Protocol I9N-MC-FCAB(b)

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3375880 in Adult Subjects with Moderate-to-Severe Atopic Dermatitis: The ADmIRe Study

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Confidential Information

LY3375880

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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1. Synopsis

Title of Study:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3375880 in Adult Subjects with Moderate-to-Severe Atopic Dermatitis: The ADmIRe study.

Rationale:
Atopic dermatitis (AD) is the most common chronic skin disease with clinical hallmarks of inflammatory lesions with an intense itch. In the World Health Organization (WHO) 2010 Global Burden of Disease survey, AD ranked first among common skin diseases with respect to disability-adjusted life-years and years lived with a disease (Murray et al. 2012; Vos et al. 2012). Currently, there is no cure for AD; thus, the aim of disease management is to improve symptoms and achieve long-term disease control with a multistep approach. There is a need for more efficacious therapies with a better safety profile than the standard of care for subjects with AD.

LY3375880 is a human immunoglobulin (Ig) G4-variant monoclonal antibody (mAb) that binds and neutralizes soluble human interleukin (IL)-33 cytokine. LY3375880 is being developed for the treatment of subjects with AD. This study will evaluate the safety and efficacy of LY3375880 in subjects with moderate-to-severe AD.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To compare the efficacy of LY3375880 to placebo as measured by IGA at Week 16 in the treatment of subjects with moderate-to-severe AD.	• Proportion of subjects achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16.
Secondary • To compare the efficacy of LY3375880 to placebo as measured by improvement in signs and symptoms at Week 16 and 52 in the treatment of subjects with moderate-to-severe AD. • To characterize the PK of LY3375880 in subjects with moderate-to-severe AD	• Proportion of subjects achieving at Week 16: o EASI-50 o EASI-75 o EASI-90 o SCORAD-75 o SCORAD-90 o IGA of 0 • Mean change from baseline to Week 16 in: o EASI score o SCORAD • Proportion of subjects achieving IGA of 0 or 1 at Week 52

Abbreviations: AD = atopic dermatitis; EASI = Eczema Area and Severity Index; EASI-50/75/90 = 50%/75%/90% reduction in the EASI score; IGA = Investigator's Global Assessment; PK = pharmacokinetic(s); SCORAD = SCORing AD.

Summary of Study Design:

Study I9N-MC-FCAB (FCAB) is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the efficacy and safety of LY3375880 subcutaneous (SC) 600 mg every 4 weeks (Q4W), 150 mg Q4W, and 50 mg Q4W as compared to placebo Q4W in adult subjects with moderate-to-severe AD. In addition, LY3375880 300mg Q4W will be evaluated during the maintenance period.

The study duration will be up to 65 weeks over 4 study periods:

- Period 1: Screening Period, lasting 8 to 35 days prior to Week 0 (baseline, Visit 2).
- Period 2: Induction Period, lasting from Week 0 (baseline, Visit 2) through Week 16 (Visit 8).
- Period 3: Maintenance Period, lasting from Week 16 (Visit 8) through Week 52 (Visit 17, inclusive).
- Period 4: Post-Treatment Follow-Up Period, lasting 8 weeks from Week 52 (after Visit 17) to Week 60 (Visit 801).

Treatment Arms and Duration:

Subjects will be randomized 1:1:1:1 at Week 0 to 1 of 4 treatment groups: placebo SC Q4W, LY3375880 SC 600 mg Q4W, LY3375880 150 mg Q4W, or LY3375880 50 mg Q4W. The study duration will be up to 65 weeks (Screening Period: Up to 5 weeks; Induction Period: 16 weeks; Maintenance Period: 36 weeks; Post-Treatment Follow-up Period: 8 weeks).

Number of Subjects:

Approximately 200 subjects will be randomized.

Statistical Analysis:

Efficacy will be conducted on the intent-to-treat population. Safety analyses will be conducted on the safety population.

Treatment comparisons of discrete efficacy variables between LY3375880 and placebo will be made using a logistic regression analysis with treatment, baseline disease severity (Investigator's Global Assessment [IGA] [3 versus 4]), and geographic region in the model. Treatment comparisons of the continuous efficacy variables will be made using a mixed-effects model of repeated measures (MMRM) analysis with treatment, baseline disease severity, geographic region, visit, and treatment-by-visit interaction as fixed categorical effects and, if a baseline score is available, baseline score and baseline score-by-visit interaction as fixed continuous effects. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, with no control for multiple comparisons.

Fisher's exact test will be used for the adverse events (AEs), discontinuations, and other categorical safety data for between-treatment group comparisons. Continuous vital signs, body weight, and other continuous safety variables including laboratory variables will be analyzed by an analysis of covariance with treatment and baseline value in the model.

2. Schedule of Activities

Table FCAB.1. I9N-MC-FCAB Schedule of Activities

	Screening	Induction Period							Maintenance Period									Posttreatment Follow-Up
	Period 1	Period 2							Period 3									Period 4
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	801
Weeks from randomization		0	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52 or ET	60
Days from randomization		0	7	14	28	56	84	112	140	168	196	224	252	280	308	336	364	420
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5
Procedure																		
Inclusion and exclusion review	X	X																
Informed consent	X																	
Clinical assessments																		
Demographics	X																	
Medical history	X																	
Previous and current AD treatments	X																	
Weight		X																
Height		X																
Vital signs (BP and Pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X																	
Symptom-directed physical examination[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ePRO (patient diary) dispensed	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Screening	Induction Period							Maintenance Period									Posttreatment Follow-Up
	Period 1	Period 2							Period 3									Period 4
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	801
Weeks from randomization		0	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52 or ET	60
Days from randomization		0	7	14	28	56	84	112	140	168	196	224	252	280	308	336	364	420
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5
ePRO (patient diary) returned		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X						X[b]										
IWRS entry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP SC injections		X			X	X	X	X	X	X	X	X	X	X	X	X		
Investigator Scales																		
IGA[c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EASI[c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCORAD[c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Outcome Measures and Other Questionnaires																		
POEM[c,d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI[c,d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Itch NRS[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin Pain NRS[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS "Baseline/Screening"	X																	
C-SSRS "Since Last Visit"		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Induction Period							Maintenance Period									Posttreatment Follow-Up
	Period 1	Period 2							Period 3									Period 4
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	801
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Days from randomization		0	7	14	28	56	84	112	140	168	196	224	252	280	308	336	364	420
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5
Laboratory Assessment																		
12-lead ECG (single)	X																	
Chest x-ray[g] (posterior–anterior and lateral views)	X																	
TB test[h]	X																	
Read PPD if applicable (48–72 hours post-PPD)[i]	X																	
Skin punch biopsies[j] (lesional, nonlesional)		X			X			X										
Clinical chemistry	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids (fasting)[k]		X						X									X	
Serum pregnancy[l]	X																	
FSH[m]	X																	
HIV, HCV,[n] HBV screening tests	X																	
HBV DNA[o]	X				X			X			X			X			X	X
Urinalysis	X	X						X				X					X	
Urine pregnancy[l]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics sample		X																
Serum IgE (total)		X			X			X									X	
Serum IgE (allergen		X						X										

	Screening	Induction Period							Maintenance Period									Posttreatment Follow-Up
	Period 1	Period 2							Period 3									Period 4
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	801
Weeks from randomization		0	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52 or ET	60
Days from randomization		0	7	14	28	56	84	112	140	168	196	224	252	280	308	336	364	420
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5
specific)[p]																		
Exploratory long-term storage samples (serum, plasma EDTA)		X		X	X	X		X		X			X		X		X	
Exploratory long-term storage samples: RNA and DNA (epigenetic)		X			X			X									X	
LY3375880 PK Samples[q]		X	X	X	X	X		X		X			X				X	X
Immunogenicity samples[q]		X			X			X		X			X				X	X
Target engagement samples (Total IL-33)		X		X	X	X		X		X			X				X	
IL-19, TARC, Periostin		X		X	X	X		X		X			X		X		X	
Flow cytometry sample		X			X			X									X	

Abbreviations: AD = atopic dermatitis; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale (11 categories of suicidal ideation/suicidal behavior); DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EDTA = ethylenediaminetetraacetic acid; ePRO = electronic subject-reported outcomes (device); ET = early termination; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; IL = interleukin; IP = investigational product; IWRS = interactive web-response system; NRS = Numeric Rating Scale; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; PPD = purified protein derivative; RNA = ribonucleic acid; SC = subcutaneous; SCORAD = SCORing AD; TARC = thymus and activation-regulated chemokine; TB = tuberculosis.

[a] The symptom-directed physical examination may be conducted at the investigator's discretion any time a subject presents with physical complaints.
[b] Subjects will be re-randomized/reassigned at Week 16 as described in Section 5.
[c] Will be collected as electronic Clinical Outcome Assessment (eCOA) data.
[d] The following measures (POEM and DLQI) should be completed by the subject prior to any clinical assessments being performed on days when study visits occur.
[e] Will be collected daily via an electronic subject diary.
[f] The Self-Harm Follow-up Form is only required if triggered by the Self-Harm Supplement Form.
[g] A posterior–anterior and lateral chest x-ray will be performed at screening unless one has been performed within the past 90 days, the x-ray and reports are available, and a repeat chest x-ray is not clinically indicated per investigator judgment.
[h] TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. See Exclusion Criterion [17] for description of TB testing. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally. (Note: Subjects who have a documented history of completing an appropriate TB treatment regimen for latent tuberculosis infection [LTBI] and with no risk of re-exposure since their treatments were completed are eligible to participate in the study if other criteria are met. These subjects should not undergo tuberculin skin test (TST) or interferon-gamma release assay (IGRA) testing unless advised to do so based on local guidelines, but must have a chest x-ray at screening.)
[i] If PPD testing was chosen to test for TB, then the subject must return and PPD test read 48 to 72 hours after Visit 1 (post-PPD).
[j] To be performed following investigator and subject disease assessments/scales.
[k] Fasting lipid profile: Subjects should not eat or drink anything except water for 12 hours prior to sample collection. If a subject attends these visits in a nonfasting state, this will not be considered a protocol violation.
[l] For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and subsequent visits according to the study schedule. If required per investigator judgment, local regulations, and/or institutional guidelines, additional pregnancy testing can occur during the study treatment period.
[m] For female subjects to confirm post-menopausal status according to Inclusion Criterion [9].
[n] For subjects who are positive for HCV antibody, a follow-up test for HCV RNA will be performed automatically. Subjects who are positive for HCV antibody and negative for HCV RNA may be enrolled.
[o] Subjects who are HBsAg negative and positive for HBcAb (and/or HBsAb in Japan) will automatically have an HBV DNA performed at screening. Any patient positive for HBcAb and negative for HBV DNA may be enrolled and must undergo HBV DNA monitoring per the schedule (see Section 9.4.8).
[p] Allergen-specific IgE testing could include, but is not limited to, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*.
[q] PK and immunogenicity samples should be collected prior to dosing on days of dosing. Sites may be prompted to draw an unscheduled PK and immunogenicity sample based on EASI score entered. See Sections 9.4.9 and 9.5.

3. Introduction

3.1. Study Rationale

LY3375880 is a human Ig G4-variant mAb that binds and neutralizes soluble human IL-33 cytokine. LY3375880 is being developed for the treatment of subjects with AD. This study will evaluate the safety and efficacy of LY3375880 in subjects with moderate-to-severe AD.

3.2. Background

Atopic dermatitis (AD) is the most common chronic skin disease with clinical hallmarks of inflammatory lesions with an intense itch. In the WHO 2010 Global Burden of Disease survey, AD ranked first among common skin diseases with respect to disability-adjusted life-years and years lived with a disease (Murray et al. 2012; Vos et al. 2012). Currently, there is no cure for AD; thus, the aim of disease management is to improve symptoms and achieve long-term disease control with a multistep approach. There is a need for more efficacious therapies with a better safety profile than the standard of care for subjects with AD.

Interleukin-33 is expressed in AD skin with increased numbers of IL-33-positive cells in areas with active lesions over nonlesional skin (Savinko et al. 2012). Serum levels of IL-33 were significantly higher (approximately 7-fold) in subjects with AD compared to healthy control subjects and correlated with disease severity (Tamagawa-Mineoka et al. 2014). IL-33 is a driver of type 2 helper T-cell (Th2)-mediated inflammation. The effects of IL-33 cause the production of other pro-inflammatory mediators, including IL-4 and IL-5. Therapeutic intervention has focused on neutralizing downstream effector cytokines such as IL-4, IL-13, or IL-5, with partial success. Dupilumab (Dupixent®; Regeneron and Sanofi) blocks signaling from both IL-4 and IL-13 and was approved by the Food and Drug Administration (FDA) in March 2017 for moderate-to-severe AD. However, in Phase 3 studies, over 60% of subjects did not achieve a high level of response (90% reduction in the Eczema Area and Severity Index score [EASI-90]), and the need for additional treatment approaches remains (Simpson et al. 2016). Interleukin-33 is upstream of IL-4 and IL-13 in the Th2 pathway, and neutralization of IL-33 would also reduce IL-5 production, leading to the hypothesis that LY3375880 has the potential for superior efficacy in AD than currently available treatments.

LY3375880 has been tested in humans in the Phase 1 study I9N-MC-FCAA (FCAA). Single doses ranging from 3 mg to 400 mg SC and 100 mg and 700 mg intravenous (IV); and multiple doses of 150 mg SC, 300 mg IV and 700 mg IV, were administered to healthy volunteers. No dose-limiting AEs were observed and dose escalation to the maximum dose of 700mg IV was achieved. As of 06 September 2018, no deaths, serious adverse events (SAEs), or discontinuations due to AEs were reported. Based on analysis of data from single-dose administration between 3 mg to 400 mg SC and 100 mg IV, the average half-life was 24 days.

Study I9N-MC-FCAB (FCAB) is the first Phase 2 study for LY3375880 and will evaluate the safety and efficacy of LY3375880 in adults with moderate-to-severe AD. Results from this study will lead to further development of LY3375880 in AD and other related diseases.

3.3. Benefit/Risk Assessment

There are currently no human data regarding the efficacy of LY3375880 in AD. IL-33 is upstream of IL-4 and IL-13 in the Th2 pathway (both cytokines inhibited by dupilumab, an approved treatment for moderate to severe AD); neutralization of IL-33 would also reduce IL-5 production, leading to the hypothesis that LY3375880 has the potential for efficacy in AD. Nonclinical data and safety data in Phase 1 support further development of LY3375880 in AD at the proposed doses.

The safety profile for LY3375880 has been presented by the results from nonclinical toxicology and safety pharmacology studies and from the Phase 1 clinical study FCAA. The primary adverse effects observed in animal studies included vasculopathy, glomerulopathy, anemia, and/or thrombocytopenia, which were attributable to immunogenicity of LY3375880. All affected animals had detectable antidrug antibodies (ADA), and the immunohistochemical and electron microscopy evaluations demonstrated the presence of, or changes associated with, immune complex deposition. Taken together, these findings suggest an immune-mediated response by the animals to the repeated administration of a humanized mAb and not attributable to LY3375880 pharmacology. The observation of immunogenicity and immune-mediated toxicity findings in monkeys is generally not considered predictive for immunogenicity and sequelae in humans. In terms of clinical safety observed in the Phase 1 Study FCAA, no dose-limiting safety issues have been identified. As of 06 September 2018, there have been no deaths, SAEs, or discontinuations due to AEs. The majority of AEs have been mild with no severe AEs reported. Furthermore, there were no renal, vascular, hematologic, or any other AEs suggestive of immune-complex disease. ADA titers in subjects have generally been low with no clinically evident impact.

Although the immune-mediated findings in the animal studies are generally not considered predictive for humans and there have been no apparent clinical effects attributable to immunogenicity in Study FCAA, subjects in Study FCAB will continue to be closely monitored for safety events, including allergic/hypersensitivity reactions, injection site reactions, or other events plausibly related to drug immunogenicity. Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses will be conducted to review unblinded safety data if deemed appropriate based on the ongoing blinded monitoring; the unblinded analyses will be conducted and reviewed by an internal assessment committee composed of personnel who do not have direct site contact or data entry/validation responsibilities.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3375880 will be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table FCAB.2 shows the objectives and endpoints of the study.

Table FCAB.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To compare the efficacy of LY3375880 to placebo as measured by IGA at Week 16 in the treatment of subjects with moderate-to-severe AD.	• Proportion of subjects achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16.

Secondary
• To compare the efficacy of LY3375880 to placebo as measured by improvement in signs and symptoms at Week 16 and 52 in the treatment of subjects with moderate-to-severe AD.
	• Proportion of subjects achieving at Week 16
	  ○ EASI-50
	  ○ EASI-75
	  ○ EASI-90
	  ○ SCORAD-75
	  ○ SCORAD-90
	  ○ IGA of 0
	• Mean change from baseline to Week 16 in
	  ○ EASI
	  ○ SCORAD
	• Proportion of subjects achieving IGA of 0 or 1 at Week 52

• To characterize the PK of LY3375880 in subjects with moderate-to-severe AD	• Serum PK Data
Exploratory Objectives/Endpoints • To evaluate signs and symptoms, health outcome measures, and QoL measures (total scores, item scores, and derivations) at each time point collected. • To explore relationships between LY3375880 exposure and study endpoints. • To characterize post-induction loss of response and maintenance of response. • To evaluate PD effects of LY3375880 in skin biopsies and peripheral blood.	

Abbreviations: AD = atopic dermatitis; EASI = Eczema Area and Severity Index; EASI-50/75/90 = 50%/75%/90% reduction in the EASI score; IGA = Investigator's Global Assessment; PD = pharmacodynamic; PK = pharmacokinetic(s); QoL = quality-of-life; SCORAD = SCORing AD.

5. Study Design

5.1. Overall Design

Study I9N-MC-FCAB (FCAB) is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the efficacy and safety of LY3375880 SC 600 mg Q4W, 150 mg Q4W, and 50 mg Q4W as compared to placebo Q4W in adult subjects with moderate-to-severe AD. In addition, LY3375880 300mg Q4W will be evaluated in the maintenance period as described below.

The study duration will be up to 65 weeks over 4 study periods:

- Period 1: Screening Period lasting from 8 to 35 days prior to Week 0 (baseline, Visit 2).
- Period 2: Induction Period, lasting from Week 0 (baseline, Visit 2) through Week 16 (Visit 8).
- Period 3: Maintenance Period, lasting from Week 16 (Visit 8) through Week 52 (Visit 17, inclusive). At Week 16, the following will occur:
    - Responders (defined as having achieved a 50% reduction in the Eczema Area and Severity Index score [EASI-50] response, regardless of whether rescue therapy has been initiated) will undergo the following re-randomizations:
        - Subjects on any dose of LY3375880 will be re-randomized at a 2:1 ratio to either maintain their current regimen or to receive placebo until loss of response (not achieving a 25% reduction in the EASI score [EASI-25] at a scheduled visit), at which point they will restart their induction period regimen.
        - Subjects on placebo will continue receiving placebo until loss of response, at which point they will be reassigned to receive LY3375880 at 300 Q4W.
    - Nonresponders will undergo the following reassignments:
        - Subjects on 50 mg Q4W will be reassigned to 150 mg Q4W.
        - Subjects on 150 mg Q4W will be reassigned to 300 mg Q4W.
        - Subjects on 600 mg Q4W will remain on their current regimen.
        - Subjects on placebo will be reassigned to receive 300 mg Q4W.
    - Subjects with persistent disease activity, defined as not achieving EASI-25 for 3 consecutive scheduled maintenance period visits, not already on 600 mg Q4W will be reassigned to 600 mg Q4W for the remainder of the study.
- Period 4: Post-Treatment Follow-Up Period, spanning approximately 8 weeks from Week 52 (after Visit 17) to Week 60 (Visit 801).

Rescue therapy is permitted starting at Week 8 for subjects who do not achieve an EASI-25 response. Refer to Section 7.7.3 for details.

Treatment Arms and Duration:

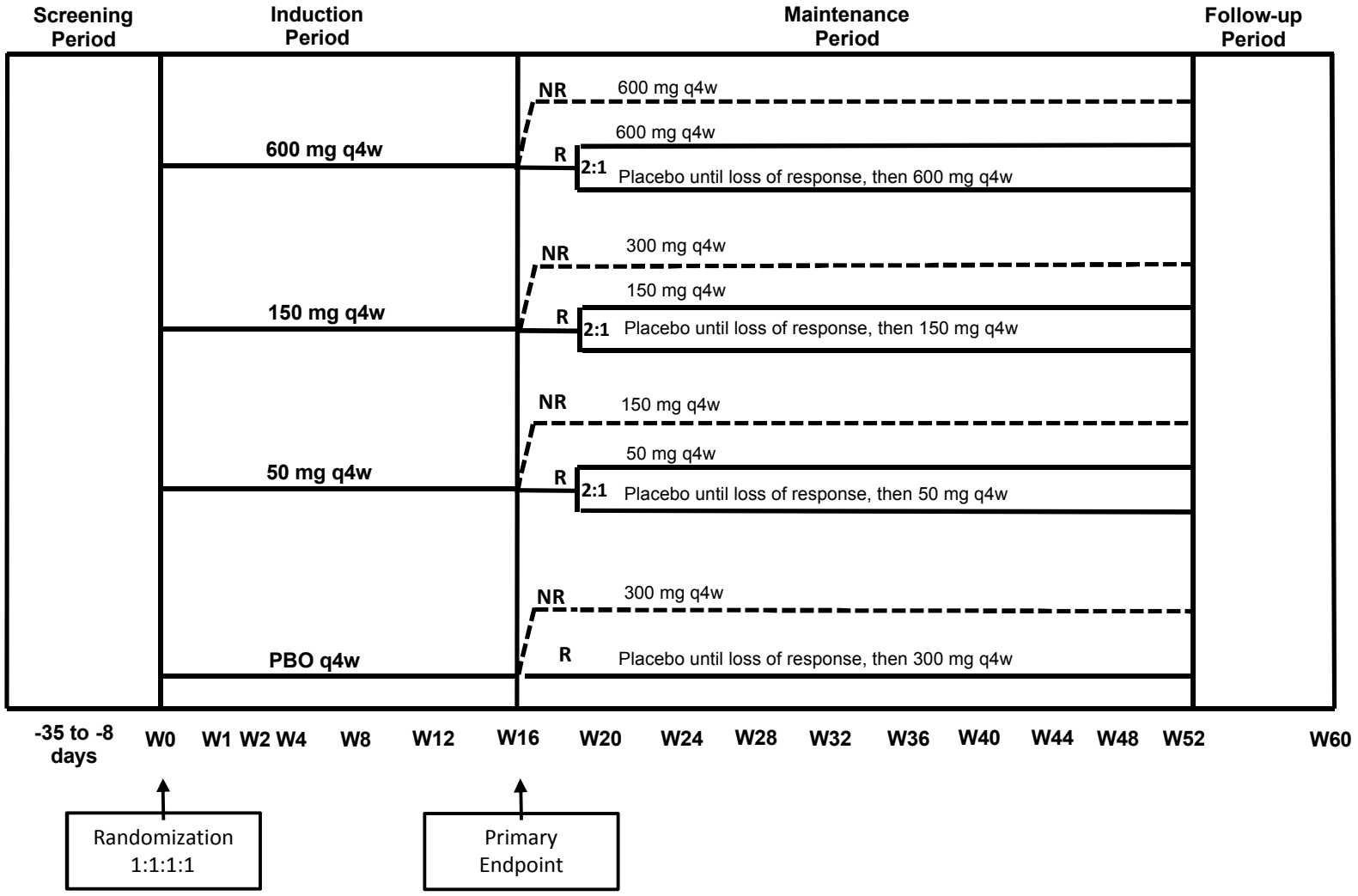
Approximately 200 subjects will be randomized 1:1:1:1 at Week 0 to 1 of 4 treatment groups in the induction period: placebo SC (Q4W), LY3375880 SC 600 mg (Q4W), LY3375880 150 mg (Q4W), or LY3375880 50 mg (Q4W). The study duration will be up to 65 weeks (Screening

Period: Up to 5 weeks; Induction Period: 16 weeks; Maintenance Period: 36 weeks; Follow-up Period: 8 weeks).

Subjects will be stratified at randomization according to disease severity (IGA [3 versus 4]) and geographic region (Japan versus non-Japan).

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Section 2). Appendix 2 describes collection of laboratory samples with the list of specific laboratory tests that will be performed for this study. Study governance considerations are described in detail in Appendix 3.

Figure FCAB.1 illustrates the study design.


Screening Period
Induction Period
Maintenance Period
Follow-up Period
600 mg q4w
150 mg q4w
50 mg q4w
PBO q4w
NR
R
2:1
600 mg q4w
Placebo until loss of response, then 600 mg q4w
300 mg q4w
150 mg q4w
Placebo until loss of response, then 150 mg q4w
150 mg q4w
50 mg q4w
Placebo until loss of response, then 50 mg q4w
300 mg q4w
Placebo until loss of response, then 300 mg q4w
-35 to -8 days
W0
W1
W2
W4
W8
W12
W16
W20
W24
W28
W32
W36
W40
W44
W48
W52
W60
Randomization 1:1:1:1
Primary Endpoint

LY3375880

Abbreviations: R = Responders.
Response to study drug is defined as achieving an EASI-50. At Week 16, responders on LY3375880 will be re-randomized to either maintain current dosing regimen or placebo until disease recurrence (EASI-25). Placebo responders will continue on placebo until disease recurrence.
NR = Nonresponders. At Week 16, nonresponders will be reassigned to 600 mg Q4W, 300mg Q4W, or 150 mg Q4W depending on treatment group.
Note: Subjects with persistent disease activity, defined as not achieving EASI-25 for 3 consecutive scheduled maintenance period visits, not already on 600 mg Q4W will be reassigned to 600 mg Q4W for the remainder of the study.

Figure FCAB.1. Study design for Study I9N-MC-FCAB.

5.2. Number of Participants

Approximately 200 participants will be randomized.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

Study FCAB is the first clinical trial evaluating the safety and efficacy of LY3375880 in subjects with moderate-to-severe AD. A moderate-to-severe subject population is appropriate for a novel investigational product (IP) with immunomodulating properties. Three active dose levels of LY3375880 to evaluate the primary endpoint will allow the evaluation of safety and efficacy across a broad dose range to fully characterize the benefit/risk profile of LY3375880 and provide information on dose selection in future studies. A double-blind, placebo-controlled design limits bias for both subject and investigator assessments and enables a clearer interpretation of active drug effect.

The treatment period includes an induction and maintenance period. The induction period of the study is designed to evaluate the primary endpoint, which is the proportion of subjects achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16. The IGA is a global disease severity scale that is widely used in AD trials, and is accepted by the FDA as a primary endpoint for trials conducted for approval of new drugs (Futamura et al. 2016; Simpson et al. 2016). A time point at Week 16 to evaluate the primary endpoint is appropriate, based on previous clinical trials of systemic therapies in AD (Simpson et al. 2016). A maintenance period spanning Weeks 16 to 52 allows for an evaluation of safety and efficacy over a longer duration. In addition to the dose regimens being tested in the induction period, an additional dosing regimen of 300mg Q4W will be evaluated during the maintenance period to obtain safety and efficacy data of an intermediate dose. Given the broad dose range being evaluated in this study, data regarding this dose will further aid in exposure–response modeling and dose selection for future studies. During the maintenance period, subjects taking LY3375880 who respond to study drug at Week 16 will be re-randomized to either maintain their current regimen or administered placebo until disease recurrence to understand durability of disease response. This information will provide the dose

and frequency of administration in future studies. Nonresponders on LY3375880 on 50 mg and 150 mg will be reassigned to the next highest dose level to evaluate whether disease activity will respond to a higher dose of active study drug. Placebo nonresponders will be reassigned to 300 mg to efficiently obtain safety and efficacy data on the intermediate dose of 300 mg Q4W not tested in the induction period.

5.5. Justification for Dose

The LY3375880 dose range of 50 mg to 600 mg SC is based on clinical safety data from the Phase 1 Study FCAA, pharmacokinetic/pharmacodynamic (PK/PD) modeling, and nonclinical toxicology data.

In the Phase 1 study FCAA, single and multiple doses of up to 700 mg IV of LY3375880 were tested in healthy subjects. As of the cutoff date of 06 September 2018, all cohorts have completed dosing. There have been no dose-limiting AEs identified and dose escalation to the highest possible dose of 700 mg IV in both the single ascending and multiple ascending dose portions was achieved. No deaths, SAEs, or discontinuations due to AEs were reported. Overall, the frequency of treatment-emergent AEs was 8/20 (40%) for subjects dosed with placebo and 11/58 (19%) for subjects dosed with LY3375880. There were no dose-related changes in AE frequency across single doses of 3 to 700 mg LY3375880 or multiple doses of 150 to 700 mg LY3375880. To date, the most commonly reported AEs in LY3375880 treated subjects have been upper respiratory tract infection reported by 3 (5.2%) subjects who received LY3375880 and 0 subjects who received placebo, headache reported by 2 (3.4%) subjects who received LY3375880 and 1 (5.0%) subject who received placebo, and skin abrasion reported by 2 (3.4%) subjects who received LY3375880 and 1 (5%) subject who received placebo. The majority of the AEs have been mild and no severe AEs have been reported. There were no clinically significant changes in clinical safety laboratory results in subjects administered LY3375880.

The available PK and target engagement data from the first 6 cohorts of the SAD portion of FCAA (3mg to 400 mg SC and 100 mg IV) as well as data from the first cohort of the multiple ascending dose (150 mg SC) were used to develop a PK/PD model. The model described the time course of the relationship of serum concentrations of LY3375880 and inhibition of IL-33. Based on simulations conducted with this model, doses between 50 mg and 600 mg administered once monthly are expected to cover a minimal–maximal effect range, assuming that maximum inhibition of IL-33 throughout the dosing interval would be required for efficacy.

The nonclinical toxicity profile of LY3375880 has been characterized in 6-week and 6-month Good Laboratory Practice-compliant general toxicology studies in cynomolgus monkeys, the only pharmacologically relevant species based on binding to human and cynomolgus IL-33. No adverse effects considered related to IL-33 neutralization were observed in monkeys. However, histologic or hematologic effects, considered related to systemic inflammation attributable to immunogenicity of LY3375880, were observed in all treated animals in the 6-month study. In 7 of the 22 treated animals, the immunogenicity-associated inflammation caused adverse histopathological or hematological findings that are most likely a consequence of immune

complex-associated type III hypersensitivity. These adverse findings included immune-mediated hemolytic anemia and/or thrombocytopenia, protein-losing glomerulopathy, and vasculopathy; clinical decline associated with these findings resulted in the euthanasia prior to scheduled termination in 3 animals and a suspension of dosing in another animal. In addition, non-adverse increased incidence and/or severity of mononuclear cell infiltrates was observed in 1 or more tissues in all treated animals. The observation of immunogenicity and immune-mediated toxicity findings in monkeys is generally not considered predictive for immunogenicity and sequelae in humans, and no safety signals suggestive of immune-complex disease have been reported in Phase 1 trial subjects. In the 6-week toxicology study, LY3375880-related effects were limited to non-dose-related decreases in circulating natural killer (NK) cells (with no impact on NK cell function); this effect was not observed in the 6-month toxicology study, suggesting these effects were not related to LY3375880. Because none of the adverse effects in the 6-month study are considered attributable to LY3375880 pharmacology, the high dose (400 mg/kg/wk) is appropriate to derive dose and exposure multiples to intended clinical doses and projected exposures supportive of the margin of safety in clinical trials. Exposure at the dose of 400 mg/kg/wk in the 6-month monkey study supports the currently planned highest clinical Phase 2 dose of 600 mg with a 224-fold multiple based on predicted human exposure (Table FCAB.3).

Table FCAB.3. Exposure Multiples for Administration of LY3375880 Based on Administered Dose and Predicted Human Exposure

Species Dose level	Dose (mg/kg)	Dose Multiple	Average Plasma Concentration (µg/mL)[a]	Exposure Multiple[b]
Human Minimum Dose[c]				
50 mg (SC) Q4W	0.71		7.2[d]	
Monkey Maximum Dose[e]				
200 mg/kg (IV) BIW	400	563×	22813[f]	3168×
Human Maximum Dose[c]				
600 mg (SC) Q4W	8.6		102[d]	
Monkey Maximum Dose[e]				
200 mg/kg (IV) BIW	400	47×	22813[f]	224×

Abbreviations: AUC = area under the concentration versus time curve; BIW = twice per week; IV = intravenous; kg = kilogram; mg = milligram; mL = milliliters; Q4W = every 4 weeks SC = subcutaneous; µg = microgram.

a AUC value expressed as average plasma concentration to normalize for differences in dosing frequency.

b Exposure multiple is the calculated average plasma concentration in animals, divided by the predicted average plasma concentration in humans.

[c] Assume human body weight = 70 kg.

[d] Value from pharmacokinetic data from Study FCAA, obtained by dividing predicted steady state $AUC_{(0\text{-}672hr)}$ values by 672 hours. At 50 mg, $AUC_{(0\text{-}672hr)}$ = 4810 µg·hr/mL; at 600 mg $AUC_{(0\text{-}672hr)}$ = 68700 µg·hr/mL.

[e] Study 20125378. At the dose of level 200 mg/kg, no adverse effects attributable to the pharmacology of LY3375880 were observed.

[f] Value calculated as average of male and female steady-state $AUC_{(0\text{-}96hr)}$ (µg·hr/mL), divided by 96 hours.

6. Study Population

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

Study investigator(s) will review subject history and screening test results at Visit 1 and Visit 2 to determine if the subject meets all inclusion and none of the exclusion criteria to qualify for randomization in the study. All screening activities must be completed and reviewed before the subject is randomized.

6.1. Inclusion Criteria

Informed Consent

[1] Are at least 18 years of age at the time of informed consent.

Note: Use local requirements to provide consent if the age of adulthood is defined as >18 years.

[2] Are able to read, understand, and give documented informed consent.

Disease Characteristics

[3] Have a diagnosis of AD at least 12 months prior to screening, as defined by the American Academy of Dermatology: Guidelines of care for the management of AD; Section 1. Diagnosis and assessment of AD (see Appendix 6).

[4] Have moderate-to-severe AD, including all of the following:

a. Eczema Area and Severity Index (EASI) score ≥16 at randomization (Visit 2).

b. IGA score of ≥3 at randomization (Visit 2).

c. ≥10% of body surface area (BSA) involvement at randomization (Visit 2).

[5] Have a documented history provided by a physician and/or investigator of inadequate response to existing topical medications within 6 months preceding screening, or 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 (e.g., IGA ≤2) after use of at least a medium-potency topical corticosteroid (TCS) for at least 4 weeks, or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter. Topical corticosteroids may be used with or without topical calcineurin inhibitors (TCNIs).

b. Subjects who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate (MTX), azathioprine, and mycophenolate mofetil (MMF), will also be considered as a surrogate for having inadequate response to topical therapy.

c. Documented history of clinically significant adverse reactions with the use of TCS such as skin atrophy, allergic reactions, and systemic effects that in the opinion of the investigator outweigh the benefits of retreatment.

[6] Have applied emollients daily for at least 14 days prior to randomization and agree to use emollients daily throughout the treatment period.

[7] Are willing and able to undergo punch biopsies according to the Schedule of Activities (Section 2).

Other Subject Characteristics

[8] **Women of childbearing potential:**

a. Agree not to breastfeed from the start of screening until 120 days after the last dose of study drug, and must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

AND

b. Must agree to either remain abstinent, if complete abstinence is their preferred and usual lifestyle, or remain in same-sex relationships, if part of their preferred and usual lifestyle, without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

OR

c. Must use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration for 120 days after the last dose of study drug.

- Two effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable because of the high failure rate when these methods are combined.
- Of note, 1 of the 2 methods of contraception may be a highly effective (<1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices).

[9] Women not of childbearing potential may participate and include those who are:

a. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

b. postmenopausal – defined as either:

- a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
  - cessation of menses for at least 1 year or
  - at least 6 months of spontaneous amenorrhea (or longer if required by local regulatory requirements) with a follicle-stimulating hormone level >40 mIU/mL; or
- a woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
- a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[10] Men, regardless of their fertility status, with nonpregnant women partners of childbearing potential must agree to either remain abstinent (if that is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (<1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus (predicted to be 120 days following the last dose of study drug).

- Men and their partners may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.)
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential (120 days following last dose of study drug).
- Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus (predicted to be 120 days following the last dose of study drug).
- Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria within the screening period, unless specifically defined otherwise.

Medical Conditions Related to AD

[11] Have received any of the following therapies within the time frames specified below:

a. Topical treatments:

Topical corticosteroids or topical immune modulators (e.g., tacrolimus or pimecrolimus) within 2 weeks prior to randomization (Visit 2) and throughout the study.

Topical phosphodiesterase type 4 (PDE-4) inhibitor (crisaborole) within 2 weeks prior to randomization (Visit 2) and throughout the study.

b. Systemic treatments:

- Systemic corticosteroids

  Oral systemic corticosteroids within 4 weeks prior to randomization (Visit 2) and throughout the study.

Parenteral corticosteroids administered by intramuscular, intra-articular, 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.

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

- Other systemic treatments

  Synthetic (oral) immunomodulators, including but not limited to Janus kinase (JAK) inhibitors (e.g., tofacitinib, ruxolitinib), cyclosporine, MTX, MMF, and azathioprine within 4 weeks prior to randomization (Visit 2) and throughout the study.

  Biologics: Any prior treatment with dupilumab, or an agent directly targeting IL-13 or IL-33 (marketed or investigational), is exclusionary. Other immunomodulating mAbs (e.g., ustekinumab, omalizumab, etc.) are prohibited within 5 half-lives prior to randomization and throughout the study.

  Leukotriene inhibitors within 4 weeks prior to randomization (Visit 2) and throughout the study.

  Any other systemic therapy used to treat AD or symptoms of AD (approved or off-label use) within 4 weeks prior to randomization, unless allowed as a concomitant therapy in Section 7.7.

c. Phototherapy, including therapeutic phototherapy (psoralen plus ultraviolet-A, ultraviolet-B), excimer laser, as well as self-treatment with tanning beds within 4 weeks prior to randomization (Visit 2) and throughout the study.

[12] Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or cutaneous lupus) that would interfere with evaluations of the effect of study medication on AD.

[13] Subjects 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 participation in the study.

[14] A history of eczema herpeticum within 12 months prior to screening or a history of 2 or more episodes of eczema herpeticum in the past.

[15] 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 (e.g., unstable chronic asthma).

Diagnostic Assessments

[16] Have any of the following specific abnormalities on screening laboratory tests:

a. Serum creatinine, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2x upper limit of normal (ULN)

b. alkaline phosphatase (ALP) ≥2x ULN

c. total bilirubin (TBL) ≥1.5x ULN

d. hemoglobin <10.0 g/dL (<100.0 g/L)

e. total white blood cell count <2500 cells/μL (<2.50x10^3/μL or <2.50 GI/L)

f. neutropenia (absolute neutrophil count <1200 cells/μL) (<1.20x10^3/μL or <1.20 GI/L)

g. lymphopenia (lymphocyte count <750 cells/μL) (<0.75x10^3/μL or <0.75 GI/L)

h. thrombocytopenia (platelets <100,000/μL) (<100x10^3/μL or <100 GI/L)

Note: For each aforementioned test, a single repeat analysis is allowed during screening, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

Infectious Disease Exclusion Criteria

[17] Have **any** history or evidence of **active** tuberculosis (TB) disease as determined on the basis of a positive medical history, physical examination, or chest radiography (per local standard of care), and regardless of previous or current TB treatments; **or** are diagnosed with latent tuberculosis infection (LTBI) at screening, defined as:

- a positive tuberculin skin test (TST, also called a purified protein derivative [PPD] or Mantoux test) result (skin induration ≥ 5mm) at 48 to 72 hours after the test date, or
- a positive interferon-gamma release assay (IGRA, e.g., QuantiFERON®-TB Gold or T-Spot®.TB).

If the QuantiFERON-TB Gold is indeterminate or the T-Spot®.TB is invalid or borderline, 1 retest is allowed according to investigator judgment. Subjects with 2 indeterminate QuantiFERON-TB Gold or 2 invalid or borderline T-Spot®. TB assays are excluded, unless they complete appropriate therapy for LTBI (defined as below).

Subjects diagnosed with LTBI at screening may be rescreened once and enrolled if they have received at least 4 weeks of appropriate ongoing prophylactic therapy for LTBI (i.e., according to WHO or US Centers for Disease Control and Prevention LTBI treatment guidelines), meet all other inclusion and exclusion criteria for participation, and also continue and complete appropriate LTBI therapy during the course of the study to remain eligible for participation in the study. The choice to perform either a TST or an IGRA test must be made by the investigator according to local licensing and standard of care. Interferon-gamma release assay test is a preferred method in subjects with a history of Bacillus Calmette–Guérin (BCG) vaccination, given the rate of false-positive TST results in this population.

Subjects who have a documented history of completing an appropriate TB treatment regimen for LTBI and with no risk of re-exposure since their treatments were completed are eligible to participate in the study if they meet all other inclusion and exclusion criteria for participation. These subjects should not undergo TST or IGRA testing unless advised to do so based on local guidelines.

Subjects with documentation of a "negative" IGRA or TST testing within 3 months before initial screening may not need to repeat TB testing at screening, based on judgment of the investigator. Source documentation must include the original laboratory report for IGRA or a record to size in millimeters of the induration response (for TST). A TST recorded as "negative" without documenting the size of induration in millimeters will not be acceptable and will require a retest.

[18] Have known hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as: (1) positive for hepatitis B surface antigen (HBsAg+) or (2) positive for hepatitis B core antibody (HBcAb+) and positive confirmatory polymerase chain reaction (PCR) for HBV deoxyribonucleic acid (DNA), regardless of hepatitis B surface antibody status or (3) for sites in Japan only, positive for HBcAb and/or positive for anti-hepatitis B surface antibody (HBsAb), and a confirmatory PCR for HBV DNA.

Subjects whose results are HBcAb positive (and/or HBsAb positive in Japan) and HBV DNA negative may be eligible to continue screening, according to investigator judgment. Such subjects will be monitored for HBV during the study as detailed in Section 9.4.8.

[19] Have known hepatitis C or test positive for hepatitis C virus (HCV) at screening, defined as a positive test result for hepatitis C virus antibody (anti-HCVAb) plus a positive confirmatory test result for HCV (e.g., HCV ribonucleic acid [RNA]).

Subjects whose results are anti-HCVAb positive and HCV RNA negative are eligible to continue screening, according to investigator judgment.

Note: Subjects who have documented anti-HCV treatment for a past HCV infection **AND** are HCV RNA negative are eligible to continue screening per investigator judgment.

[20] Have evidence of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and/or test positive for HIV antibodies at screening.

[21] Have received a BCG vaccination within 12 months or received live/live attenuated vaccine(s) within 3 months of baseline or intend to receive such during the study. Live/live attenuated vaccines should be avoided for at least 5 drug half-lives after the last dose of study drug.

Note: Use of nonlive (inactivated) vaccinations are allowed for all subjects.

[22] History of an endoparasitic, opportunistic, chronic/recurring, or clinically serious infections (such as infections requiring IV antibiotics, hospitalization, or prolonged treatment) within 6 months prior to screening, or deemed by the investigator to be immunocompromised or at high risk of infectious complications (e.g., indwelling urinary catheter), such that participation in the study would pose an unacceptable risk to the subject. Refer to Appendix 5 for examples of opportunistic infections to consider.

[23] Active skin infection that requires treatment with topical OR systemic antibiotics within 4 weeks prior to randomization.

[24] Any other active infection treated with systemic anti-infectives within 4 weeks prior to randomization.
Note: Subjects with an active upper respiratory infection that is only being treated symptomatically and does not require anti-infectives may be considered for enrollment if other eligibility criteria are met.

[25] Have evidence of active/infectious herpes zoster infection ≤12 weeks prior to screening (herpes zoster lesions remain active until all vesicles are crusted over), or any history of disseminated/complicated herpes zoster (e.g., multidermatomal involvement, ophthalmic zoster, central nervous system, or other internal organ involvement).

Medical Conditions in General

[26] Are largely or wholly incapacitated permitting little or no self-care, such as being bedridden.

[27] Have significant allergies to humanized mAbs or any components of the LY3375880 product formulation.

[28] Have an unstable or uncontrolled illness, including but not limited to cerebrocardiovascular (e.g., unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association Class III/IV]), respiratory, gastrointestinal, hepatic, renal, endocrine, hematologic, or neurologic disorders that would potentially affect subject safety within the study or confound efficacy and safety assessments.

[29] Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the subject's participation in the study.

[30] Have active malignancy or have been in remission from a malignancy for less than 5 years, with the following exceptions:

a. Cervical carcinoma in situ that has been appropriately treated with no evidence of recurrence or metastatic disease for at least 3 years.

b. Basal cell or squamous epithelial carcinoma of the skin that has been appropriately treated with no evidence of recurrence for at least 3 years.

c. In situ colon cancer or noninvasive malignant colon polyps that had been appropriately removed with no evidence of recurrence for at least 3 years.

[31] Presence of significant uncontrolled neuropsychiatric disorder or judged by the investigator to be at risk for suicide;

OR

marked "yes" to Columbia-Suicide Severity Rating Scale (C-SSRS) Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion

OR

marked "yes" to suicide-related behavior questions on the "Suicidal Behavior portion of the C-SSRS

AND

the ideation or behavior occurred within the past 6 months prior to Visit 1 or anytime during the screening period prior to randomization.

Note: A subject does not necessarily have to be excluded if they have self-injurious behavior that would be classified as nonsuicidal self-injurious behavior. If this situation arises, the subject should be referred to a psychiatrist or appropriately trained professional as indicated.

[32] Have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within the 2 years prior to screening. Subjects who partake in legal marijuana use, whether recreational or medical, must agree to refrain from use during the study.

[33] Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.

Other Exclusions

[34] Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.

[35] Are currently enrolled in any other clinical trial 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 of the following IPs under the defined conditions:

- any nonbiologic IP within 5 half-lives prior to screening
- any biologic IP (not directly targeting IL-13 or IL-33) within 90 days or 5 drug half-lives (whichever is longer) prior to screening.

[36] Have previously been randomized in this study or any other study investigating LY3375880.

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

[38] Are Eli Lilly and Company (Lilly) employees or their designee.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Subjects who do not meet the criteria for participation in this study (screen failure) may be rescreened only once under certain circumstances (e.g., having previously failed criteria [4], [11], [16], [23], [24]) and with sponsor approval. Subjects may be rescreened once for administrative reasons (e.g., falling out of the screening window because of scheduling reasons). When rescreening is performed after being screen failed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Subjects in rescreening who have previously completed screening chest radiography and/or TB tests according to the protocol do not need to repeat these procedures if they were performed within 90 days before their rescreening date of consent but may do so at the discretion of the investigator. All other screening procedures must be conducted at rescreen to ensure all eligibility criteria are met.

7. Treatments

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

7.1. Treatments Administered

The study involves a comparison of each LY3375880 dosing regimen (600 mg, 300 mg in Maintenance period, 150 mg, and 50 mg SC Q4W) with placebo. Table FCAB.4 shows the treatment regimens. Subcutaneous LY3375880 should be administered as 3 to 4 injections (maximum volume: 2 mL per injection) preferably in the abdomen in separate quadrants, whenever possible. All subjects should be monitored after dosing according to investigator practice or local standard of care. Detailed instructions for IP administration will be provided separately by the sponsor.

Table FCAB.4. Treatment Regimens

Treatment Name	LY3375880	Placebo
Dosage Formulation	LY3375880 for clinical trial use supplied as solution in vial, manufactured to contain 200 mg/2 mL of LY3375880 (100 mg/mL)	0.9% Sodium chloride
Dosage Levels	600 mg SC Q4W, 300 mg SC Q4W (In Maintenance period only) 150 mg SC Q4W, 50 mg SC Q4W	NA
Route of Administration	SC injection(s)	SC injection(s)

Abbreviations: NA = not applicable; Q4W = every 4 weeks; SC = subcutaneous.

The investigator or designee is responsible for:

- explaining the correct use of the IP to the site personnel.
- verifying that instructions are followed properly.
- maintaining accurate records of IP dispensing and collection.
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

Clinical study materials will be labeled according to the country's regulatory requirements.

LY3375880 is supplied for clinical trial use as solution in vial with study-specific labels. The 2-mL vial is manufactured to contain 200 mg of LY3375880 (100 mg/mL).

Commercially available 0.9% sodium chloride solution will be used as a placebo for this study.

When prepared for dosing according to instructions, it will not be possible to distinguish between LY3375880 and placebo.

Detailed instructions for the preparation and handling of LY3375880 will be provided by the sponsor.

The IP must be prepared by an unblinded site personnel qualified to prepare study drug who is not involved in any other study-related procedures to protect the blinding.

7.2. Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized 1:1:1:1 to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign packages containing double-blind IP to each subject. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the packages into the IWRS.

To achieve between-group comparability, the randomization will be stratified by IGA (3 versus 4) and by geographic region (Japan versus non-Japan).

7.2.1. Selection and Timing of Doses

Study visits at which IP is administered are preferred, if possible, to occur on the same day of the week. In any case, the study visits should occur within the visit window specified on the Schedule of Activities (see Section 2). The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

The induction period of the study is double blind. The maintenance period of the study is double blind unless a subject has persistent disease activity defined as not achieving EASI-25 for 3 consecutive scheduled maintenance period visits. In this circumstance, the subject is reassigned to 600 mg Q4W for the remainder of the study unless they were already on that regimen. Therefore, the treatment regimen can be inferred in this scenario, but will not be considered as an unblinding event as described in procedures in this section.

To preserve the blinding of the study, the unblinded site personnel qualified to prepare study drug should not be involved in any study-related procedures, and a minimum number of Lilly personnel will have access to the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The safety of the subject must always be the first consideration in making such a determination. If a subject's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

IPs will be supplied by Lilly or its representative, in accordance with current good manufacturing practices, and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

Follow storage and handling instructions stated on the IP label. Detailed instructions regarding preparation and handling of IPs will be provided by the Sponsor.

7.6. Treatment Compliance

All doses of study medication will be administered at the study site by site personnel. Deviations from the prescribed dosage regimen should be recorded in the eCRF.

Every attempt will be made to select subjects who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the subject before randomization.

If a subject is noncompliant with study procedures and/or IP administration, the investigator should assess the subject to determine the reason for noncompliance and educate and/or manage the subject, as appropriate, to improve compliance. Overall compliance with therapy is defined to be missing no more than 20% of the expected doses within the protocol-defined dosing interval and not missing 2 consecutive doses. If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the subject may be discontinued from the study.

7.7. Concomitant Therapy

All concomitant medication, whether prescription or over the counter, used at baseline and/or during the course of the study, must be recorded on the Concomitant Medication eCRF. Subjects will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study. For AD therapies permitted as part of rescue therapy, see Section 7.7.3.

7.7.1. Prohibited Medications and Procedures

The following therapies will not be allowed during the course of the study (Refer to Exclusion Criteria [11], [21], [23], [24], and [36] for details regarding washout periods for study eligibility):

- Topical Treatments: TCS, topical immune modulators (e.g., tacrolimus or pimecrolimus) or topical PDE-4 inhibitor (e.g., crisaborole) except when given as rescue therapy as described in Section 7.7.3.
- Systemic corticosteroids: oral or parenteral corticosteroids (intramuscular, intra-articular or IV) Note: Intranasal or inhaled steroid use is allowed during the trial.
- Other Systemic treatments:
    - Synthetic (oral) immunomodulators, including, but not limited to, JAK inhibitors (e.g. tofacitinib, ruxolitinib), cyclosporine, MTX, MMF, and azathioprine.
    - Biologics: Immunomodulating mAbs (including but not limited to dupilumab, ustekinumab, omalizumab, etc.).
    - Leukotriene inhibitors
- Phototherapy, including therapeutic phototherapy (psoralen ultraviolet-A, ultraviolet-B), excimer laser as well as self-treatment with tanning beds.
- Any investigational therapy that is not LY3375880.
- Bleach baths
- Allergen immunotherapy.
- Live vaccines.

7.7.2. Permitted Medications

Treatment with concomitant AD therapies during the study is permitted only as described below:

- Daily use of emollients is required as background treatment. Moisturizers with additives such as antipruritics or antiseptics are not permitted. If daily applications are missed, it will not be considered a protocol violation.
- Oral and topical antihistamines including, but not limited to, diphenhydramine, hydroxyzine, acrivastine, bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, mizolastine, and rupatadine are allowed.
- Topical anesthetics

Note: Subjects should not apply emollients or other topical treatments on the day of their study visit prior to the procedures to allow adequate assessment of skin dryness.

Any changes in concomitant medications must be recorded in the Concomitant Therapy of Special Interest eCRF.

7.7.3. Rescue Therapy

Rescue therapy is permitted **starting at Week 8** for subjects who do not achieve an EASI-25 response. If the subject meets criteria, the decision to implement rescue is according to investigator judgment and is not a requirement. Rescue therapy should only be initiated at a visit at which an EASI-25 is not met.

Choice of rescue therapy treatment

- Triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment. In the event where either of these topical formulations is not available, an alternate, equivalent potency TCS cream and/or ointment may be used.
- Investigators may also select to use TCNIs and/or crisaborole where approved. If TCNIs are prescribed, use should be limited to problem areas only (e.g., face, neck, skin folds, genital areas, etc.).
- On the days of study visits, topical therapy should not be applied before the subject has undergone all study procedures and clinical evaluations in order to allow adequate assessment of skin dryness.
- Subjects rescued to topical therapy will continue to take IP and use of rescue therapy will be documented in the eCRF.

In subjects who do not improve sufficiently with the prescribed provided rescue topical therapy after 7 days, a higher potency TCS may be used and IP may continue. It is recommended that if a subject reaches “clear” to “almost clear” skin after topical rescue, then medium- and/or high-potency TCS and TCNI should be stopped, and low–potency TCS (e.g., hydrocortisone 2.5% ointment) should be used once daily for an additional 7 days, then stopped. If lesions return, subjects can be retreated with TCS 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 and if the investigator determines that a subject requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of AD but is contraindicated in this study, the subject should be discontinued from the study. In such cases, discontinuation from the study occurs prior to introduction of the new agent.

Note that subjects who receive rescue therapy during the induction period will be considered nonresponders for the primary analysis, but will undergo re-assignment/re-randomization at Week 16 based on EASI-50 response according to Section 5.1, and will not automatically be considered nonresponders for purposes of treatment assignment.

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.

7.8. Treatment after the End of the Study

Study drug is experimental and will be provided to study subjects only according to the protocol; it will not be made available to subjects after they have completed or discontinued from the study unless the subject qualifies to continue study drug in another protocol.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of IP:

- **Subject Decision**
  - the subject requests to discontinue IP.
- **Discontinuation due to a hepatic event or liver test abnormality:** Subjects who are discontinued from IP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via designated data transmission methods. Discontinuation of the IP for abnormal liver tests **should be** considered by the investigator when a subject meets one of the following conditions after consultation with the Lilly-designated medical monitor:
  - ALT or AST >8x upper ULN
  - ALT or AST >5x ULN for more than 2 weeks.
  - ALT or AST >3x ULN and TBL level >2x ULN or international normalized ratio (INR) >1.5.
  - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
  - ALP >3x ULN
  - ALP >2.5x ULN and TBL >2x ULN
  - ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- **Discontinuation due to HBV DNA results**
  - Subjects who are HBcAb positive (and/or HBsAb positive in Japan) at screening and are enrolled in the study will be discontinued from the IP if the result of the HBV DNA testing becomes detectable at any time during the study.

Subjects who discontinue the IP early will continue in the study according to the Schedule of Activities (Section 2), unless there is a reason to discontinue from the study (Section 8.2).

8.1.2. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor's medical monitor and the investigator to determine if the subject may continue in the study. If the investigator and the sponsor CRP agree that it is medically appropriate to continue, the investigator must obtain

documented approval from the sponsor CRP to allow the inadvertently enrolled subject to continue in the study with or without treatment with IP. Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.2. Discontinuation from the Study

Subjects may choose to withdraw from the study for any reason at any time, and the reason for early withdrawal will be documented.

Some possible reasons that may lead to permanent discontinuation include the following:

- enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).
- investigator decision
    - The investigator decides that the subject should be discontinued from the study.
    - If the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.
- Subject decision
    - The subject requests to be withdrawn from the study.

Subjects discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A subject 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 are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this 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.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

9.1.1.1. Validated Investigator's Global Assessment for AD (vIGA-AD)

The IGA used in this study, the vIGA-AD (referred to as the IGA throughout the protocol) measures the investigator's global assessment of the subject's overall severity of their AD, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification.

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Eczema Area and Severity Index Scores

The EASI assesses extent of disease at 4 body regions and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification each on a scale of 0 to 3. The EASI confers a maximum score of 72. The EASI evaluates 2 dimensions of AD: disease extent and clinical signs (Hanifin et al. 2001).

Body surface area affected by AD will be derived from data collected as part of the EASI assessment.

9.1.2.2. SCORing AD

The SCORing AD (SCORAD) index uses the rule of nines to assess disease extent and evaluates 6 clinical characteristics to determine disease severity: (1) erythema, (2) edema/papulation, (3) oozing/crusts, (4) excoriation, (5) lichenification, and (6) dryness. The SCORAD index also assesses subjective symptoms of pruritus and sleep loss. These 3 aspects: extent of disease, disease severity, and subjective symptoms combine to give a maximum possible score of 103 (Stalder et al. 1993; Kunz et al. 1997; Schram et al. 2012).

9.1.3. Health Outcomes and Quality-of-Life Measures

The subject self-reported questionnaires will be administered via either an electronic subject diary or via an electronic tablet and in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

9.1.3.1. Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) is a simple, 7-item, patient-administered scale that assesses disease severity in children and adults. Subjects respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the last week. Response categories include "No days," "1-2 days," "3-4 days," "5-6 days," and "Every day," with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0 to 28, with higher total scores indicating greater disease severity (Charman et al. 2004).

9.1.3.2. Itch Numeric Rating Scale

The Itch Numeric Rating Scale (NRS) is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing the "worst itch imaginable." Overall severity of a subject's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016).

9.1.3.3. Skin Pain Numeric Rating Scale

Skin Pain NRS is a subject-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing the "worst pain imaginable." Overall severity of a subject's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours.

9.1.3.4. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a simple, patient-administered, 10-item, validated, quality-of-life (QoL) questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include "not at all," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as 0. Scores range from 0 to 30, with higher scores indicating greater impairment of QoL. A DLQI total score of 0 to 1 is considered as having no effect on a subject's health-related QoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

9.1.4. Appropriateness of Assessments

All assessments utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant except Skin Pain NRS, which is currently being developed and validated according to regulatory guidances.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the subject to discontinue the IP before completing the study. The subject should be followed 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.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to IP, via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the IP, study device, and/or study procedure and the AE. The investigator answers "yes/no" when making this assessment. The investigator will record all relevant AE and SAE information in the eCRF.

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

If a subject's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged insubject hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in insubject hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the subject has signed the ICF and has received IP. However, if an SAE occurs after signing the ICF, but prior to receiving IP, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly 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 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. Subjects with a serious hepatic AE should have additional data collected using the hepatic safety eCRF.

Pregnancy (during maternal or paternal exposure to IP) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the subject disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

Injection site reactions and allergic/hypersensitivity reactions are AEs of special interest. In the event of an injection site reaction or allergic/hypersensitivity reaction, additional questions will be triggered in the eCRF to provide further details regarding the reaction.

In the event of anaphylaxis or generalized urticaria, additional laboratory samples should be collected after the subject has been stabilized (ideally 1 to 2 hours, and no more than 12 hours after the event), whenever possible. Follow-up samples should be obtained at the next scheduled visit or after 4 weeks, whichever is later. Specific instructions for the collection and handling of samples will be provided by the sponsor.

9.2.3. Complaint Handling

Lilly collects product complaints on IPs and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

9.3. Treatment of Overdose

In case of suspected overdose, hematology, chemistry, vital signs and oxygen saturation should be monitored and supportive care provided as clinically indicated. There is no known antidote for LY3375880.

9.4. Safety

Any clinically significant findings from ECG testing, physical examination, vital signs measurements, or laboratory measurements that result in a diagnosis and that occur after the subject receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.1. Electrocardiograms

A single 12-lead standard ECG will be obtained locally at Visit 1 and read by a qualified physician (the investigator or qualified designee) at the site to determine whether the subject meets entry criteria.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

9.4.2. Vital Signs

For each subject, vital signs should be measured according to the Schedule of Activities (Section 2).

9.4.3. Physical Exam

For each subject, a complete physical examination (excluding pelvic and rectal examinations unless clinically indicated) will be performed at Visit 1 (Screening). A symptom-directed physical examination may be performed at other visits as specified in the Schedule of Activities (Section 2) as clinically indicated.

9.4.4. Laboratory Tests

For each subject, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2). With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

9.4.5. Columbia Suicide Severity Rating Scale

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by appropriately trained site personnel. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

9.4.6. Self-Harm Supplement and Follow-Up Forms

Suicide-related events (behavior and/or ideations) will be assessed and evaluated with each administration of the C-SSRS. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors. If the number of behavioral events is greater than zero, it will lead to the completion of the self-harm follow-up form. The Self-Harm Follow-up form is a series of questions that provides a more detailed description of the behavior cases.

9.4.7. Chest X-ray and Tuberculosis Testing

Posteroanterior and lateral chest radiography will be performed at screening for all subjects unless these have been obtained within 90 days prior to initial screening and the radiographs or report is available for investigator review. Variations on the chest radiography view requirements will only be permitted if the country/local guidelines of care for standard TB screening differ from these protocol specifications.

All subjects will undergo a TB test at screening (TST or interferon γ release test). Refer to Exclusion Criterion [17] for details regarding TB testing.

See Section 6.4 for subjects who are rescreening for this study and have undergone radiography and/or TB testing as part of their initial screening.

9.4.8. Hepatitis B Virus DNA Monitoring

Subjects whose results are HBsAg negative and HBcAb positive (and/or HBsAb positive in Japan) at screening, will have an HBV DNA test performed by the central laboratory. Subjects whose results are HBV DNA negative (undetectable) may be enrolled into the study, according to investigator judgment, with HBV DNA monitoring as detailed in the Schedule of Activities (Section 2). If the result of the HBV DNA testing becomes positive at any time during the study, the subject will be permanently discontinued from IP (see Section 8.1) and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of subjects with hepatitis (for example, infectious disease physician or hepatologist) should be consulted. The timing of discontinuation from the study drug and any other immunosuppressant therapy should be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

9.4.9. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against the LY3375880. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity sample. All samples for immunogenicity should be taken predose. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

In addition, subjects who were deemed responders at Week 16 may be prompted to collect an immunogenicity sample at the first scheduled visit where loss of response is observed (i.e., EASI-25 was not achieved) in the maintenance period. This will allow an evaluation of ADA status at the time of retreatment for subjects randomized to placebo until loss of response during the maintenance period. To prevent unblinding of treatment regimen, all subjects who are deemed responders at Week 16 will have PK and immunogenicity collected upon loss of response.

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of the LY3375880 at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3375880.

Treatment-emergent ADA positive (TE ADA+) are defined in Section 10.2.6.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and ethical review boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the LY3375880. Any samples remaining after 15 years will be destroyed.

9.4.10. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. In the event that safety monitoring uncovers an issue that needs to be addressed by

unblinding at the group level, members of an internal assessment committee can view unblinded data and conduct additional analyses of the unblinded safety data. The internal assessment committee is composed of personnel who do not have direct site contact or data entry/validation responsibilities. Details are specified in the statistical analysis plan (SAP). In addition, the Safety Internal Review Committee and the Global Subject Safety expedited reporting team can also unblind at the individual SAE case level, when appropriate.

9.4.10.1. Hepatic Safety Monitoring

If a study subject experiences elevated ALT ≥3x ULN, ALP ≥2x ULN, or elevated TBL ≥2x ULN, liver testing should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Discontinuation criteria of IPs, either temporary interruption or permanent discontinuation, due to abnormal ALT, AST, TBL, or ALP, are detailed in Section 8.

Hepatic Safety Data Collection

Additional safety data should be collected via the hepatic eCRF if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2x ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

See Appendix 4 for a description of selected tests that may be obtained in the event of a treatment-emergent hepatic abnormality.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 4 mL each will be collected to determine the plasma concentrations of LY3375880. The actual date and time (24-hour clock time) of each dose and PK sampling blood draw will be recorded. It is essential that the actual times of dosing and sampling are recorded accurately. In addition, subjects who were deemed responders at Week 16 may be prompted to collect a PK sample at the first scheduled where loss of response is observed (i.e., EASI-25 was not achieved) in the maintenance period. This will support the evaluation of ADA status at the time of retreatment for subjects randomized to placebo until loss of response during the maintenance period. To prevent unblinding of treatment regimen, all subjects who are deemed responders at Week 16 will have PK and immunogenicity collected upon loss of response.

In addition to the planned PK sampling as described, a maximum of 2 samples may be collected at additional time points during the study 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 time [24-hour clock time] of each sampling will be recorded.

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

Bioanalytical samples collected to measure IP concentration will be retained for a maximum of 1 year following the last subject visit for the study.

9.6. Pharmacodynamics

Samples collected (as specified in the schedule of activities) to measure TARC, Periostin, IL-19 will be identified by the subject number (coded) and retained at a facility selected by Lilly or its designee for a maximum of 1 year following the last subject visit for the study at a facility selected by Lilly or its designee.

9.7. Pharmacogenomics

9.7.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) 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 response to LY3375880 and to investigate genetic variants thought to play a role in AD or associated diseases. Assessment of variable response 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 subject only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last subject visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3375880 or after LY3375880 becomes 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, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics (PD), mechanism of action, variability of subject response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Samples for biomarker research (serum, plasma, whole blood RNA, whole blood for epigenetics, and skin biopsies for mRNA expression profiling and immunohistochemistry) will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow. Blood samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3375880, pathways associated with AD or associated diseases, mechanism of action of LY3375880, and/or research method or in validating diagnostic tools or assay(s) related to AD or associated diseases.

Skin biopsy samples from AD lesions and adjacent nonlesional tissue will be collected and used to study biomarkers related to AD and/or related to the mechanism of action of LY3375880. Techniques used may include but are not limited to immunohistochemistry and microarray expression profiling. Samples may be used for exploratory microarray expression profiling or transcriptome sequencing. Detailed instructions for sample collection and handling will be provided by the sponsor. Samples will be sent to a sponsor-designated laboratory for immunohistochemistry.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last subject visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3375880 or after LY3375880 becomes commercially available.

9.9. Medical Resource Utilization and Health Economics

Health Economics and Medical Resource Utilization parameters will not be evaluated in this study.

10. Statistical Considerations

Approximately 200 subjects will be randomized at a 1:1:1:1 ratio in the blinded induction dosing period to LY3375880 50 mg, 150 mg, 600 mg, and placebo (50 subjects per dosing regimen).

Assuming 36% and 8% of subjects achieve an IGA score of 0 or 1 (clear or almost clear skin) and ≥2-point improvement from baseline at Week 16 for LY3375880 and placebo, respectively, pairwise comparisons to placebo have at least 90% power using a 2-sided Fisher's exact test at the 0.05 significance level, with no adjustment for multiple comparisons.

10.1. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent.
Safety	All randomized participants who take at least 1 dose of their assigned double-blind study treatment. Participants will be included in the treatment group they were randomized to.
Intent-to-Treat (ITT)	All randomized subjects, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.
Maintenance Period	All ITT subjects who received at least 1 dose of study treatment and have entered the maintenance period at Week 16 (Visit 8).

10.2. Statistical Analyses

10.2.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by Lilly or its designee.

Efficacy analyses will be conducted on the intent-to-treat (ITT) population. This set includes all randomized subjects, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.

Safety analyses will be conducted on the safety population. This set includes all data from all randomized subjects receiving at least 1 dose of the IP according to the treatment to which the subjects were randomized.

When reported, descriptive statistics will include the number of subjects, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures.

Treatment comparisons of discrete efficacy variables between LY3375880 and placebo will be made using a logistic regression analysis with treatment, baseline disease severity (IGA 3 versus 4), geographic region, and, if applicable, baseline scores (such as baseline EASI score for a comparison of EASI-75) in the model. The percentages, difference in percentages, and 95% confidence interval (CI) of the difference in percentages will be reported. Treatment-by-region interaction will be added to the logistic regression model of the primary and key secondary

variables as a sensitivity analysis. If this interaction is significant at a 2-sided 0.1 level, further inspection will be used to assess whether the interaction is quantitative (i.e., the treatment effect is consistent in direction but not size of effect) or qualitative (the treatment is beneficial for some but not all regions).

When evaluating continuous measures over time, a restricted maximum likelihood-based mixed-effects model of repeated measures (MMRM) will be used. The model will include treatment, baseline disease severity, geographic region, visit, and treatment-by-visit interaction as fixed categorical effects and, if a baseline score for the measure is available, baseline score and baseline score-by-visit interaction as fixed continuous effects. An unstructured (co)variance structure will be used to model the between- and within-subject errors. If this analysis fails to converge, other structures will be tested. The Kenward–Roger method will be used to estimate the degrees of freedom. Type III sums of squares for the least squares means will be used for the statistical comparison; 95% CI will also be reported. Contrasts will be set up within the model to test treatment groups at specific time points of interest. Further details on the use of MMRM will be described in the SAP.

Fisher's exact test will be used for the AEs, discontinuation, and other categorical safety data for between-treatment group comparisons. Continuous vital signs and other continuous safety variables including laboratory variables will be analyzed by an analysis of covariance with treatment and baseline value in the model.

The Kaplan–Meier product limit method will be used to estimate the survival curves for time-to-event variables.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 with no control for multiple comparisons, unless otherwise stated.

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 clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.2.1.1. Missing Data Imputation

- Nonresponder imputation (NRI): All subjects who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the analysis of categorical efficacy variables at discontinuation and subsequent visits. Subjects who receive rescue therapy will be analyzed as nonresponders at rescue and subsequent visits.
- MMRM: Continuous variables will be assumed to be missing after rescue or discontinuation for which an MMRM analysis will be performed.

10.2.1.2. Maintenance Period Considerations

For maintenance period efficacy measures, unless otherwise stated, baseline will be the last available value before the initial randomization in the induction period, which in most cases will be the value recorded at Week 0 (Visit 2).

For maintenance period safety measures, unless otherwise stated, baseline will be the last available value before the initial dose in the maintenance period, which in most cases will be the value recorded at Week 16. Additional information on baseline for efficacy and safety analyses will be available in the SAP.

Maintenance phase analyses are exploratory; therefore, only descriptive statistics will be provided. Change from baseline and 95% CI will be calculated by treatment for continuous variables. The proportion and 95% CI will be reported by treatment for categorical variables.

Additional sensitivity analyses for the primary and key secondary endpoints may be done and will be specified in the SAP.

10.2.2. Treatment Group Comparability

10.2.2.1. Subject Disposition

All subjects who discontinue from the study or the study treatment will be identified, along with their reason for discontinuation. Reasons for discontinuation from the study will be summarized by treatment group.

10.2.2.2. Subject Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures.

10.2.2.3. Concomitant Therapy

Concomitant medications will be summarized for subjects who enter each treatment period and will be presented by anatomical therapeutic chemical drug classes using the latest version of the WHO drug dictionary.

10.2.2.4. Treatment Compliance

Treatment compliance with IP will be summarized for subjects who enter the Induction and Maintenance periods. A subject will be considered as having missed the visit if he or she fails to attend for administration of the IP within the required treatment window as defined in the Schedule of Activities (Section 2). Overall compliance with therapy is defined to be missing no more than 20% of the expected doses within the protocol-defined dosing interval and not missing 2 consecutive doses. The proportion of subjects who demonstrate overall compliance during the Induction Period will be compared between treatment groups using Fisher's exact test.

10.2.3. Efficacy Analyses

10.2.3.1. Primary Analyses

The primary efficacy measure is the binary outcome of response defined as IGA score of 0 or 1 (clear or almost clear skin) and ≥2-point improvement from baseline at Week 16. Primary analysis will be conducted using the previously described logistic regression model.

10.2.3.2. Secondary Analyses

The previously described logistic regression model will be used to analyze the proportion of subjects achieving the following:

- IGA of 0 at Week 16
- EASI-50, EASI-75, and EASI-90 at Week 16, where EASI-75 and EASI-90 are defined as having an improvement of at least 75% and 90% from baseline, respectively.
- SCORAD75 and SCORAD90 at Week 16, where SCORAD75 and SCORAD90 are defined as having an improvement of at least 75% and 90% from baseline, respectively.
- IGA of 0 or 1 at Week 52

The previously described MMRM model will be used to analyze mean change from baseline for:

- EASI score
- SCORAD score

10.2.3.3. Exploratory Analyses

Improvement in signs and symptoms, health outcome measures, and QoL measures (total scores, item scores, and derivations) at each time point collected (induction and maintenance) will be summarized using descriptive statistics and the previously described models for discrete and continuous endpoints. The Kaplan–Meier product limit method will be used to estimate the survival curves for time-to-event variables such as loss of response and maintenance of response.

10.2.4. Safety Analyses

All safety data will be descriptively summarized for the safety population by treatment group and analyzed using the methods described in Section 10.2.1.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities and summarized by system organ class, preferred term, severity, and relationship to IP. A TEAE is defined as an event that first occurred or worsened in severity after baseline. For each event classification term, the number of subjects experiencing a TEAE with that classification term will be tabulated.

Treatment-related TEAEs are defined as events that are indicated by the investigator on the eCRF to be related to treatment. For events that are gender specific, the denominator and computation of the percentage will include only subjects from the given gender.

10.2.5. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of PK/PD data will be performed using a nonlinear mixed-effect modeling approach as implemented in NONMEM software on a computer that meets or exceeds the minimum system requirements for this program. It is possible that other validated equivalent software programs may be used if appropriate. The version of any software used for the analysis will be documented. Population PK analyses will be performed to characterize the PK of LY3375880. These analyses will include model-based and graphical evaluations of the data. Estimates of PK model parameters and covariate effects and corresponding CIs will be reported. Analyses of exposure–response relationships will be conducted using both exploratory graphical approaches and model-based approaches. Exploratory graphical analysis approaches for categorical clinical endpoints (e.g., IGA, EASI, etc.) may consist of graphs showing the percentage of subjects that achieve the clinical endpoint at different percentiles (e.g., quartiles) of exposure of LY3375880 at Week 16. Measures of exposure may include population PK estimated average steady-state concentrations (Css, avg) or observed trough concentrations at the time of the clinical endpoint. Model-based analyses of the categorical clinical endpoints will utilize population exposure–response logistic regression models, where maximum effect (E_{max}) or other model structures may be used to relate exposure to the probability of achieving the endpoint. These models may be used to evaluate subject factors that may impact the relationship between exposure and the probability of achieving the endpoint. Longitudinal exposure–response models for EASI scores or response rates may be developed, which relate the time course and magnitude of LY3375880 exposure to the time course and magnitude of EASI response.

Exploratory analyses examining the relationships between LY3375880 exposure and PD biomarker responses may be conducted. Additional analyses may be conducted if they are deemed appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

10.2.6. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and with TE ADA+ to LY3375880 will be tabulated. TE ADA+ 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 those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADA were detected at baseline (treatment-boosted ADA). For the TE ADA+ subjects, time to first TE ADA+ result, distribution of maximum titers, and titer evolution over time will be described. The frequency of neutralizing antibodies will be tabulated in TE ADA+ subjects. The relationship between the presence of antibodies to LY3375880, IL-33 target engagement, PK parameters, efficacy, and safety parameters will be assessed, as well as the potential impact of rechallenge on ADA responses.

10.2.7. Other Analyses

10.2.7.1. Health Economics

The health outcome measures will be analyzed using methods described for continuous or categorical data as described for efficacy measures in Section 9.1.

10.2.7.2. Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoint defined as IGA score of 0 or 1 (clear or almost clear skin) and ≥2-point improvement from baseline at Week 16 using NRI for the ITT Population. Subgroups to be evaluated may include region, age, sex, race, baseline IgE levels, baseline levels of type II immune response analytes, etc.

A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. If the interaction is statistically significant at $\alpha = 0.10$, the nature of the interaction will be explored.

Definitions for the levels of the subgroup variables, the analysis methodology, and any additional subgroup analyses will be defined in the SAP. This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

10.2.8. Interim Analyses

Analysis for the primary database lock will be conducted when all patients have completed the induction phase (or discontinued induction treatment). At least 1 interim analysis prior to analysis for the primary database lock will be conducted when approximately 40% to 60% patients have completed the induction phase (or discontinued induction treatment). All interim analyses will be used to support planning activities associated with the development program and to aid development of PK/PD modeling. No adjustment of Type I error will be performed.

The assessment will be conducted by an internal assessment committee with a limited number of prespecified team members who do not have direct site contact or data entry/validation responsibilities. A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. To minimize bias, the SAP and PK/PD analysis plan will be finalized and approved before unblinding. Unblinding details are specified in the SAP. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses may be conducted to review unblinded safety data; the analyses will be conducted and reviewed by an internal assessment committee composed of personnel who do not have direct site contact or data entry/validation responsibilities. Details are specified in the SAP.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AD	atopic dermatitis
ADA	antidrug antibodies
AE	adverse event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject 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.
BSA	body surface area
CI	confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EASI-25	25% reduction in the Eczema Area and Severity Index score
EASI-50	50% reduction in the Eczema Area and Severity Index score
EASI-75	75% reduction in the Eczema Area and Severity Index score

EASI-90	90% reduction in the Eczema Area and Severity Index score
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IGA	Investigator's Global Assessment
IL	interleukin
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.
INR	international normalized ratio
IP	Investigational product. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

IV	intravenous
IWRS	interactive web-response system
JAK	Janus kinase
LSM	least squares mean
LTBI	latent tuberculosis infection
mAb	monoclonal antibody
MMF	mycophenolate mofetil
MMRM	mixed-effects model of repeated measures
MTX	methotrexate
NRI	nonresponder imputation
NRS	Numeric Rating Scale
PCR	polymerase chain reaction
PD	pharmacodynamics(s)
PDE-4 inhibitor	phosphodiesterase type 4 inhibitor
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure
PPD	purified protein derivative
Q4W	every 4 weeks
QoL	quality-of-life
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	SCORing AD
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TBL	total bilirubin

TCNI	topical calcineurin inhibitor
TCS	topical corticosteroids
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, which does not necessarily have to have a causal relationship with this treatment.
Th2	type 2 helper T-cell
TST	tuberculin skin test
ULN	upper limit of normal
vIGA-AD	validated Investigator's Global Assessment for atopic dermatitis
WHO	World Health Organization

Appendix 2. Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Bicarbonate
Mean cell hemoglobin	Chloride
Mean cell hemoglobin concentration	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Platelets	Alkaline phosphatase
	Alanine aminotransferase (ALT)
Absolute counts of:	Aspartate aminotransferase (AST)
	Gamma-glutamyl transferase (GGT)
Neutrophils, segmented	Blood urea nitrogen (BUN)
Neutrophils, juvenile (bands)	Creatinine with calculated eGFR
Lymphocytes	Calcium
Monocytes	Phosphorus
Eosinophils	Glucose (random, fasting)
Basophils	Albumin
	Total protein
Urinalysis[a,b,c]	Fasting lipid profile[d]
Specific gravity	
	Other Tests[a]
pH	Hepatitis B surface antigen (HBsAg)[e]
Protein	Anti-Hepatitis B core antibody (HBcAb)[e]
Glucose	HBV DNA[f]
Ketones	Anti-Hepatitis B surface antibody (HBsAb)[e]
Bilirubin	Human immunodeficiency virus (HIV)[e]
Urobilinogen	Hepatitis C antibody[e,g]
Blood	Exploratory (Long Term) storage samples (serum, plasma)
Nitrite	
	DNA for epigenetics, and mRNA)
	Pharmacogenetic sample
	Pregnancy Test[h]
	Follicle-stimulating hormone[e,i]
	Serum immunoglobulin (total and allergen-specific IgE)
	QuantiFERON®-TB Gold or T-SPOT®.TB[j]
	PPD (local testing)
	LY3375880 plasma levels
	Target engagement (Total IL-33)
	Immunogenicity
	IL-19
	TARC
	Periostin

Abbreviations: eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; IgE = immunoglobulin E; IL = interleukin; PPD = purified protein derivative; RBC = red blood cell; TARC = thymus and activation-regulated chemokine; TB = tuberculosis; WBC = white blood cell.

[a] Assayed by sponsor-designated laboratory.
[b] Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.
[c] Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.
[d] Fasting lipid profile. Subjects should not eat or drink anything except water for 12 hours prior to test. If a subject attends these visits in a nonfasting state, this will not be considered a protocol violation.
[e] Test required at Visit 1 only to determine eligibility of subject for the study.
[f] For subjects who meet criteria for HBV DNA testing at screening and HBV DNA monitoring in the study (Section 9.4.8).
[g] A positive hepatitis C antibody result will be confirmed with an alternate hepatitis C method.
[h] For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a local urine pregnancy test will be performed at Visit 2 and subsequent visits according to the study schedule. If required per investigator judgment, local regulations, and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.
[i] For female subjects to confirm post-menopausal status according to Inclusion Criterion [9].
[j] The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring the following:

- that the subject understands the potential risks and benefits of participating in the study.
- that informed consent is given by each subject. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product. A new ICF and subject number must be obtained if a subject will be rescreened after being screen failed from the study.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

Appendix 3.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- relevant curricula vitae.

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.4. Investigator Information

Physicians with an appropriate specialty and training will participate as investigators in this clinical trial.

Appendix 3.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.6. Final Report Signature

Lilly will select a qualified investigator from among investigators participating in the design, conduct, and/or analysis of the study to serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.

- Review and verify data reported to detect potential errors.

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

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

An electronic data capture system (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.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (questionnaires, scales, self-reported diary data, rating scales, etc.) must be directly recorded by the subject/investigator site personnel, into an instrument (hand-held smart phone or tablet). The eCOA data will serve as the source documentation and the investigator must not maintain a separate written or electronic record of these data.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive 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/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with the Lilly, its designee, or the clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline phosphatase isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

Bacterial
Bartonellosis (disseminated disease only)
Campylobacteriosis (invasive disease only)
Legionellosis
Listeria monocytogenes (invasive disease only)
Nocardiosis
Tuberculosis
Non-tuberculous mycobacterial disease
Salmonellosis (invasive disease only)
Shigellosis (invasive disease only)
Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral
BK virus disease including polyomavirus-associated nephropathy
Cytomegalovirus disease
Hepatitis B virus reactivation
Hepatitis C virus progression
Herpes simplex (invasive disease only)
Herpes zoster (any form)
Post-transplant lymphoproliferative disorder (Epstein–Barr virus)
Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus [excluded from the study]
Fungal
Aspergillosis (invasive disease only)
Blastomycosis
Candidiasis (invasive disease or pharyngeal)
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Paracoccidioides infections
Penicillium marneffei
Pneumocystis jirovecii (formerly *Pneumocystis carinii*)
Sporothrix schenckii
Other invasive fungi: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Protozoan
Leishmaniasis (visceral only)
Microsporidiosis
Toxoplasmosis
Trypanosoma cruzi infection (Chagas disease) (disseminated disease only)

This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy, for the purposes of Exclusion Criterion [22]. This list is not exhaustive. Investigators should use their clinical judgment, as well as discussion with the Lilly-designated medical monitor, in determining if other infections may be considered opportunistic, for the purposes of Exclusion Criterion [22].

Consider tuberculosis (TB) and non-TB mycobacterial disease to be opportunistic infections in the context of biologic therapy. See Section 6.2 for the approach to screening for latent TB infection within the study. Subjects with any history of **active** TB are excluded from the study, regardless of previous or current TB treatments.

Source: Adapted from Winthrop et al. (2015).

Appendix 6. American Academy of Dermatology: Criteria for the Diagnosis and Assessment of Atopic Dermatitis

Features to be considered in diagnosis of subjects with AD:

Essential Features—Must be present:

- pruritus
- eczema (acute, subacute, chronic)
  - typical morphology and age-specific patterns*
  - chronic or relapsing history

*Patterns include the following:

1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions

Important Features—Seen in most cases, adding support to the diagnosis:

- early age of onset
- atopy
  - personal and/or family history
  - Immunoglobulin E reactivity
- xerosis

Associated Features—These clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used for defining or detecting AD for research and epidemiologic studies:

- atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
- keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- ocular/periorbital changes
- other regional findings (e.g., perioral changes/periauricular lesions)
- perifollicular accentuation/lichenification/prurigo lesions

Exclusionary Features—It should be noted that a diagnosis of AD depends on excluding conditions, such as:

- scabies
- seborrheic dermatitis
- contact dermatitis (irritant or allergic)

- ichthyoses
- cutaneous T-cell lymphoma
- psoriasis
- photosensitivity dermatoses
- immune deficiency diseases
- erythroderma of other causes

Source: Eichenfield et al. (2014).

Appendix 7. Protocol Amendment I9N-MC-FCAB(b) Summary: Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3375880 in Adult Subjects with Moderate-to-Severe Atopic Dermatitis: The ADmIRe Study

Overview

Protocol I9N-MC-FCAB Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3375880 in Adult Subjects with Moderate-to-Severe Atopic Dermatitis: The ADmIRe Study has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The major overall changes and rationale for the changes made to this protocol are as follows:

Section	Change	Rationale
6.1 Inclusion Criteria	For Inclusion Criterion [4]. Disease activity requirements of IGA ≥3, EASI ≥16, and BSA ≥10% will be required at randomization only instead of requiring them at both screening and randomization.	The protocol requires a washout period during screening for patients currently using TCS and other treatments for AD, which can result in an increase in disease activity over the course of the screening period. Therefore, the disease activity criteria requirements were removed at screening to eliminate unnecessary restrictions to enrollment. This will not affect interpretation of efficacy data since the requirements remain the same as at baseline. Patient safety is not impacted by this change.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Inclusion Criteria:

[4] Have moderate-to-severe AD, including all of the following:

a. Eczema Area and Severity Index (EASI) score ≥16 ~~at screening (Visit 1) and~~ at randomization (Visit 2).

b. IGA score of ≥3 ~~at screening (Visit 1) and~~ at randomization (Visit 2).

c. ≥10% of body surface area (BSA) involvement ~~at screening (Visit 1) and~~ at randomization (Visit 2).

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