug-related SAEs and AEs will be reported.

9.3.3. Secondary Endpoint Analysis

9.3.3.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3872386 (ADC), total antibody, LY3558533 (free payload), prednisone, and prednisolone will be calculated using standard noncompartmental methods of analysis.

9.3.3.2. Pharmacokinetic Statistical Inference

The descriptive statistics for the PK parameters will be provided for each dose level or route of administration. Where appropriate, the geometric mean and geometric coefficient of variation will be reported. If data allows, the dose proportionality for LY3872386 may be assessed for AUC and C_{max} using a power model to estimate the slope of the power model, which represents the ratio of dose-normalized geometric means.

9.3.4. Exploratory Endpoints Analysis

9.3.4.1. Efficacy Endpoints

Efficacy analyses will be conducted on the mITT population. Due to the small sample size, statistical hypothesis tests will not be performed for any efficacy analysis. Instead, efficacy outcomes will be summarized with descriptive statistics. Binary efficacy outcomes will be summarized with the frequency and percent of responders in each treatment group CCI [redacted] All efficacy analyses will only be performed for MAD Part B of the study. The exploratory efficacy analyses will estimate the effect of the treatment on the exploratory endpoints.

CCI [redacted]

9.3.4.2. Receptor Occupancy, White Blood Cell Subpopulations, and Pharmacodynamics

RO, WBC subpopulations, and PD consequences (including CCI PD markers and immunoglobulins) will be explored using several methods. The measures of concentrations will be graphically evaluated across dose levels and explored as a surrogate for target engagement and/or mechanism of action. Model-based analyses to utilize the data to estimate RO, relationships with PK, and/or safety may also be performed, if appropriate. Exploratory analyses of dose and/or exposure relationships between LY3872386 and RO, WBC subpopulations, and PD may be conducted.

9.3.4.3. Injection Site Reactions

CCI

9.3.4.4. Evaluation of Immunogenicity

ADAs may be characterized. The frequency and percentage of subjects with preexisting ADA and with TE ADA to LY3872386 may be tabulated.

TE ADAs are defined as those with

- a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADA were detected at baseline (treatment-induced ADA), or
- a 4-fold (2 dilutions) increase in titer compared to baseline if ADA were detected at baseline (treatment-boosted ADA).

The frequency of neutralizing antibodies and/or LY3872386 and LY3558533 cross-reactive antibodies may also be tabulated in TE ADA+ subjects, when available.

The relationship between the presence of antibodies and the PK parameters, RO, and PD response, including safety and efficacy to LY3872386, may be assessed.

9.3.4.5. Pharmacodynamic Parameter Estimation

PD parameter estimates for CCI and other biomarkers will be calculated using standard noncompartmental methods of analysis or other approaches deemed necessary by the sponsor.

9.3.5. Other Analyses

9.3.5.1. Other Safety Analyses

9.3.5.1.1. Clinical Laboratory Parameters, Vital Signs, and Electrocardiograms

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics.

Prior to any statistical analyses of the QT interval, QT values will be corrected for heart rate based on QTcF. The relationship between concentrations of LY3872386 and changes from

baseline QTcF will be explored to assess the effect of LY3872386 concentration on changes from baseline QTcF.

Additional analyses will be performed if warranted upon review of the data.

The baseline for safety parameters will be defined as the last evaluable value before the first dose.

9.4. Interim Analyses

If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

9.4.1. Interim Access to Data During the Study

The Lilly sponsor team is not blinded, while the investigator will remain blinded during these reviews. Interim access to safety and tolerability data is scheduled to occur after every dosing session. The purpose of these reviews is to guide dose selection for future dosing sessions and/or inform the design of subsequent studies.

Access to PK data will also occur on a rolling basis during dose escalation as it becomes available. However, IADs are planned to evaluate exposure and available RO data. A review of these data will help guide implementation of this study (such as adjustment to blood sampling time) and support subsequent studies.

Four IADs to facilitate AD cohorts and progression to Phase II trial are planned. IADs are planned at the following time points:

- *First IAD*: 30 days post dose from Part A SAD Cohorts 4 and 5
    - dose justification for Part B MAD Cohort 1, Period 1
- *Second IAD*: 30 days post dose from Part A SAD Cohorts 6 and 7
    - dose justification for Part B MAD Cohort 2, Period 1
- *Third IAD*: end of Part A SAD cohorts and 30 days post dosing of half of the participants from Part B MAD Cohort 1, Period 1
    - dose justification for Part B MAD Cohort 1, Period 2, and
- *Fourth IAD*: End of Part C.

Since PK and RO data will be evaluated on a rolling basis as data become available, review of these data is not limited to the IADs mentioned earlier. These periodic reviews of PK and RO data are not considered as formal interim analyses. Any IAD may be skipped, and additional analysis may be added. If an unplanned IAD is deemed necessary, the Lilly clinical pharmacologist, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

The investigator and the Lilly clinical pharmacologist or sponsor team will determine dose escalation based upon their review of the safety data and PK data when available and/or required.

9.5. Sample Size Determination

The study will enroll up to CCI evaluable participants (CCI healthy volunteers and up to CCI patients with AD).

CCI

For purposes of this study, a participant completes the study when all scheduled procedures shown in the SoA have been finished. Participants who withdraw before completing all dosing administrations may be replaced. A replacement participant will complete the entire study period. Participants who discontinued the study following the required dose administration(s) but before completing may be replaced at the discretion of the sponsor and investigator. CCI

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
- applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, 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 sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives 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 or the participant's legally authorized representative and is kept on file.

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.

10.1.5. Committees Structure

No data monitoring committee will be involved in this study.

10.1.6. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

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 does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case by case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.7. Data Quality Assurance

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

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

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

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

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 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, 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 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.

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Trial and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Trial 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 if the results are deemed to be of significant medical importance.

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

Samples will be retained at a facility selected by the sponsor or its designee. Sample retention enables the use of new technologies, response to regulatory questions, and investigation of variable responses that may not be observed until later in the development of LY3872386 or after LY3872386 becomes commercially available.

This table lists the maximum retention period for sample types.

Sample Type	**Custodian**	**Maximum Retention Period After Last Participant Visit**
Genetic	Sponsor or designee	Up to 15 years
Exploratory biomarkers	Sponsor or designee	Up to 15 years
Skin biopsies	Sponsor or designee	Up to 15 years
Pharmacokinetics	Sponsor or designee	Up to 1 year
Immunogenicity	Sponsor or designee	Up to 15 years

Any samples remaining after the retention period will be destroyed.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory except for the following which will be performed at the local laboratory:

- Safety testing for immediate participant assessment
- Screening assessments in Part A and Part C.

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.

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

Additional tests may be performed at any time during the study as determined necessary by the investigator to address any immediate patient safety concerns.

Investigators must document their review of the laboratory safety results.

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

Safety Laboratory Tests

Hematology[a]	**Clinical Chemistry[a]**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium (total)
Mean cell hemoglobin concentration	Phosphorus/Phosphate
Leukocytes (white blood cells [WBCs])	Glucose (fasting)
Platelets	Blood urea nitrogen (BUN)
Differential WBC (absolute counts) of	Creatinine
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase (ALP)
Basophils	Aspartate aminotransferase (AST)
B Cells	Alanine aminotransferase (ALT)
T Cells	Gamma-glutamyl transferase (GGT)
NK cells	Insulin[e]
Hemoglobin A1c	**Bedside Glucose Monitoring (fasting)[f]**
Urinalysis[a]	**Serum Immunoglobulins[a]**
Specific gravity	IgA
pH	IgM
Protein	IgE
Glucose	IgG
Ketones	IgD
Bilirubin	
Urobilinogen	**Fasting Lipid Panel[a]**
Leukocytes	Total cholesterol
Blood	Triglycerides
Nitrite	Low-density lipoprotein (LDL)
Microscopic examination of sediment[b]	High-density lipoprotein (HDL)
	LDL/HDL ratio
Urine Drug Screen[c]	Hepatitis B surface antigen[g,h]
Amphetamine	Hepatitis B core antibody[g,h]
Barbiturates Benzodiazepines Cocaine Cannabis Methylenedioxymethamphetamine (MDMA) Opiates Oxycodone Phencyclidine Tricyclic antidepressants Cotinine (nicotine)	Hepatitis B surface antibody[g,h] Hepatitis B DNA[h] Hepatitis C antibody[g,h]
Ethanol breath testing[c]	HIV[g,h]
QuantiFERON®-TB Gold test or TST	Pregnancy test[i]

Beta D-glucan[d]	FSH[i]
Cortisol (serum, cosyntropin stim, and urine)	Thyroid-stimulating hormone (including T3/T4 tests) Syphilis test (including RPR and TPPA as appropriate)[g]

Abbreviations: DNA = deoxyribonucleic acid; ED = early discontinuation; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; Ig = immunoglobulin; NK cell = natural killer cell; RBC = red blood cell; RPR = Rapid Plasma Regain; TPPA = Treponema Pallidium Particle Agglutination.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. The omission of calculated values will not be considered as a protocol violation.

[a] To be done centrally. If needed for safety, site may also perform locally.

[b] Test only if dipstick result is abnormal.

[c] Urine drug screen and ethanol breath testing may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities. Unscheduled testing is allowed.

[d] Evaluation of beta-D-glucan may be performed at a local laboratory. Beta-D-glucan is required at screening for Part B only (to be performed centrally), and if an investigator believes it is warranted, at subsequent visits (may be performed centrally or locally), a beta-D-glucan test may be included in the work up panel at any time during the study. If the beta-D-glucan test is positive, pneumocystis pneumonia (PCP) needs to be ruled out. If PCP is ruled out and the investigator deems the patient fit to continue, the patient may continue in the study. If a patient has a confirmed diagnosis of PCP during the study, the patient must discontinue the study.

[e] Not performed at screening.

[f] Bedside glucose monitoring is performed using standard glucose monitors and capillary blood taken from fingerstick. Fasting should be approximately 2 hours, at a minimum.

[g] Performed at screening only.

[h] These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review" for hepatitis B, C, and HIV.

[i] To be performed on all female participants.

10.2.1. Blood Sampling Summary

These tables summarize the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

10.2.1.1. Part A: SAD of LY3872386 in Healthy Participants

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical chemistry[a], including insulin and fasting lipid panel	4.5	8	36
Clinical chemistry[a], including insulin, fasting lipid panel, serum immunoglobulins	8	6	48
Hematology, including TBNK	4	12	48
TSH, T3/T4	3.5	2	7
Pharmacokinetics[b]	6	19	114
CCI			
Cortisol	2	9	18
Cosyntropin stim – Cortisol (pre stim and 30-, 60-min post stim)	2	6 x 3 time points	36
Ex vivo stimulation	1	5	5
Cytokines (IL-4, IL-5, sCD163)	2.5	8	20
CCI			
Blood discard for cannula patency	1	5	5
Blood samples for receptor occupancy flow cytometry	2	11	22
Immunogenicity[b]	5	5	25
Pharmacogenetics	3	1	3
Total			501.5
Total for clinical purposes (rounded up to nearest 10 mL)			510

Abbreviations: CCI IL = interleukin; IV = intravenous; CCI PK = pharmacokinetic; SC = subcutaneous; TBNK = T, B, and Natural Killer; TSH = thyroid-stimulating hormone.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional 3 samples may be drawn if required.

[c] If more than 1 laboratory blood draw is scheduled at the same time, these blood draws should be prioritized in the following order: (1) safety laboratory tests, (2) PK samples, (3) receptor occupancy samples, and (4) exploratory samples.

10.2.1.2. Part B: MAD of LY3872386 in Patients with AD (CCI Dosing Schedule)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical chemistry[a], including insulin and fasting lipid panel	4.5	7	31.5
Clinical chemistry[a], including insulin, fasting lipid panel, and serum immunoglobulins	8	4	32
Hematology, including TBNK	4	11	44
TSH, T3/T4	3.5	3	10.5
Pharmacokinetics[b]	6	22	132
CCI			
Cosyntropin stim – Cortisol (pre stim and 30-, 60-min post stim)	2	10 x 3 time points	60
Cytokines (IL-4, IL-5, IL-13, sCD163)	5	8	40
Chemokine Panel (MSD V-Plex [TARC, MDC], Periostin)	2.5	4	10
CCI			
Blood discard for cannula patency	1	6	6
Blood samples for receptor occupancy flow cytometry	2	11	22
Immunogenicity[b]	5	6	30
Pharmacogenetics	3	1	3
Total			534
Total for clinical purposes (rounded up to nearest 10 mL)			540

Abbreviations: CCI IL = interleukin; IV = intravenous; MDC = Macrophage-derived chemokine; CCI PK = pharmacokinetic; SC = subcutaneous; TARC = Thymus- and activation-regulated chemokine; TBNK = T, B, and Natural Killer; TSH = thyroid-stimulating hormone.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional 3 samples may be drawn if required.

[c] If more than 1 laboratory blood draw is scheduled at the same time, these blood draws should be prioritized in the following order: (1) safety laboratory tests, (2) PK samples, (3) receptor occupancy samples, and (4) exploratory samples.

10.2.1.3. Part B: MAD of LY3872386 in Patients with AD (CCI Dosing Schedule)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical chemistry[a], including insulin and fasting lipid panel	4.5	5	22.5
Clinical chemistry[a], including insulin, fasting lipid panel, and serum immunoglobulins	8	4	32
Hematology, including TBNK	4	8	32
TSH, T3/T4	3.5	3	10.5
Pharmacokinetics[b]	6	20	120
CCI			
Cosyntropin stim – Cortisol (pre stim and 30-, 60-min post stim)	2	6 x 3 time points	36
Cytokines (IL-4, IL-5, IL-13, sCD163)	5	8	40
Chemokine Panel (MSD V-Plex [TARC, MDC], Periostin)	2.5	4	10
CCI			
Blood discard for cannula patency	1	6	6
Blood samples for receptor occupancy flow cytometry	2	12	24
Immunogenicity[b]	5	11	55
Pharmacogenetics	3	1	3
Total			509
Total for clinical purposes (rounded up to nearest 10 mL)			510

Abbreviations: CCI IL = interleukin; IV = intravenous; MDC = Macrophage-derived chemokine; CCI PK = pharmacokinetic; SC = subcutaneous; TARC = Thymus- and activation-regulated chemokine; TBNK = T, B, and Natural Killer; TSH = thyroid-stimulating hormone.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional 3 samples may be drawn if required.

[c] If more than 1 laboratory blood draw is scheduled at the same time, these blood draws should be prioritized in the following order: (1) safety laboratory tests, (2) PK samples, (3) receptor occupancy samples, and (4) exploratory samples.

10.2.1.4. Part C: Prednisone in Healthy Participants - CCI Dosing Groups

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical chemistry[a], including insulin and Day 30 fasting lipid panel	4.5	7	31.5
Fasting lipid panel (Day 1)	2.5	2	5
Hematology, including TBNK	4	7	28
TSH, T3/T4	3.5	2	7
Serum immunoglobulins	5	4	20
Pharmacokinetics[b]	3	51	153
CCI	[redacted]	[redacted]	[redacted]
Cortisol	2	30	60
Cosyntropin stim – Cortisol (pre stim and 30-, 60-min post stim)	2	5 x 3 time points	30
Cytokines (IL-4, IL-5, sCD163)	5	3	15
CCI	[redacted]	[redacted]	[redacted]
Blood discard for cannula patency	1	21	21
Pharmacogenetics	3	1	3
Total			465
Total for clinical purposes (rounded up to nearest 10 mL)			470

Abbreviations: CCI IL = interleukin; IV = intravenous; CCI PK = pharmacokinetic; SC = subcutaneous; TBNK = T, B, and Natural Killer; TSH = thyroid-stimulating hormone.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional 3 samples may be drawn if required.

[c] If more than 1 laboratory blood draw is scheduled at the same time, these blood draws should be prioritized in the following order: (1) safety laboratory tests, (2) PK samples, (3) receptor occupancy samples, and (4) exploratory samples.

10.2.1.5. Part C: Prednisone in Healthy Participants - CCI Dosing Group

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical chemistry[a], including insulin	4.5	7	31.5
Hematology, including TBNK	4	7	28
TSH, T3/T4	3.5	2	7
Serum immunoglobulins	5	4	20
Pharmacokinetics[b]	3	30	90
CCI			
Cortisol	2	7	14
Cosyntropin stim – Cortisol (pre stim and 30-, 60-min post stim)	2	3 x 3 time points	18
Cytokines (IL-4, IL-5, sCD163)	5	5	25
Ex vivo stimulation	13	4	52
CCI			
Blood discard for cannula patency	1	21	21
Pharmacogenetics	3	1	3
Total			407.5
Total for clinical purposes (rounded up to nearest 10 mL)			410

Abbreviations: CCI IL = interleukin; IV = intravenous; CCI PK = pharmacokinetic; SC = subcutaneous; TBNK = T, B, and Natural Killer; TSH = thyroid-stimulating hormone.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional 3 samples may be drawn if required.

[c] If more than 1 laboratory blood draw is scheduled at the same time, these blood draws should be prioritized in the following order: (1) safety laboratory tests, (2) PK samples, (3) receptor occupancy samples, and (4) exploratory samples.

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 unfavourable 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:

a) Results in death

b) 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.

c) 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.

d) 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.

e) Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f) 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 Complaint

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

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

Product complaints related to study interventions used in clinical trials are collected in order 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 product complaint or problem with the study intervention so that the situation can be assessed.

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

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

AE, SAE, and Product Complaint Recording

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

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

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

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

There may be instances when copies of medical records for certain cases are requested by 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 adverse event 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 adverse event 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 adverse event 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.

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 Paper Form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the Lilly clinical pharmacologist.

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 will be provided to the site.

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 towards 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 comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (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 • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral tubal ligation, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman • at any age at least 6 weeks postsurgical 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, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Males

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 190 days after the last dose of the study intervention.
Contraception for men with partners of childbearing potential	either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, and • for 190 days after the last dose of the study intervention.
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

Females

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

Must…	Must not…
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, and not plan a pregnancy during the study	use periodic abstinence methods o calendar o ovulation o symptothermal, or o postovulation 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 NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Contraception	Agree to use 2 methods of effective contraception, where at least 1 method must be highly effective. These methods of contraception must be used during the study and for at least 130 days after the last dose of the study intervention.

Examples of different methods of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization[a] (including fallopian tube ligation, bilateral tubal ligation, and hysteroscopic sterilization*) • combination of oral contraceptive pill and mini pill* • progestin-only contraceptive pill (mini-pill)* • implanted contraceptives* • injectable contraceptives* • contraceptive patch* (only women <198 pounds or 90 kg) • total abstinence • vasectomy (for men in clinical trials and for female partner if only sexual partner) • fallopian tube implants* (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring*, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide* • diaphragms with spermicide or cervical sponges* • barrier method with the use of a spermicide o condom with spermicide o diaphragm with spermicide*, or o female condom with spermicide* Note: Male and female condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

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

* Not available in Japan.

[a] Hysterectomy, bilateral salpingo-oophorectomy, bilateral tubal ligation, bilateral salpingectomy, or bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a WNOCBP.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- 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. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to LY3872386 or autoimmune and inflammatory disorders and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3872386 and/or interventions of this drug class and autoimmune and inflammatory disorders. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3872386 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3872386 or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

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

Hepatic Evaluation Testing

See Section 8.2.8 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for the 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 Immunoglobulin M (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[a]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[a]
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[a]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)**[b]
Hepatic Coagulation Panel	**Anti-actin antibody**[c]
Prothrombin time, INR (PT-INR)	**IgA (quantitative)**
Urine Chemistry	**IgG (quantitative)**
Drug screen	**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[a]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[a]
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[a]	

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

[b] Not required if anti-actin antibody is tested.

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

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
Ab	antibody
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AD	atopic dermatitis
ADA	anti-drug antibodies
ADC	antibody drug conjugate
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration 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.
C_{max}	maximum observed drug concentration
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

Term	Definition
CRU	clinical research unit
CSR	clinical study report
CT	computed tomography
DAR	drug to antibody ratio
DDI	drug-drug interaction
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) 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.
CCI	[redacted]
EC_{50}	half maximal effective concentrations
ECG	electrocardiogram
eCRF	Electronic CRF
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
CCI	[redacted]
GCP	good clinical practice
GLP	good laboratory practice
GR	glucocorticoid receptor
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human Ether-a-go-go Related Gene
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal

Term	Definition
IB	Investigator's Brochure
IAD	interim access to data
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
IL	interleukin
IL-4R	interleukin-4 receptor
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 (IP)	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
IRR	infusion-related reaction
CCI	[redacted]
IV	intravenous
IWRS	Interactive Web Response System
LTBI	latent tuberculosis infection

Term	Definition
K_D	equilibrium dissociation constant
mAb	monoclonal antibody
MAD	multiple-ascending dose
mAb	monoclonal antibody
NOAEL	no observed adverse effect level
NRS	numeric rating scale
CCI [redacted]	[redacted]
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
PK/PD	pharmacokinetics/pharmacodynamics
PO	oral administration
CCI [redacted]	[redacted]
PR	pulse rate
PT	prothrombin time
CCI [redacted]	[redacted]
[redacted]	[redacted]
QD	once daily
QSP	quantitative systems pharmacology
RO	receptor occupancy
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
CCI [redacted]	[redacted]
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.

Term	Definition
TB	tuberculosis
TBL	total bilirubin
TCNI	topical calcineurin inhibitors
TCS	topical corticosteroid
TE	treatment-emergent
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.
TK	toxicokinetic
ULN	upper limit of normal
CCI	[redacted]
[redacted]	[redacted]
WBC	white blood cells
WNOCBP	women not of child-bearing potential
WOCBP	women of child-bearing potential

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment a: 12 October 2023

Overall Rationale for the Amendment:

This protocol has been amended to correct previous errors in assessments and time points in the schedule of activities and to correct volume errors in the blood sampling summary. These changes are presented in the summary of changes table.

Minor editorial changes have also been made and are not presented in the summary of changes table.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1: Part A: Single-Ascending Dose of LY3872386 in Healthy Participants	Updated the vital signs assessment on Day 1 to indicate that it should not be predose only. Moved the thyroid-stimulating hormone, including T3/T4 test from screening to Day -1. Updated the cortisol assessment to no longer specify "basal," moved the test from screening to Day -1, and added a predose and 12-hour cortisol assessment to Day 1. Added a cosyntropin stimulation test to Day 15 ± 1d.	Corrections to previous errors.
Section 1.3.2: Part B: Multiple-Ascending Dose of LY3872386 in Patients with Atopic Dermatitis	CCI [redacted] **Dosing Schedule:** Moved the thyroid-stimulating hormone, including T3/T4 test from screening to predose on Day 1. CCI [redacted] **Dosing Schedule:** Moved the thyroid-stimulating hormone, including T3/T4 test from screening to predose on Day 1.	Correction to previous error. Corrections to previous errors.

Section # and Name	Description of Change	Brief Rationale
	Updated the immunogenicity assessments on Day 15 ± 1d, Day 43 ± 1d, and Day 71 ± 1d to indicate that it should not be predose. Updated the LY3872386, total antibody, and LY3558533 concentration assessment on Day 15 ± 1d, Day 43 ± 1d, and Day 71 ± 1d to indicate that it should not be predose. Updated the receptor occupancy assessment on Day 15 ± 1d, Day 43 ± 1d, and Day 71 ± 1d to indicate that it should not be predose. Updated the cytokine panel assessment on Day 15 ± 1d, Day 43 ± 1d, and Day 71 ± 1d to indicate that it should not be predose. Updated the CCI assessment on Day 15 ±1d to indicate that it should not be predose.	
Section 1.3.3: Part C: Open-Label Multiple Dose of Prednisone in Healthy Participants	**Prednisone CCI -mg and -mg Dosing Schedule:** Moved the thyroid-stimulating hormone, including T3/T4 test from screening to Day -1. Specified that a urinalysis assessment should be collected predose on Day 2 and Day 7 during the Day 2 to 13 window and predose on Day 21 during the Day 15 to 29 window and also added a urinalysis assessment to Day 44 ± 4d. Added a predose prednisone and prednisolone concentration time point to Day 1. Updated the cortisol assessment to no longer specify "basal," moved the test from screening to Day -1, added a predose and 12-hour cortisol	Corrections to previous errors.

Section # and Name	Description of Change	Brief Rationale
	assessment to Day 1, and specified that the Day 31 assessment is not predose. Removed the 24 hour urinary free cortisol assessment from Day 44 ± 4d and from ED. Added a predose cosyntropin stimulation test to Day 7. **Prednisone [redacted]-mg Dosing Schedule:** Moved the thyroid-stimulating hormone, including T3/T4 test from screening to Day -1. Added a predose prednisone and prednisolone concentration time point to Day 1. Updated the cortisol assessment to no longer specify "basal," moved the test from screening to Day -1, and added a 12-hour cortisol time point to Day 1. Added a predose 24 hour urinary free cortisol assessment to Day 6 and removed the assessments from Day 14 ± 4d and ED.	Corrections to previous errors.
Section 4.1: Overall Design	Changed the dosing timing for the remaining non-sentinel participants in both IV and SC cohorts from "approximately 10 to 15 minutes after the completion of the administration" to "approximately 30 minutes after the start of the previous administration."	Correction to address FDA feedback.
Section 4.3: Justification for Dose	Updated the text to no longer specify "basal" cortisol.	Correction to previous error.

Section # and Name	Description of Change	Brief Rationale
Section 5.2: Exclusion Criteria	Updated Exclusion Criterion #28 to state that current smokers will be excluded if they use ">10 cigarettes or other tobacco products per day and are unable/unwilling to stop smoking tobacco products while in the study and have a positive cotinine test" as opposed to "or have a positive cotinine test."	Correction to previous errors.
Section 5.2.1: Additional Exclusion Criteria for Part B (Patients with Atopic Dermatitis)	Specified that Exclusion Criterion #49 is only for Japanese participants.	Correction to previous errors.
Section 6.1: Study Interventions Administered	Updated the study intervention table to include formulation details (0.9% sodium chloride solution) for placebo. Added dosing information (single administration, CCI for 12 weeks, and CCI for 12 weeks) for LY3872386 administration.	Correction to address FDA feedback. Correction to previous error.
Section 6.2: Preparation, Handling, Storage, and Accountability	Added text to include that preparation, handling, and storage information of study interventions could also be found in the Pharmacy Manual/Pharmacy Preparation Instructions.	Correction to address FDA feedback.
Section 8.2.2: Vital Signs	Specified that the text "On Day 1, blood pressure and PR will be assessed at predose, end of infusion (for IV only), and 3-, 6-, and 12-hour postdose" applies only to Part A.	Correction to previous error.
Section 8.2.8: Hepatic Safety Monitoring, Evaluation, and Criteria for Study Drug Interruption or Discontinuation	In the evaluation for possible causes of abnormal liver tests, clarified that recent illnesses include those of "systemic infection."	Correction to previous error.
Section 10.2: Appendix 2: Clinical Laboratory Tests	Added footnote e to insulin test to indicated that it will not be performed at screening. Specified that ethanol testing is a breath test in both the Safety Laboratory Tests table and in footnote c.	Corrections to previous errors.

Section # and Name	Description of Change	Brief Rationale
	Moved ethanol breath testing from under the urine drug screen section to a separate, standalone laboratory test. Removed "propoxyphene" test from urine drug screen.	Test is no longer part of the standard confirmation list and would require an additional monitoring service.
Section 10.2.1: Blood Sampling Summary	**Part A: SAD of LY3872386 in Healthy Participants:** Reduced the number of blood samples for clinical chemistry [a], including insulin and fasting lipid panel from 14 to 8. Added a separate line item for clinical chemistry [a], including insulin, fasting lipid panel, serum immunoglobulins to state 8 mL for blood volume per sample, 6 for number of blood samples, and 48 mL for total volume. Increased the TSH, T3/T4 blood volume per sample from 2.5 mL to 3.5 mL. Removed serum immunoglobulin line item. Reduced the CCI [redacted] volume per sample from CCI [redacted] mL to CCI [redacted] mL Additional updates in the blood sampling summary table (number of samples, total volume, etc.) have been made to reflect the changes in the Schedule of Activities for Part A.	Corrections to previous errors.

Section # and Name	Description of Change	Brief Rationale
	Part B: MAD of LY3872386 in Patients with AD (CCI Dosing Schedule): Reduced the number of blood samples for clinical chemistry [a], including insulin and fasting lipid panel from 11 to 7. Added a line item for clinical chemistry [a], including insulin, fasting lipid panel, and serum immunoglobulins to state 8 mL for blood volume per sample, 4 for number of blood samples, and 32 mL for total volume. Increased the TSH, T3/T4 blood volume per sample from 2.5 mL to 3.5 mL. Removed serum immunoglobulin line item. Reduced the immunogenicity blood volume per sample from 10 mL to 5 mL. Additional updates in the blood sampling summary table (number of samples, total volume, etc.) have been made to reflect the changes in the Schedule of Activities for Part B CCI. **Part B: MAD of LY3872386 in Patients with AD (CCI Dosing Schedule):** Reduced the number of blood samples for clinical chemistry [a], including insulin and fasting lipid panel from 9 to 5.	Corrections to previous errors.

Section # and Name	Description of Change	Brief Rationale
	Added a line item for clinical chemistry [a], including insulin, fasting lipid panel, and serum immunoglobulins to state 8 mL for blood volume per sample, 4 for number of blood samples, and 32 mL for total volume. Increased the TSH, T3/T4 blood volume per sample from 2.5 mL to 3.5 mL. Removed serum immunoglobulin line item. Reduced the immunogenicity blood volume per samples from 10 mL to 5 mL. Additional updates in the blood sampling summary table (number of samples, total volume, etc.) have been made to reflect the changes in the Schedule of Activities for Part B CCI. **Part C: Prednisone in Healthy Participants CCI -mg and [redacted]-mg Dosing Groups:** Increased the fasting lipid panel (Day 1) number of samples from 1 to 2. Increased the TSH, T3/T4 blood volume per sample from 2.5 mL to 3.5 mL. Additional updates in the blood sampling summary table (number of samples, total volume, etc.) have been made to reflect the changes in the Schedule of Activities for Part C CCI -mg and [redacted]-mg.	Corrections to previous errors.

Section # and Name	Description of Change	Brief Rationale
	Part C: Prednisone in Healthy Participants [redacted]-mg Dosing Group: Increased the TSH, T3/T4 blood volume per sample from 2.5 mL to 3.5 mL. Updated the serum immunoglobulin blood volume per sample from 4 mL to 5 mL. Additional updates in the blood sampling summary table (number of samples, total volume, etc.) have been made to reflect the changes in the Schedule of Activities for Part C [redacted]-mg.	Corrections to previous errors. Corrections to previous errors.

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