Protocol Addendum J4E-MC-FR01 (c)

A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

NCT05911841

Approval Date: 06-May-2024

Title Page

Master Protocol Title: A Master Protocol for Randomized, Controlled, Phase 2 Clinical Trials of Multiple Interventions for the Treatment of Adults with Moderate-to-Severe Atopic Dermatitis

Master Protocol Number: J4E-MC-IMMB(b)

ISA Title: A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

ISA Number: J4E-MC-FR01

ISA Amendment Number: c

Compound: LY3454738

ISA Brief Title: A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

Study Phase: 2

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Numbers:

IND: 163615

EU trial number: 2022-502888-38-00

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

Document ID: VV-CLIN-150737

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	12-Sep-2023
Amendment (a)	13-Mar-2023
Original Protocol	09-Dec-2022

Amendment [c]

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or rights of the study participants
- reliability and robustness of the data generated in the clinical study, and
- conduct or management of the trial.

Overall Rationale for the Amendment

The main purpose of this amendment is to

- collect more data in CCI [redacted] patients, and
- revise the interim plan.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis (Objectives, Endpoints, and Estimands) 3. Objectives, Endpoints, and Estimands	The secondary endpoint for efficacy is CCI [redacted] studied for that objective. Added additional secondary objective and endpoint for CCI [redacted] participants as "Proportion of CCI [redacted] EASI-75 at Week 16."	To collect more information about CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
9.3.3. Secondary Endpoints/Estimands Analysis	Added the analyses methods [redacted] EASI-75 at Week 16.	
1.1. Synopsis (Study Population) 4.1. Overall Design 9.5. Sample Size Determination	(Text with strikethrough is replaced by text in bold) The text is updated to include the change in study population which is an addition of 60 [redacted]	To collect more information about [redacted] in atopic dermatitis.
9.2. Analyses Sets	Added [redacted] population in Maintenance Analysis Set.	
[redacted]		
9.5. Sample Size Determination	With the updated planned sample size, the text is updated	

Section # and Name	Description of Change	Brief Rationale
	as "an EASI-75 response at Week 16 of CCI [redacted] ~~98%~~ power for pairwise comparisons with placebo."	
1.1. Synopsis (Study Population) 9.5. Sample Size Determination	(Text with strikethrough is replaced by text in bold) "~~Up to~~ CCI [redacted]	To allow to over enroll if needed.
1.1. Synopsis (Number of Participants) 9.5. Sample Size Determination	(Text with strikethrough is deleted) "~~Up to~~ approximately 260 participants will be randomized to study intervention."	
1.3. Schedule of Activities	A new row for estimated glomerular filtration rate (eGFR) is added which will be determined at Week 16, Week 40, and ED Visits.	To monitor kidney function throughout the study.
4.1. Overall Design	The randomization text is updated and the text below is added to include the changes in the CCI [redacted]	CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted]	
4.1. Overall Design 9.5. Sample Size Determination	The table is revised to include the updated planned sample CCI CCI [redacted]	

CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
CCI		

Table of Contents

1. Protocol Summary

1.1. Synopsis

ISA Title: A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

ISA Brief Title: A Phase 2, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of LY3454738 in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis

Regulatory Agency Identifier Number(s):

IND: 163615

EU trial number: 2022-502888-38-00

Rationale:

LY3454738 is a humanized IgG4-variant monoclonal antibody (mAb) that binds to and agonizes the human inhibitory checkpoint CD200R. CD200R is expressed on many cell types involved in the pathogenesis of atopic dermatitis (AD). CCI [redacted] CCI [redacted] Activating CD200R with an agonist mAb is a potential therapeutic strategy for AD and other inflammatory disorders. This study will evaluate the safety and efficacy of LY3454738 in adults with moderate-to-severe AD.

Study J4E-MC-FR01 (FR01) is a Phase 2 study to evaluate the efficacy and describe the safety of LY3454738 in adult patients with moderate-to-severe AD. Results of this study will be used to guide the dose selection for future studies and to further characterize the benefit/risk profile of LY3454738. Study FR01 is an ISA of the master IMMB protocol.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary To compare the efficacy of LY3454738 versus placebo as measured by EASI-75 in the treatment of CCI moderate-to-severe AD	Proportion of participants achieving EASI-75 at Week 16
CCI	
Estimands The primary estimand is treatment difference between each dosing regimen of LY3454738 and placebo CCI CCI in achieving a successful response at Week 16 without use of any prohibited or rescue medication for AD or early permanent discontinuation.	

Abbreviations: AD = atopic dermatitis; CCI EASI = Eczema Area and Severity Index; CCI CCI CCI

Overall Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient dose-ranging study to evaluate the efficacy and describe the safety of LY3454738 as compared to placebo during a 16-week induction period in adult participants with moderate-to-severe AD using these induction dosing regimens given CCI

- LY3454738 CCI mg CCI
- LY3454738 CCI mg CCI
- LY3454738 CCI mg CCI and
- placebo CCI

The blinded CCI-week maintenance treatment period begins CCI CCI Participants having at least an CCI response at Week 16 will receive a maintenance dosing regimen, also CCI as listed here.

Week 16 responders who were originally randomized to this induction regimen...	Will receive this maintenance regimen:
LY3454738 CCI mg CCI	by rerandomization in CCI ratio: LY3454738 CCI mg CCI or placebo
LY3454738 CCI mg CCI	LY3454738 CCI mg CCI
LY3454738 CCI mg CCI	LY3454738 CCI mg CCI
placebo	placebo CCI

The maintenance period includes an "escape arm" for participants whose EASI response suggests the need for a higher dose. The escape therapy is LY3454738 CCI mg CCI
A participant will receive this escape therapy under the conditions listed here.

Begin LY3454738 CCI mg CCI as escape therapy...	if the participant...
At Week 16	has not achieved an CCI response at Week 16.
At Weeks CCI	has not achieved an CCI response at Weeks CCI

A participant receiving escape therapy will continue receiving escape therapy through the last dosing visit of the study (Week CCI unless the participant is discontinued from study intervention.

Topical rescue medication is permitted (not required) in the induction period from Week 8 until Week 16 for participants who do not achieve an CCI response. In the maintenance period, use of topical rescue medication is permitted (not required) from Week CCI until the end of the study for participants who do not achieve an CCI response. Participants who receive at least 2 doses of escape therapy at 2 consecutive visits will be permanently discontinued from study intervention if they fail to achieve an CCI response.

This study design includes investigator and participant blinding (masking). An internal assessment committee (IAC) will exist for the purpose of reviewing safety data in an unblinded fashion.

In summary, Study FR01 includes 4 study periods over a total study duration of approximately CCI weeks:

- Screening: from CCI days prior to randomization at Week 0 (Study Day 1)
- Treatment Period – Induction: from randomization at Week 0 (Study Day 1) through assessments at Week 16
- Treatment Period – Maintenance: from dose administration at Week 16 CCI CCI , and
- Posttreatment Follow-Up: 2 visits, the last visit being CCI after randomization CCI .

Brief Summary:

Activating CD200R with an agonist monoclonal antibody is a potential therapeutic strategy for atopic dermatitis and other inflammatory disorders. CCI CCI

The purpose of this study is to measure improvement in atopic dermatitis signs and symptoms after treatment with various dosing regimens of CCI administered LY3454738 compared to placebo in adult participants with moderate-to-severe atopic dermatitis.

- The LY3454738 dosing regimens to be compared to placebo in this study are these:

Induction Period				Maintenance Period			
LY3454738 CCI	mg CCI			LY3454738 CCI	mg CCI		
LY3454738 CCI	mg CCI			LY3454738 CCI	mg CCI		
LY3454738 CCI	mg CCI			LY3454738 CCI	mg CCI		

- The total study duration for a participant is approximately CCI weeks, inclusive of the screening period, treatment periods, and posttreatment follow-up period.
- Treatment is administered from Study Day 1 (randomization visit [Week 0]) through the last dose given at Week CCI in the maintenance period.
- After Study Day 1, the visit frequency is approximately CCI for the first 16 weeks, specifically, at Weeks CCI CCI Note: Not every visit includes administration of a treatment dose. Posttreatment follow-up visits occur at Week CCI CCI

Study Population:

The study population of Study FR01 includes adult male or female participants from 18 to 70 years of age, inclusive, who have a diagnosis of atopic dermatitis which is moderate to severe as measured by

- Eczema Area and Severity Index (EASI) score CCI
- vIGA-AD® score ≥3, and
- ≥10% of body surface area (BSA) involvement (per EASI BSA).

Based on the entry criteria of the master IMMB protocol, participants in Study FR01 must also be candidates for systemic therapy and have a history of inadequate response to, or intolerance to, topical medications.

Participants will be excluded from Study FR01 if they

- have used certain atopic dermatitis treatments during a specified time period ("washout period") before the first dose of study intervention
- are unstable with respect to use of chronic treatments to improve sleep, and
- are unsuitable for study participation due to medical history or a current serious health condition.

CCI

Number of Participants:

Approximately 260 participants will be randomized to study intervention.

Intervention Groups and Duration:

The study includes 4 periods over a total study duration of approximately CCI weeks. These are the treatment groups from randomization at Week 0 and until Week 16:

- LY3454738 CCI mg CCI
- LY3454738 CCI mg CCI
- LY3454738 CCI mg CCI and
- placebo CCI

Participants having at least an CCI response at Week 16 will receive a maintenance dosing regimen, as listed here.

Week 16 responders who were originally randomized to this induction regimen...	**Will receive this maintenance regimen:**
LY3454738 CCI mg CCI	by rerandomization in CCI ratio: LY3454738 CCI mg CCI or placebo
LY3454738 CCI mg CCI	LY3454738 CCI mg CCI
LY3454738 CCI mg CCI	LY3454738 CCI mg CCI
placebo	placebo CCI

Maintenance dosing continues up to and including Week CCI

Participants will receive LY3454738 CCI mg CCI as "escape therapy" if they

- have not achieved an CCI response at Week 16, or
- have not achieved an CCI response at Weeks CCI

Once started, escape therapy continues through the last dosing visit of the maintenance period.

Topical rescue medication is permitted from Week 8 until Week 16 for participants who do not achieve an CCI response; topical rescue medication started during the induction period should be stopped at, or before, Week 16. Likewise, during the maintenance period, topical rescue medication is permitted from Week CCI until the end of the study for participants who do not achieve an CCI response.

Ethical Considerations of Benefit/Risk:

Based on available clinical and nonclinical data, there are no anticipated risks that would require safety monitoring in this study beyond what is typical for clinical studies involving humanized mAbs. The administration of therapeutic monoclonal antibodies to humans can be associated with CCI
CCI
CCI
CCI Efficacy results from a Phase 1 study support the hypothesis that LY3454738 has the potential to treat atopic dermatitis. Taking into account the measures taken to minimize risk to participants in this study, and in the context of the cumulative knowledge of LY3454738, the benefit/risk balance for participants in this Phase 2 study is assessed to be acceptable.

Data Monitoring Committee: Yes (Internal Assessment Committee).


CCI

1.3. Schedule of Activities (SoA)

Table 1. Activities for screening/baseline and induction treatment periods of Study J4E-MC-FR01.
For activities at unscheduled visit or early discontinuation visit, see Table 2.

Week	CCI										**Comment**
Study day											Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	CCI Study Day 1	—	±1	±3	±3	±3	±3	±3	±3	±3	±3	Minimum interval between Visit 401 of the master IMMB protocol and Study Day 1: • Participants doing CCI 15 days • All other participants: 8 days
CRF visit number	V0		CCI									
Consent and demographics												
Informed consent	(X)											Signed, documented consent for ISA FR01 must be obtained before any ISA-specific tests or procedures are performed. Relevant ICF may be signed up to 90 days before Study Day 1.
Inclusion and exclusion criteria: confirmation of eligibility		X										Inclusion and exclusion criteria of both the master IMMB protocol and this ISA must be confirmed before participant is randomized to a study intervention and receives a first dose. See Section 5 of this ISA. See also Section 5 of the master IMMB protocol.
Prespecified medical history		X										Eye Disease History form.
Concomitant medications		X	X	X	X	X	X	X	X	X	X	Rescue medication and background emollients are documented as concomitant medications.
Adverse events (AEs)		X	X	X	X	X	X	X	X	X	X	AE collection begins when the master protocol ICF is signed. CCI events will be solicited at each visit. For AESIs, additional data are collected. See Section 8.3.1.
Physical evaluation												
Weight		X									X	

Table 1. Activities for screening/baseline and induction treatment periods of Study J4E-MC-FR01.
For activities at unscheduled visit or early discontinuation visit, see Table 2.

Week	CCI										**Comment**
Study day											Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	CCI Study Day 1	—	±1	±3	±3	±3	±3	±3	±3	±3	±3	Minimum interval between Visit 401 of the master IMMB protocol and Study Day 1: • Participants doing CCI 15 days • All other participants: 8 days
CRF visit number	V0		CCI									
Symptom-directed physical assessment		X									X	Perform as shown here and as needed based on participant status and standard of care. May be performed by qualified personnel per local regulations. Assess for TB risk factors, and for signs and symptoms of active TB, including an assessment of peripheral lymph nodes. See Sections 8.2.2 and 8.2.8 of the master IMMB protocol.
Vital signs		X	X	X	X	X	X	X	X	X	X	Includes pulse rate, blood pressure, respiratory rate, and body temperature. Measured after the participant has been sitting at least 5 minutes. See Section 8.2.1 of the master IMMB protocol.
ECG 12-lead (single) (local)											X	A local ECG will be collected according to instructions in Section 8.2.4 of the master IMMB protocol.
Patient-reported outcomes (electronic)												Complete prior to any clinician-administered assessments.
Dermatology Life Quality Index (DLQI)		X			X		X		X		X	
Patient-Oriented Eczema Measure (POEM)		X			X		X		X		X	
SCORing Atopic Dermatitis (subjective) (SCORAD)		X	X	X	X		X		X		X	

Table 1. Activities for screening/baseline and induction treatment periods of Study J4E-MC-FR01. For activities at unscheduled visit or early discontinuation visit, see Table 2.												
Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	CCI Study Day 1	—	±1	±3	±3	±3	±3	±3	±3	±3	±3	Minimum interval between Visit 401 of the master IMMB protocol and Study Day 1: • Participants doing CCI 15 days • All other participants: 8 days
CRF visit number	V0		CCI									
Atopic Dermatitis Control Tool (ADCT)		X			X		X		X		X	
Hospital Anxiety Depression Scale (HADS)		X			X		X		X		X	
Patient-reported outcomes (paper)												
Asthma Control Questionnaire-5 (ACQ-5)		X									X	
Clinician-administered assessments (electronic)												
vIGA-AD		X	X	X	X		X		X		X	
Eczema Area and Severity Index (EASI)		X	X	X	X		X		X		X	
SCORing Atopic Dermatitis (objective) (SCORAD)		X	X	X	X		X		X		X	
Fitzpatrick Scale of Skin Phototypes		X										
Clinician-administered assessments (paper)												
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Assessed		X			X		X		X		X	AE collection should occur prior to collection of the C-SSRS. Adapted for the assessment of ideation and behavior categories only.

Table 1. Activities for screening/baseline and induction treatment periods of Study J4E-MC-FR01.
For activities at unscheduled visit or early discontinuation visit, see Table 2.

Week	CCI										**Comment**
Study day											Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	CCI Study Day 1	—	±1	±3	±3	±3	±3	±3	±3	±3	±3	Minimum interval between Visit 401 of the master IMMB protocol and Study Day 1: • Participants doing CCI 15 days • All other participants: 8 days
CRF visit number	V0		CCI									
Participant diary (electronic)												
CCI												
Diary dispense												Diary is dispensed during Visit 401 of the master IMMB protocol. Diary contains the following assessments: CCI CCI Atopic Dermatitis Sleep Scale, and Skin Pain Numeric Rating Scale.
Diary review		X	X	X	X	X	X	X	X	X	X	Diary contains the following assessments: CCI CCI Atopic Dermatitis Sleep Scale (ADSS), and Skin Pain Numeric Rating Scale (Skin Pain NRS).

Table 1. Activities for screening/baseline and induction treatment periods of Study J4E-MC-FR01.
For activities at unscheduled visit or early discontinuation visit, see Table 2.

Week	CCI										**Comment**
Study day											Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	CCI Study Day 1	—	±1	±3	±3	±3	±3	±3	±3	±3	±3	Minimum interval between Visit 401 of the master IMMB protocol and Study Day 1: • Participants doing CCI 15 days • All other participants: 8 days
CRF visit number	V0		CCI									
Diary return		(X)										Collect diary only from participants who are not eligible for randomization (screen failed).
Participant education												
CCI												
Diary education	(X)									X		Education is provided at Visit 401 of the master IMMB protocol and as shown for this ISA. Additional education can be provided as needed at any time.
Laboratory tests and sample collections												Collect before dosing unless otherwise specified.
Hematology		X			X		X		X		X	
Clinical chemistry		X			X		X		X		X	
Urine or serum pregnancy test (local)		X			X		X		X		X	For WOCBP, a pregnancy test must be performed, with the result available **within 24 hours** prior to dosing (see Section 8.2.7 of this ISA and Section 8.2.7 of the master IMMB protocol). Additional pregnancy tests should be performed at any time if a menstrual period is missed, or there is clinical suspicion of pregnancy, or as required by local law or regulation.

Table 1. Activities for screening/baseline and induction treatment periods of Study J4E-MC-FR01.
For activities at unscheduled visit or early discontinuation visit, see Table 2.

Week	CCI										**Comment**
Study day											Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	CCI Study Day 1	—	±1	±3	±3	±3	±3	±3	±3	±3	±3	Minimum interval between Visit 401 of the master IMMB protocol and Study Day 1: • Participants doing CCI 15 days • All other participants: 8 days
CRF visit number	V0		CCI									
Urinalysis		X									X	
Estimated glomerular filtration rate (eGFR)											X	Calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2021).
Hepatitis B virus (HBV) DNA		X							X			Only for participants who are anti-HBc positive at Visit 401 (see Section 8.2.9 of the master IMMB protocol).
CCI												

Table 1. Activities for screening/baseline and induction treatment periods of Study J4E-MC-FR01.
For activities at unscheduled visit or early discontinuation visit, see Table 2.

Week	CCI										**Comment**
Study day											Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	CCI Study Day 1	—	±1	±3	±3	±3	±3	±3	±3	±3	±3	Minimum interval between Visit 401 of the master IMMB protocol and Study Day 1: • Participants doing CCI 15 days • All other participants: 8 days
CRF visit number	V0		CCI									
Immunogenicity (ADA) samples		X	X		X				X		X	On dosing visits, collect samples before dosing. Collect additional samples at specified times relative to onset of CCI events (see Section 8.3.1.1 and Attachment 1, Section 10.1.2).
Stored samples												
Genetics sample		X										Sample can be obtained at or after Study Day 1.
CCI												
Randomization and dosing-related activities												
Register visit with IWRS		X	X	X	X	X	X	X	X	X	X	
Randomization to study intervention via IWRS		X										
Rerandomization via IWRS											X	
Dispense study intervention via IWRS		X		X	X	X	X	X	X	X	X	No dose is given at Week 1. The dose dispensed at Week 16 is the first dose of the maintenance period.
Administer study intervention		X		X	X	X	X	X	X	X	X	No dose is given at Week 1.

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01). Note: The posttreatment follow-up visits are required for all randomized participants.												
Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	Rescue medication and background emollients are documented as concomitant medications.
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	AE collection begins when the master protocol ICF is signed. CCI events will be solicited at each visit. For AESIs, additional data are collected. See Section 8.3.1.
Physical evaluation												
Weight			X			X		X			X	
Symptom-directed physical assessment			X			X		X	X		X	Perform as shown here and as needed based on participant status and standard of care. May be performed by qualified personnel per local regulations. Assess for TB risk factors, and for signs and symptoms of active TB, including an assessment of peripheral lymph nodes. See Sections 8.2.2 and 8.2.8 of the master IMMB protocol.

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01).
Note: The posttreatment follow-up visits are required for all randomized participants.

Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	Includes pulse rate, blood pressure, respiratory rate, and body temperature. Measured after the participant has been sitting at least 5 minutes. See Section 8.2.1 of the master IMMB protocol.
ECG 12-lead (single) (local)			X				X	X			X	A local ECG will be collected according to instructions in Section 8.2.4 of the master IMMB protocol.
Patient-reported outcomes (electronic)												Complete prior to any clinician-administered assessments.
Dermatology Life Quality Index (DLQI)	X	X	X	X	X	X	X	X		X	X	
Patient-Oriented Eczema Measure (POEM)	X	X	X	X	X	X	X	X		X	X	
SCORing Atopic Dermatitis (subjective) (SCORAD)	X	X	X	X	X	X	X	X	X	X	X	
Atopic Dermatitis Control Tool (ADCT)	X	X	X	X	X	X	X	X		X	X	
Hospital Anxiety Depression Scale (HADS)	X	X	X	X	X	X	X	X		X	X	

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01).
Note: The posttreatment follow-up visits are required for all randomized participants.

Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
Patient-reported outcomes (paper)												
Asthma Control Questionnaire-5 (ACQ-5)						X					X	
Clinician-administered assessments (electronic)												
vIGA-AD	X	X	X	X	X	X	X	X	X	X	X	
Eczema Area and Severity Index (EASI)	X	X	X	X	X	X	X	X	X	X	X	
SCORing Atopic Dermatitis (objective) (SCORAD)	X	X	X	X	X	X	X	X	X	X	X	
Fitzpatrick Scale of Skin Phototypes												Not performed in these study periods.
Clinician-administered assessments (paper)												
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Assessed	X	X	X	X	X	X	X	X	X	X	X	AE collection should occur prior to collection of the C-SSRS. Adapted for the assessment of ideation and behavior categories only.
Participant diary (electronic)												

CCI

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01).
Note: The posttreatment follow-up visits are required for all randomized participants.

Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
CCI												
Diary review	X	X	X	X	X	X	X	X	X	X	X	Diary contains the following assessments: CCI CCI Atopic Dermatitis Sleep Scale (ADSS), and Skin Pain Numeric Rating Scale (Skin Pain NRS).
Diary return								X			X	
Participant education												
CCI												
Diary education												Education can be provided as needed at any time.

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01).
Note: The posttreatment follow-up visits are required for all randomized participants.

Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
Laboratory tests and sample collections												Collect before dosing unless otherwise specified.
Hematology			X			X		X		X	X	
Clinical chemistry			X			X		X		X	X	
Urine or serum pregnancy test (local)	X	X	X	X	X	X	X	X		X	X	For WOCBP, a pregnancy test must be performed, with the result available **within 24 hours** prior to dosing (see Section 8.2.7 of this ISA and Section 8.2.7 of the master IMMB protocol). Additional pregnancy tests should be performed at any time if a menstrual period is missed, or there is clinical suspicion of pregnancy, or as required by local law or regulation.
Urinalysis						X		X			X	
Estimated glomerular filtration rate (eGFR)						X		X				Calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2021).

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01).
Note: The posttreatment follow-up visits are required for all randomized participants.

Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
Hepatitis B virus (HBV) DNA		X			X			X			X	Only for participants who are anti-HBc positive at Visit 401 (see Section 8.2.9 of the master IMMB protocol).

CCI

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01).
Note: The posttreatment follow-up visits are required for all randomized participants.

Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
Immunogenicity (ADA) samples			X			X		X			X	On dosing visits, collect samples before dosing. Collect additional samples at specified times relative to onset of CCI events (see Section 8.3.1.1 and Attachment 1, Section 10.1.2).
Stored samples												
Genetics sample												Sample can be obtained at or after Study Day 1.
CCI												
Randomization and dosing-related activities												
Register visit with IWRS	X	X	X	X	X	X	X	X		X	X	
Dispense study intervention via IWRS	X	X	X	X	X	X						The last dose is given at Week 40.

Table 2. Activities for maintenance and posttreatment follow-up periods, early discontinuation visit, and unscheduled visit (Study J4E-MC-FR01).
Note: The posttreatment follow-up visits are required for all randomized participants.

Week	CCI											**Comment**
Study day												Study Day 1 is day of first dose.
Visit interval tolerance (window) in days	±3	±3	±3	±3	±3	±3	±3	—	—	±7	±7	
CRF visit number	CCI							ED	—	V808	V812	
Administer study intervention	X	X	X	X	X	X						The last dose is given at Week CCI

Abbreviations: ADA = anti-drug antibodies; AESI = adverse event of special interest; anti-HBc = hepatitis B core antibody; CRF = case report form; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation visit; ICF = informed consent form; ISA = intervention-specific appendix; IWRS = interactive web-response system; TB = tuberculosis; UV = unscheduled visit; V = case report form visit; WOCBP = women of childbearing potential.

2. Introduction

2.1. Study Rationale

LY3454738 is a humanized IgG4-variant mAb that binds to and agonizes the human inhibitory checkpoint CD200R. CD200R is expressed on many cell types involved in the pathogenesis of AD. CCI [redacted] CCI [redacted] Activating CD200R with an agonist mAb is a potential therapeutic strategy for AD and other inflammatory disorders. This study will evaluate the safety and efficacy of LY3454738 in adults with moderate-to-severe AD.

2.2. Background

Immune checkpoint regulators such as CD200R are critical modulators of the immune system, allowing the initiation of a productive immune response and preventing the onset of autoimmunity by negatively regulating the response once the pathogen is eliminated.

CD200R is expressed on multiple cell types. Specifically, CD200R is expressed on the surface of myeloid cells (mast cells, basophils, macrophages, and dendritic cells), and on T cells, B cells, neutrophils, microglia, and retina (Broderick et al. 2002; Wright et al. 2003). The CD200R ligand, CD200, is expressed on the surface of a variety of cell types, including vascular endothelial cells, fibroblasts, T and B cell subsets, and neurons (Wright et al. 2003).

The pathogenesis of AD involves dysregulation of adaptive and innate immune responses. Skin-resident cells such as dendritic cells, mast cells, keratinocytes, macrophages, and innate lymphoid cells contribute to the inflammation of skin in AD. Likewise, T cells, plasmacytoid dendritic cells, monocytes, and granulocytes also contribute to AD pathology (Egawa and Weniger 2015). CD200R is expressed on many of these cell types. Hence, activating CD200R with an agonist mAb such as LY3454738 is a potential strategy for the treatment of AD.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Risks associated with LY3454738

No dose-limiting safety issues have been identified in clinical studies of participants receiving single or repeat doses of LY3454738. In a Phase 1 study comparing LY3454738 versus placebo in AD (Study FRCC), CCI [redacted] CCI [redacted] CCI [redacted] Based on these data and on other available clinical and nonclinical data, there are no anticipated risks that would require safety monitoring in this study beyond what is typical for clinical studies involving humanized mAbs.

The administration of therapeutic mAbs to humans can be associated with CCI [redacted] CCI [redacted]

CCI [redacted]

Risks and discomforts associated with study procedures

Participants will use additive-free emollients during the study but will refrain from other topical AD treatments, with the exception of rescue medication as described in Section 6.9.1. Participants accustomed to using TCS and other topical treatments may experience increased discomfort due to itching during the study.

Risk mitigations

The study entry criteria of the master IMMB protocol and of this ISA exclude potential participants who may be at greater risk of developing infections, CCI [redacted] CCI [redacted] or malignancies. Participants who may be at greater risk for adverse effects related to TCS withdrawal (Hajar et al. 2015) are also excluded.

To reduce the burden of untreated AD symptoms, qualifying participants are permitted to receive rescue medication during certain study periods (Sections 4.1 and 6.9.1).

All participants will have appropriate predose safety assessments, including symptom-directed physical assessments, clinical safety laboratory tests, suicidality/self-harm evaluations, vital signs, and evaluation of reported AEs, during the treatment period. The design includes posttreatment follow-up visits at which safety assessments are also conducted.

CCI [redacted] Ongoing study-level monitoring of safety data will be performed, as described in Section 8.2 of the master IMMB protocol. Interim analyses of unblinded safety data will also be conducted, as described in Section 9.4 and Attachment 3, Section 10.3, of this ISA.

2.3.2. Benefit Assessment

Efficacy results from Study FRCC support the hypothesis that LY3454738 has the potential to treat AD. CCI [redacted]

Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, and in the context of the cumulative knowledge of LY3454738, the benefit/risk balance for participants in this Phase 2 study is assessed to be acceptable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3454738 may be found in the IB.

3. Objectives, Endpoints, and Estimands

This table lists objectives and endpoints for the evaluation of LY3454738 versus placebo.

Objectives	Endpoints
Primary To compare the efficacy of LY3454738 versus placebo as measured by EASI-75 in the treatment of CCI moderate-to-severe AD	Proportion of participants achieving EASI-75 at Week 16

CCI

Abbreviations: CCI AD = atopic dermatitis; CCI CCI EASI = Eczema Area and Severity Index; CCI CCI CCI

3.1. Estimands

The primary clinical question of interest is: in the target patient population, what is the difference between each dosing regimen of LY3454738 and placebo in achieving a successful response at Week 16 without use of any prohibited or rescue medication for AD or early permanent discontinuation?

The estimand is described by the following attributes:

- Population: CCI participants with moderate-to-severe AD.
- Endpoint: The primary endpoint and all secondary efficacy endpoints, that is, EASI-75 CCI CCI
- How to account for ICEs:
  - A composite strategy will be used for all types of ICEs of interest, CCI CCI CCI
  - CCI
  - CCI

- Population-level summary:
  - For binary endpoints CCI [redacted] the population-level summary will be the unconditional difference in response rate at Week 16 between each dosing regimen of LY3454738 and placebo.
  - For continuous endpoints (percent change from baseline in EASI CCI [redacted] mean difference at Week 16 between each dosing regimen and placebo.
- Rationale for estimand: The composite estimand is the standard from prior AD studies CCI [redacted] From the perspective of ICEs:
  - If a participant used any prohibited or rescue medication for AD, the participant was not receiving sufficient benefits from study intervention.
  - If a participant early discontinued study intervention, the participant experienced a burden of study intervention that outweighed its benefits.

4. Study Design

4.1. Overall Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient dose-ranging study to evaluate the efficacy and describe the safety of multiple LY3454738 induction and maintenance dosing regimens in adult participants with moderate-to-severe AD. The study population includes CCI CCI participants, all with diagnosed AD which is moderate to severe as measured by EASI score ≥16, vIGA-AD score ≥3, and ≥10% of BSA involvement at randomization.

Study periods

A schematic of the design of this ISA is presented CCI Assessments, sample collections, and study drug administrations occur at the visits shown in the SoA (Section 1.3).

Screening period and randomization to treatment within this ISA (Visit 0)

Screening for this ISA can begin up to CCI days before Study Day 1 (day of first dose). Informed consent for participation in this ISA must be obtained before any ISA-specific tests or procedures are performed. Screening activities for this ISA are listed in the SoA (Section 1.3) in the columns for CRF Visit 0 (V0).

Before a participant is randomized to a study intervention, the participant's eligibility according to the study entry criteria of both the master IMMB protocol (Section 5) and this FR01 ISA (Section 5) must be confirmed.

CCI

Induction regimen	CCI	Approximate total number of participants planned
LY3454738 CCI mg CCI		96
LY3454738 CCI mg CCI		68
LY3454738 CCI mg CCI		28
Placebo		68

Blinded induction period

Randomized participants will begin the double-blind, placebo-controlled, 16-week induction period when the initial dose is administered on Study Day 1.

Topical rescue medication is permitted from Week 8 until Week 16 for participants who do not achieve an CCI response, as described in Section 6.9.1. Topical rescue medication started during the induction period should be stopped at, or before, Week 16.

Blinded maintenance period

The blinded CCI-week maintenance treatment period begins with the dose administered at Week 16. Participants having at least an CCI response at Week 16 will receive a maintenance dosing regimen, as listed here.

Week 16 responders who were originally randomized to this induction regimen...	**Will receive this maintenance regimen:**
LY3454738 CCI mg CCI	by rerandomization in CCI ratio: LY3454738 CCI mg CCI or placebo
LY3454738 CCI mg CCI	LY3454738 CCI mg CCI
LY3454738 CCI mg CCI	LY3454738 CCI mg CCI
placebo	Placebo CCI

The maintenance period includes an "escape arm" for participants whose EASI response suggests the need for a higher dose. The escape therapy is LY3454738 CCI mg CCI. A participant will receive this escape therapy under the conditions listed here.

Begin LY3454738 CCI mg CCI as escape therapy...	**if the participant...**
At Week 16	has not achieved an CCI response at Week 16.
At Weeks CCI	has not achieved an CCI response at Weeks CCI CCI

A participant receiving escape therapy will continue receiving escape therapy through the last dosing visit of the study (Week CCI unless the participant is discontinued from study intervention.

Topical rescue medication in the maintenance period is permitted from Week CCI until the end of the study for participants who do not achieve an CCI response, as described in Section 6.9.1.

Posttreatment follow-up period

All participants are expected to have 2 follow-up visits after the last dosing visit, as listed here.

Condition	**First follow-up visit**	**Second follow-up visit**
If the participant **did not** discontinue study intervention early...	occurs approximately 8 wk after last dosing visit	occurs approximately 12 wk after last dosing visit
If the participant **did** discontinue study intervention early...	occurs after ED and with an approximately 8-week interval between the last dose and this visit	occurs after ED and with an approximately 12-week interval between the last dose and this visit

Blinding

This study design includes investigator and participant blinding (masking) (Section 6.4). Blinding of the participant's original induction and maintenance treatments will continue until all participants have completed their last posttreatment follow-up visit or have discontinued the study. All blinded assessments and sample collections should be completed before a dose is administered at the dosing visits.

Internal assessment committee

During the study, an IAC will review the safety data in an unblinded fashion, as described in the master IMMB protocol, Appendix 1, Section 10.1.5.

4.2. Scientific Rationale for Study Design

EASI-75 as the primary endpoint measure

The EASI and SCORAD are both regarded as acceptable instruments to measure the clinical signs of AD (Schmitt et al. 2013). Study FR01 uses a 75% reduction relative to the baseline EASI score (EASI-75) as the primary measure of efficacy. The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin et al. 2001).

Duration of treatment period and posttreatment follow-up

The duration of the induction period (16 weeks) and the primary endpoint at Week 16 is based on previous clinical trials of systemic therapies in AD (Simpson et al. 2016). The remaining duration of the study is intended to allow exploratory assessments of various LY3454738

maintenance dosing regimens. To reduce participant burden, topical rescue medication is permitted under certain circumstances (Section 6.9.1).

The posttreatment follow-up period allows for continued monitoring of safety and maintenance of response after the last dose. The duration of this period is considered sufficient to wash out LY3454738 based on the half-life of the CCImg dose, CCI CCI

Appropriateness of study population

The study inclusion criteria will enable enrollment of patients who are representative of the general population with moderate-to-severe AD. The EASI score ≥16, IGA score ≥3, and ≥10% of BSA involvement at baseline have been used as inclusion criteria in other studies of AD (Simpson et al. 2016).

Choice of placebo control, number of treatment groups, and escape arm

A double-blind, placebo-controlled design limits bias for the participant assessments and investigator assessments and enables a clearer interpretation of the effects of the active study intervention.

The multiple dosing regimens enable an evaluation of safety and efficacy across several doses and frequencies, thereby providing information to guide the selection of dosing regimens for future studies.

The maintenance "escape arm" for nonresponders gives participants an opportunity to remain in the study and receive potential benefit from a higher dose.

4.2.1. Patient Input into Design

Not applicable.

4.3. Justification for Dose

The LY3454738 dose range of CCI mg to CCI mg CCI is based on clinical safety data from the Phase I Study FRCC, CCI The chosen dose levels and regimens are anticipated to provide an exposure range that is pharmacologically active and cover a range of clinical response.

In the Phase I study FRCC, CCI CCI CCI CCI

In the maintenance period, CCI regimens of LY3454738 and placebo are included to determine whether less frequent dosing can maintain the response attained with CCI induction dosing regimens.

4.4. End of Study Definition

A participant is considered to have completed this FR01 ISA if the participant has completed all periods of the study, including the last scheduled procedure shown in the SoA of this ISA (Section 1.3).

The end of this ISA is defined as the date of the last scheduled procedure of the last participant in Study FR01 globally.

5. Study Population

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

All screening evaluations, including those specified in the master IMMB protocol, must be completed and reviewed to confirm that each potential participant meets all eligibility criteria (that is, both master protocol and ISA-specific criteria) before the participant is randomized and receives the first dose of study intervention in this ISA.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

5.1. ISA-Specific Inclusion Criteria

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

Informed consent

[1000] Are capable of giving, and have given, signed informed consent, which includes consent to compliance with the requirements and restrictions listed in the ICF(s) and in this ISA, including compliance with the use of contraceptives as specified in this ISA (see Attachment 2, Section 10.2.2).

[1001] Are considering and capable of undergoing the study procedures applicable to the participant's study site.

Participant characteristics

[1002] Are from 18 to 70 years of age (inclusive) at the time of signing the ICF(s).

Disease-specific characteristics

[1003] Have moderate-to-severe AD, defined as meeting all of the following criteria, at the first dosing visit:

[1003a] EASI score ≥16
[1003b] vIGA-AD score ≥3, and
[1003c] ≥10% of BSA involvement (per EASI BSA).

[1004] Have applied at least 1 emollient every day for at least 2 weeks before the day of the first dose of study intervention in this ISA and agree to daily use of at least 1 emollient continuously throughout the study.

5.2. ISA-Specific Exclusion Criteria

Participants are excluded from this ISA if any of the following criteria apply.

[1005] Have, in the screening period (Visit 0), any of the skin conditions, infections, or medical conditions listed in Section 5.2 of the master IMMB protocol.

Previous or current therapies

[1006] Have received any of the following therapies during the specified time period ("washout") or are anticipated to need any of these therapies during the study:

Criterion	Therapy	Time period ("washout") before the first dose of study intervention[a]	Note
CCI			
[1006b]	Corticosteroids that are • parenteral (administered via intra-articular, intramuscular, or IV route), or • rectally administered (enemas or suppositories)	6 weeks	Intranasal, inhaled, or ophthalmic (ocular) steroids are allowed at any time.
[1006c]	Oral systemic corticosteroids	4 weeks	
CCI			
[1006e]	Other systemic therapy used to treat AD or symptoms of AD, whether approved/marketed or off-label use	4 weeks	
[1006f]	Any investigational CCI	4 weeks or 5 half-lives (whichever is longer)	
[1006g]	Phototherapy, including • therapeutic phototherapy (psoralen plus ultraviolet A, ultraviolet B) • excimer laser, or • tanning beds	4 weeks	
[1006h]	Topical immune modulators, including TCIs (for example, tacrolimus, pimecrolimus), and JAK inhibitors (for example, ruxolitinib, delgocitinib)	2 weeks	
[1006i]	PDE4 inhibitors (for example, crisaborole)	2 weeks	
[1006j]	Bleach bath	2 weeks	
[1006k]	TCS	2 weeks	

[a] The washout period in this table includes the day of the first dose of study intervention.

[1007] Have received any live vaccine (that is, live attenuated) within less than 4 weeks before the day of the first dose of study intervention in this ISA, or intend to receive a live vaccine during the study, or within 14 weeks (about 5 half-lives) after receiving the last dose of study intervention.

Note: The following are not considered live vaccines: RNA vaccines, vaccines with inactive viral elements, and/or nonreplicating viral vector vaccines. Nonlive SARS-CoV-2 vaccines authorized by local regulatory bodies are allowed during or after the study.

[1008] Have received a BCG vaccination or treatment within less than 4 weeks before the day of the first dose of study intervention in this ISA, or intend to receive BCG vaccination or treatment during the study, or within 14 weeks after receiving the last dose of study intervention.

[1009] Are unstable with respect to use of chronic treatments to improve sleep:

[1009a] Have started or restarted using a prescription sleep medication during the 2 weeks before the day of the first dose of study intervention in this ISA

[1009b] Have changed the dose of a prescription sleep medication during the 2 weeks before the day of the first dose of study intervention in this ISA, or

[1009c] Are likely to need to start or change the dose of prescription sleep medication during this ISA, in the opinion of the investigator.

Note: Individuals on a stable dose of prescription sleep medication at screening may be eligible to be enrolled if other study entry criteria are met, but such individuals should remain on the stable dose throughout the study unless, in the investigator's opinion, the dose should be changed or stopped to address a safety concern (Section 6.9.2).

Other previous or current medical conditions

[1010] Have 1 or more of the following conditions suggesting a possibly greater risk of clinically significant CCI reactions:

[1010a] known CCI LY3454738, related compounds, or any components of the formulation, or

[1010b] history of CCI reactions that in the opinion of the investigator may predispose the participant to a clinically significant CCI to LY3454738 or to any components of the formulation.

Previous or concurrent clinical trial participation

[1011] Have received LY3454738 in any other clinical study.

Other

[1012] Are unable or unwilling to make themselves available for the required number of study visits or are unwilling to follow study restrictions and procedures, including restrictions on the use of concomitant therapies for AD, such as TCS.

5.3. Lifestyle Considerations

Participants should be instructed not to donate blood or blood products for 18 weeks after their last dose of study intervention.

Participants must agree to the contraception criteria detailed in Attachment 2, Section 10.2.2, of this ISA, and they must agree not to breastfeed at any time during the study.

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this ISA (screen failure at the ISA level) cannot be rescreened for this same ISA (FR01) using the same participant number.

See the master IMMB protocol for additional information.

5.5. Criteria for Temporarily Delaying Randomization of a Participant

Not applicable. See the master IMMB protocol.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

This study involves placebo and [redacted] dose levels of LY3454738 administered with [redacted], as shown in this table.

Intervention Name	LY3454738	Placebo [redacted]
Nominal Dose Levels	[redacted] mg [redacted] mg [redacted] mg [redacted] mg	Not applicable
Frequency of Administration	[redacted]	[redacted] and as needed to maintain the blind
Route of Administration	[redacted]	[redacted]
Authorized as defined by EU Clinical Trial Regulation	Not authorized	Authorized and not used according to authorization

Abbreviations: EU = European Union; [redacted]

Background therapy will be used as shown in this table.

Intervention Name	**Background therapy:** emollient without additives such as antipruritics or antiseptics, as described in Section 6.1.2 of the master IMMB protocol
Dose Levels	Per local approved label, if applicable
Frequency of Administration	Daily or per local approved label, if applicable
Route of Administration	Topical
Authorized as defined by EU Clinical Trial Regulation	Not authorized[a]

Abbreviation: EU = European Union.

[a] This medicinal product is not authorized in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council. However, emollients are authorized according to EU Regulation 1223/2009 and are being used according to their authorization.

LY3454738 will be supplied for clinical trial use as a [redacted] The drug product vials will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule.

Preparing the study interventions for dosing

An unblinded pharmacist or other unblinded qualified individual will prepare the study interventions [redacted] (see Section 6.4).

[redacted]

CCI

Monitoring of participants after dosing

All participants should be monitored for 30 minutes or longer after dosing, according to investigator practice or local standard of care. Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the CCI and until completion of all required postdosing activities.

Supply and labeling of study interventions

See the master IMMB protocol.

6.1.1. Medical Devices

Not applicable to this ISA.

6.1.2. Background Therapy

See the master IMMB protocol.

6.2. Preparation, Handling, Storage, and Accountability

See the master IMMB protocol.

6.3. Assignment to Study Intervention

Assignment to treatment groups within this ISA will be determined by a computer-generated random sequence using an IWRS. The randomization ratios are described in Section 4.1.

The randomization will be stratified based on the following factors:

CCI

- baseline disease severity: baseline vIGA-AD 3 versus baseline vIGA-AD 4, and
- sex assigned at birth: male or female.

6.4. Blinding

This is a double-blind study. Participants, investigators, and all individuals involved in the treatment or clinical evaluation of the participants will remain blinded to each participant's original induction and maintenance treatments until all participants have completed their last posttreatment follow-up visit or have discontinued the study.

The switching of an individual participant to the escape arm is not blinded. The investigator will be aware of each participant's EASI response and of the fact that participants meeting certain EASI criteria (specified in Section 4.1) will be switched to LY3454738 CCI mg CCI as escape therapy. The participant's original induction and maintenance treatments will nevertheless remain blinded until all participants have completed their last posttreatment follow-up visit or have discontinued the study.

Use of an unblinded pharmacist

To maintain the blind, persons otherwise uninvolved in the study, for example, unblinded pharmacists or other unblinded qualified individuals, will prepare the study interventions CCI CCI When LY3454738 is prepared for dosing according to the detailed instructions provided by the sponsor, it will not be possible to distinguish LY3454738 from placebo.

Blinded study personnel will administer the study intervention to the participants.

Emergency unblinding

See the master IMMB protocol.

6.5. Study Intervention Compliance

The date and time of each dose administered will be recorded in the source documents and will be recorded in the CRF. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. Deviations from the prescribed dosage regimen are identifiable via the CRF.

6.6. Dose Modification

The dosing regimens used in this study are described in Sections 4.1 and 6.1. No modifications to the specified regimens (dose or frequency) are permitted, except for reasons of immediate participant safety.

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

Continued access to the study interventions of this ISA will not be provided to participants after they have finished participating in this ISA.

6.8. Treatment of Overdose

An overdose of LY3454738 is considered to be any dose greater than the highest dose of LY3454738 planned for use in this study.

In the event of an actual or suspected overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced, and

- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate for at least 14 weeks. Hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care should be provided as necessary (see the IB for LY3454738).

6.9. Prior and Concomitant Therapy

See the master IMMB protocol for general instructions about recording any vaccine, therapy, or medication that the participant receives during the study.

6.9.1. Rescue Medication

Rescue medication during induction period

CCI [redacted] CCI [redacted] If a participant meets this criterion during this time period, the decision to implement rescue medication is per the investigator's judgment and is not a protocol requirement. Rescue medication started during this period must be stopped at the Week 16 visit.

Rescue medication during maintenance and posttreatment follow-up periods

Use of rescue medication is permitted **starting at Week** CCI and until the end of the study for participants who **do not achieve an** CCI [redacted] **response**. If a participant meets this criterion during this time period, the decision to implement rescue medication is per the investigator's judgment and is not a protocol requirement.

Medications for use as rescue

This table lists the allowed rescue medications.

Allowed as rescue medication[a]	Alternative or limitation
• triamcinolone 0.1% cream • hydrocortisone 2.5% ointment, or • both	If these are not available, an alternate, equivalent potency TCS cream or ointment can be used.
• TCIs • crisaborole, or • both	If these are prescribed, their use should be limited to problem areas only, for example, face, neck, skin folds, and genital areas.

a Rescue medications should be used according to their local product labeling.
Abbreviations: TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Additional medications and considerations for use as rescue

This table describes additional medications and considerations for use as rescue.

If a participant...	then...
does not improve sufficiently after using the specified rescue medication for 7 days	a higher potency TCS may be used.
reaches "clear" to "almost clear" skin after rescue with medium- and/or high-potency TCS and TCI	the medium- and/or high-potency TCS and TCI should be stopped, and a low-potency TCS, for example, hydrocortisone 2.5% ointment, should be used once daily for an additional 7 days, and then stopped.

If a participant...	then...
has lesions return after stopping rescue	retreat with TCS with or without TCIs and/or crisaborole as before, at the discretion of the investigator.

Time of administration of rescue medication

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue medication. An unscheduled visit can be used for this purpose if necessary. This is to allow adequate assessment of skin dryness at the visit.

Documentation of rescue medication

Rescue medication must be recorded as stated in Section 6.9 of the master IMMB protocol.

Discontinuation due to inadequate control with rescue medication

Participants receiving rescue medication will continue to receive the assigned study interventions. A participant should be discontinued from study intervention and proceed to the posttreatment follow-up period if, in the investigator's judgment, there is inadequate response to rescue medication, as specified in Section 7.1.2.

6.9.2. Permitted Concomitant Therapy

Permitted concomitant therapies for AD

Concomitant therapies for AD during the study are permitted only as described here:

- Daily use of emollients is required as background therapy, as described in Section 6.1 and Section 6.1.2 of the master IMMB protocol.
- Rescue medication (for example, triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment; TCIs and/or crisaborole; medium- and/or high-potency TCS and TCI) is permitted but not required, as described in Section 6.9.1.
- Use of topical and oral nonsedating antihistamines is permitted.

Permitted concomitant therapies for other conditions

Concomitant therapies for conditions other than AD are generally allowed unless described as prohibited in Section 6.9.3. Here is guidance for some of the permitted concomitant therapies:

- Intranasal or inhaled steroids: Use of intranasal or inhaled steroids is allowed at any time for participants with such conditions as asthma and allergic rhinitis.
- Prescription sleep medications: Individuals on a stable dose of prescription sleep medication at screening should remain on this stable dose throughout the study unless, in the investigator's opinion, the dose should be changed or stopped to address a safety concern.

6.9.3. Prohibited Concomitant Therapy

Medications and treatments prohibited before randomization to a study intervention are listed in the exclusion criteria of this ISA (Section 5.2).

This table lists therapies prohibited throughout the study, that is, from randomization until the last posttreatment follow-up visit of this ISA.

Prohibited Concomitant Therapy	Note
CCI	
Systemic corticosteroids, including, but not limited to, oral or parenteral corticosteroids (intra-articular, intramuscular, IV, or rectally administered)	Note: Intranasal or inhaled or ophthalmic (ocular) steroid use is allowed at any time (Section 6.9.2).
CCI	
Phototherapy, including therapeutic phototherapy (psoralen plus ultraviolet A, ultraviolet B), excimer laser, and tanning beds	
Any investigational therapy except the study interventions used in this ISA	
CBD products and any of the following substances if medically prescribed for the treatment of symptoms of AD or other conditions: marijuana, marijuana extract, and THCs-containing products	
Bleach baths	
Allergen immunotherapy	
Live vaccines or BCG vaccination	• The following are not considered live vaccines: RNA vaccines, vaccines with inactive viral elements, and/or nonreplicating viral vector vaccines. • Nonlive SARS-CoV-2 vaccines authorized by local regulatory bodies are allowed during or after the study. • Live vaccines and BCG vaccination are prohibited both during the study and within 14 weeks after the last dose of study intervention.

Abbreviations: AD = atopic dermatitis; BCG = Bacillus Calmette-Guerin; CBD = cannabidiol; IV = intravenous; JAK = Janus kinase; RNA = ribonucleic acid; TCS = topical corticosteroid; THC = tetrahydrocannabinol.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

See the master IMMB protocol.

7.1.1. Temporary Discontinuation of Study Intervention

See the master IMMB protocol.

7.1.1.1. Elevated Liver Test Results

See the master IMMB protocol.

7.1.2. Permanent Discontinuation of Study Intervention

Possible reasons for permanent discontinuation of study drug include, but are not limited to, the reasons listed here as well as reasons listed in Section 7.1.2 of the master IMMB protocol.

- Inadequate response to rescue medication in participants who have been receiving rescue medication: at the **second** of **2** consecutive visits, the investigator determines that rescue medication is inadequate to control the participant's AD symptoms and the participant needs treatment with an AD therapy which is prohibited by the protocol. In such cases, the participant is to be discontinued from the study drug before starting the protocol-prohibited AD therapy.
- Nonresponse in participants who are receiving escape therapy: Participant receiving at least 2 doses of escape therapy **at 2 consecutive visits** fails to achieve an CCI response.

7.2. Participant Discontinuation/Withdrawal from the Study

See the master IMMB protocol.

7.3. Lost to Follow up

See the master IMMB protocol.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoAs of the master IMMB protocol and this ISA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Since key efficacy and patient-reported outcomes data may be collected via an electronic tablet and/or diary, adherence to the data collection modality specified in the SoA is also essential and is required for study conduct.

Unless otherwise specified in the SoA of this ISA, all blinded assessments and sample collections should be completed before a dose is administered at the dosing visits.

8.1. Efficacy Assessments

Efficacy-related assessments occur at visits specified in the SoA of this ISA (Section 1.3).

See Appendix 6, Section 10.6, of the master IMMB protocol for descriptions of these assessments:

- EASI
- vIGA-AD
- SCORAD
- POEM
- DLQI
- ADCT
- CCI
- ADSS
- Skin Pain NRS

This ISA also includes the ACQ-5 and HADS, which are described here.

Asthma Control Questionnaire-5 (ACQ-5)

The ACQ-5 is a participant-reported, 5-item questionnaire that assesses the following domains:

- awoken at night by symptoms
- limitation of normal daily activities
- morning symptoms
- shortness of breath (dyspnea), and
- wheezing.

The 5 questions are scored on a 7-point Likert scale with a recall period of 1 week. The scores range from 0 to 6 (higher score = lower asthma control). The total ACQ-5 score is the mean score of all questions; a lower score represents better asthma control. The ACQ-5 has been shown to reliably measure asthma control and distinguish participants with well-controlled asthma (score ≤0.75 points) from those with uncontrolled asthma (score ≥1.5 points) (Juniper et al. 1999; Juniper et al. 2006).

Hospital Anxiety Depression Scale (HADS)

The HADS is a validated, participant-reported instrument that assesses both anxiety and depression for the previous week. Fourteen items are rated on a 4-point scale from 0 to 3 (Zigmond and Snaith 1983; White et al. 1999). Higher numbers indicate greater dysfunction (Zigmond and Snaith 1983; Herrmann 1997; Snaith 2003).

This table describes the scoring.

HADS Subscale	Number of Questions	Rating Score for Each Question	Score	Total Score Range
Anxiety	7	0-3	Sum of odd items	0-21
Depression	7	0-3	Sum of the even items	0-21

Total scores of each subscale greater than or equal to 8 are interpreted as potential cases.

Total scores of each subscale greater than or equal to 11 are interpreted as clinically significant symptoms (Zigmond and Snaith 1983).

8.2. Safety Assessments

Visits and order of safety assessments

Safety assessments occur at visits specified in the SoA (Section 1.3) of this ISA, in addition to the screening safety assessments specified in the SoA for the master IMMB protocol.

See the master IMMB protocol for

- the preferred order of completing multiple safety assessments at the same visit (IMMB Section 8)
- general provisions for safety monitoring during the study (IMMB Section 8.2), and
- safety data collection and reporting requirements (IMMB Section 8.3).

8.2.1. Vital Signs

See the master IMMB protocol.

8.2.2. Physical Examinations

See the master IMMB protocol for a description of

- TB assessment
- complete physical examination, and
- symptom-directed physical assessments.

Height and weight will be measured and recorded as specified in the SoA of this ISA.

8.2.3. Skin Assessment with Fitzpatrick Scale of Skin Phototypes

See the master IMMB protocol.

8.2.4. Electrocardiograms

For each participant, 12-lead ECGs will be collected as specified in the IMMB SoA (Section 1.3) and the SoA of this ISA.

See the master IMMB protocol for a description of the

- timing of collection of ECGs
- interpretation of collected ECGs
- actions to be taken after a clinically significant finding on ECGs, and
- documentation of review of ECGs.

8.2.5. Chest Imaging

See the master IMMB protocol.

8.2.6. Clinical Safety Laboratory Tests

In this ISA, Attachment 1 (Section 10.1) and the SoA (Section 1.3) provide a list of clinical laboratory tests to be performed during this ISA. See the master IMMB protocol for clinical laboratory tests performed at Visit 401.

All protocol-required laboratory assessments, as defined in this ISA and as defined in the master IMMB protocol, must be conducted in accordance with the SoA, standard collection requirements, and the laboratory manual.

Reviewing and recording test results

See the master IMMB protocol for instructions about reviewing and recording clinical laboratory test results.

Repeat testing after a clinically significant abnormal finding

All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 14 weeks after the last dose of study intervention, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Fasting visits

Fasting is not required before any clinical trial visits in this study.

Laboratory tests after CCI [redacted] event

See Attachment 1, Section 10.1.2, of this ISA for clinical laboratory samples to be collected after CCI [redacted] event.

Allowance for additional laboratory testing

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

8.2.7. Pregnancy Testing

Pregnancy testing is to be performed for WOCBP at the visits specified in the SoA (Section 1.3). If the specified visit includes administration of study intervention, the pregnancy test must be "negative" **within 24 hours** before the study intervention is administered.

See Section 8.2.7 of the master IMMB protocol for additional information.

8.2.7.1. Optional FSH Testing

See the master IMMB protocol.

8.2.8. Tuberculosis Testing and Monitoring

See the master IMMB protocol.

8.2.9. Hepatitis B Testing and Monitoring.

See the master IMMB protocol.

8.2.10. Hepatitis C Testing

See the master IMMB protocol.

8.2.11. Hepatic Safety Testing and Monitoring

See the master IMMB protocol for guidance about the close hepatic monitoring, comprehensive hepatic evaluation, and suggested actions and follow-up assessments.

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

See the master IMMB protocol.

8.2.12. Suicidal Ideation and Behavior Risk Screening and Monitoring

Screening for suicidal ideation or behavior

Screening for suicidal ideation or behavior includes the C-SSRS, as specified in the SoA for the master IMMB protocol.

Monitoring for suicidal ideation and behavior and depressive symptomatology

During the treatment and posttreatment periods of this ISA as specified in the SoA (Section 1.3), the C-SSRS (adapted for the assessment of ideation and behavior categories only) will be used to monitor for suicidal ideation and behavior. See the master IMMB protocol for a description of the C-SSRS.

Discontinuation of participants with signs of suicidal ideation or behavior

Participants who have signs of suicidal ideation or behavior should be considered for discontinuation of study intervention, following a risk assessment (see Section 7.1.2 of the master IMMB protocol).

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

See the master IMMB protocol for instructions on

- timing and mechanism for collecting adverse events and product complaints
- adverse event monitoring with a systematic questionnaire, and
- collection of pregnancy information.

8.3.1. Adverse Events of Special Interest

For this ISA, the AESIs include

If these AESIs are reported, sites will be prompted to collect additional data as described in the following subsections.

Nonleading (spontaneous) AE collection should occur before the collection of any solicited AE or AE follow-up questionnaires.


CCI

8.5. Pharmacodynamics

CCI

8.6. Genetics

Where local regulations and IRB/IEC allow, a whole blood sample will be collected from consenting participants, as specified in the SoA (Section 1.3) of this ISA, for pharmacogenetic analysis.

Additional information

See the master IMMB protocol for information about

- use of genetics samples
- confidentiality of genetics samples, and
- retention of genetics samples.

8.8. Immunogenicity Assessments

Predose venous blood samples will be collected to determine antibody production against the study intervention.

Collection visits and times

The visits and times for collecting samples for ADA testing are specified in the SoA (Section 1.3) of this ISA. The actual date and time (24-hour clock time) of each sample collection must be recorded accurately on the appropriate forms. To aid interpretation of these results, a venous blood sample will be collected at same time points to determine the serum concentrations of LY3454738. All samples for immunogenicity should be taken predose when applicable and possible.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3454738. Antibodies may be further characterized for their neutralizing ability.

Samples collection for CCI [redacted] event

If CCI [redacted] event is suspected, additional blood samples will be obtained for ADA analyses, as described in Attachment 1, Section 10.1.2, of this ISA.

Additional information

See the master IMMB protocol for additional information about retention of ADA samples.

8.9. Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters will not be collected in this ISA.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

The null hypotheses corresponding to the primary and secondary estimands are these: there is no difference between LY3454738 and placebo in CCI participants with moderate-to-severe AD with respect to

- proportion of participants achieving EASI-75 at Week 16 (primary)

CCI

9.1.1. Multiplicity Adjustment

No adjustments for multiplicity will be performed.

9.2. Analyses Sets

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

Analysis Set	Description	Populations	Analyses Conducted on This Analysis Set
Induction Analysis Set	All randomized participants who receive at least 1 dose of study intervention. Participants will be included in the analysis set according to their randomly assigned intervention.	• Overall CCI	• vIGA-AD • EASI • SCORAD CCI • PROs
Maintenance Analysis Set	All randomized participants who enter the maintenance period. Participants will be included in the analysis set according to their randomly assigned interventions at Week 0 and Week 16.	• Overall CCI	• vIGA-AD • EASI • SCORAD CCI • PROs

Analysis Set	Description	Populations	Analyses Conducted on This Analysis Set
Safety	All randomized participants receiving at least 1 dose of study intervention. Participants will be included in the analysis set according to the intervention they actually received.	• Overall CCI	Safety data analyses for induction and/or maintenance period
Pharmaco-kinetics (PK)	All randomized participants receiving at least 1 dose of study intervention and have PK data available.	• Overall	PK data analyses for induction and/or maintenance period

Abbreviations: EASI = Eczema Area and Severity Index; NRS = Numeric Rating Scale; PK = pharmacokinetic; PROs = patient-reported outcomes; SCORAD = SCORing Atopic Dermatitis.

Additional analysis sets will be defined in the ISA-SAP to support exploratory analyses.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee. All statistical tests, unless otherwise noted, will be 2-sided and will be performed at a significance level of 0.05. Unless indicated otherwise in the ISA-SAP, the analyses will be conducted as described in this section.

Changes to the data analysis methods

Any change to the data analysis methods described in this ISA will require an amendment only if the change affects a principal feature of the ISA. Any other change to the data analysis methods described in the ISA and the justification for making the change will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate. Complete details of the planned analyses will be documented in the ISA-SAP.

Summary of data

Continuous data will be summarized in terms of mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentage. Comparison between each LY3454738 dosing regimen and placebo will be performed for all efficacy and patient-reported endpoint analyses during the induction period with no adjustment for multiple comparisons.

Induction dose selection

Dose selection at the end of the induction period will be based on comparisons between each regimen and placebo using dose-response modeling. Dose selection rules and specifics will be detailed in the ISA-SAP.

Baseline definition

For efficacy and PRO analyses, baseline will be defined as the last available value before the first dose of study intervention. In most cases, this value will be what is recorded at the randomization visit (Visit 0). For efficacy measures, if a participant does not take any study intervention, the last available value on or prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value.

For induction period safety analyses, the baseline period is defined as the time from Visit 401 to the first dose of study intervention. For the safety analyses during the maintenance period, baseline is defined as the last available value before the first dose of study intervention during the maintenance period. In most cases, this will be the measure recorded at Week 16. For the safety analyses during the posttreatment follow-up period, baseline is defined as the last nonmissing assessment on or prior to entering the posttreatment period, that is, on or prior to Week 44 or ED visit.

Missing data

For the estimand defined in Section 3.1, missing data after accounting for ICEs is expected to be uncommon. Thus, the handling of any missing data remaining after accounting for ICEs will be specified in the ISA-SAP. Missing data imputation methods for supplementary estimands will be described in the ISA-SAP.

Induction treatment comparisons

For binary efficacy and PROs, CCI [redacted]

For continuous efficacy and patient-reported outcomes, CCI [redacted]

Maintenance treatment comparisons

The efficacy of different maintenance regimens will primarily be assessed with descriptive statistics across the maintenance period. Frequencies and percentages will summarize binary outcomes, and means and standard deviations will summarize continuous outcomes. The ISA-SAP may include additional exploratory analyses for maintenance efficacy, including, but not limited to, inferential efficacy analyses and the efficacy of different maintenance regimens across differing levels of response at induction, for example, CCI [redacted] EASI-75 responders at Week 16.

9.3.2. Primary Endpoints/Estimands Analysis

Treatment comparisons between each LY3454738 dosing regimen and placebo in proportion of CCI participants achieving EASI-75 at Week 16 will be conducted with CCI at a significance level of 0.05.

The analysis will be conducted using the induction analysis set CCI CCI where participants who have ICEs of interest prior to Week 16 will be considered as nonresponders.

Treatment response rates, treatment differences versus placebo, and their corresponding 95% CIs will be provided according to study intervention to which participants are randomized at Visit 0.

CCI

9.3.5. Safety Analyses

See Section 9.3.5 of the master IMMB protocol for safety analyses, including but not limited to, AEs and SAEs.

9.3.6. Other Analyses

See the master IMMB protocol (Section 9.3.6) for participant disposition and characteristics, concomitant therapy, treatment compliance, PROs, subgroups, and sensitivity analyses.

9.3.6.1. Pharmacokinetic/Pharmacodynamic Analyses

Serum concentrations of LY3454738 will be listed by time point and dosing regimen using descriptive statistics. The PK of LY3454738 may also be characterized using graphical evaluations and mixed-effect (population PK) modeling approaches. CCI

CCI

CCI

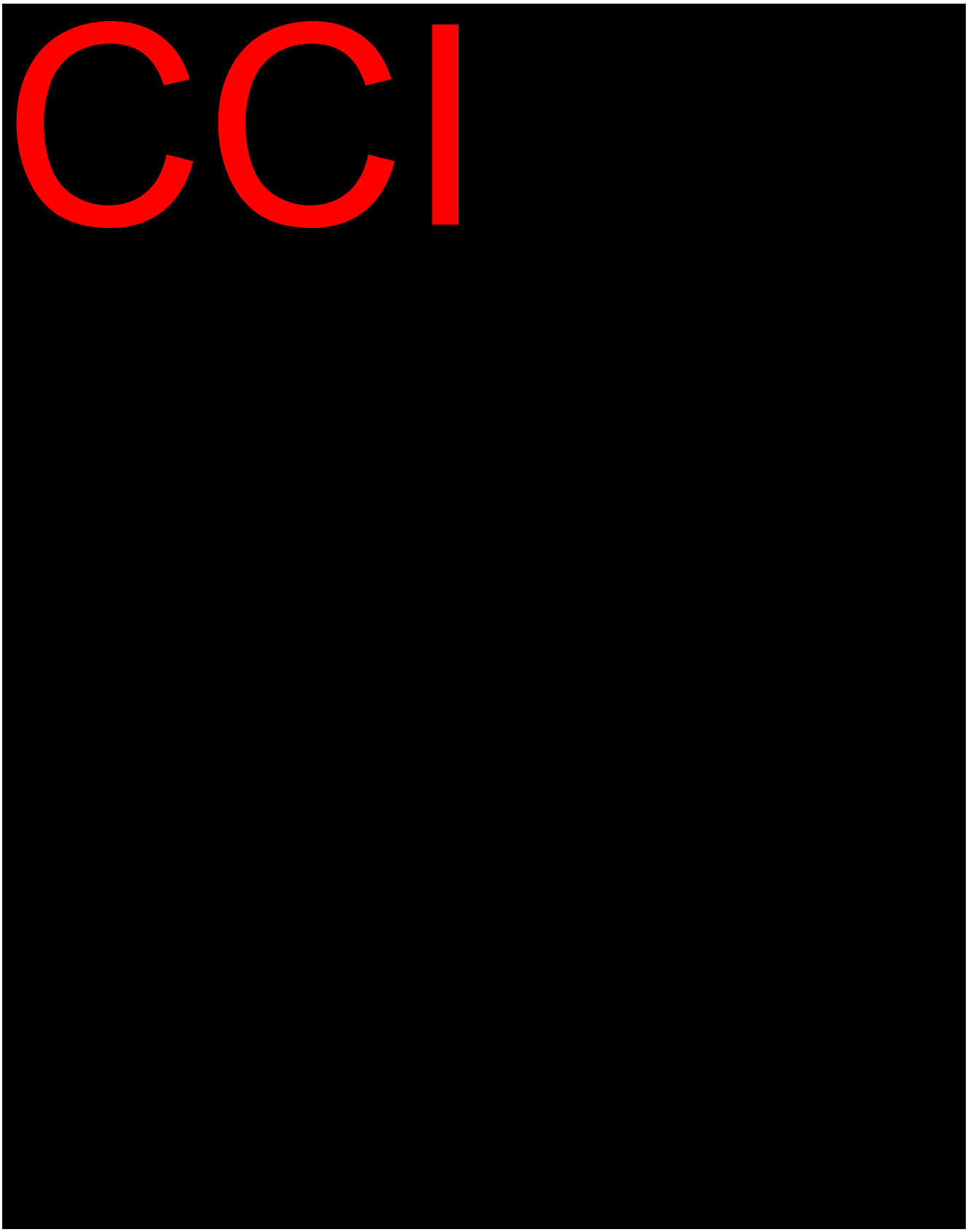
Data from this study may be combined with other study data, if appropriate. Details on PK and PK/PD analyses will be provided in an ISA-SAP or a separate ISA PK/PD analysis plan.

9.3.6.2. Immunogenicity Analyses

Upon assay validation, the frequency and percentage of participants with preexisting ADA and with TE ADA may be tabulated. TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution, if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared with baseline, if ADAs were detected at baseline (treatment-boosted ADA).

The frequency of neutralizing antibodies may also be tabulated in TE ADA-positive participants, when available.

The relationship between the presence of ADA and LY3454738 concentrations or PK parameters and PD response, including safety and efficacy, may be assessed.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CCI

9.5. Sample Size Determination

Approximately 260 participants will be randomized to study intervention.

CCI

The planned sample size for CCI CCI participants is shown in this table by each induction dosing regimen.

CCI

With this planned sample size, an EASI-75 response at Week 16 of 52% and 12% for LY3454738 and placebo, respectively, CCI participants achieve at least 91% power for pairwise comparisons with placebo using a 2-sided chi-square test at the 0.05 significance level, with no adjustment for multiple comparisons.

10. Attachments to the ISA

This section provides information specific to the FR01 ISA. For supporting documentation and operational considerations applicable to all ISAs, see Section 10 of the master IMMB protocol.

10.1. Attachment 1: Clinical Laboratory Tests

Use of central or local laboratories

Clinical laboratory tests will be performed by a central laboratory or by a local laboratory as detailed in the tables in this attachment.

In circumstances where the sponsor approves local laboratory testing in lieu of the central laboratory testing specified in the tables, the local laboratory must be qualified in accordance with applicable local regulations.

Laboratory tests for inclusion/exclusion of potential study participants

See Section 5 of the master IMMB protocol for laboratory tests that are part of the master IMMB protocol eligibility criteria. See Section 5 of this ISA for additional laboratory testing (if any) that may be required to assess eligibility.

Allowance for additional laboratory testing

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

Investigator responsibilities

Investigators must document their review of the laboratory safety results.

Provision of laboratory test results

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

10.1.1. Clinical Laboratory Tests Performed During This ISA

This section lists the clinical laboratory tests performed at the visits specified in the SoA (Section 1.3) of this ISA.

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

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

	Notes
Hormones (females)	
Serum pregnancy	Performed locally. For WOCBP only. See Section 8.2.7.
Urine pregnancy	Performed locally. For WOCBP only. See Section 8.2.7.
Follicle-stimulating hormone (FSH)	Optional. Performed locally. See Section 8.2.7.1.

	Notes
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	Perform if abnormalities were detected on urinalysis.

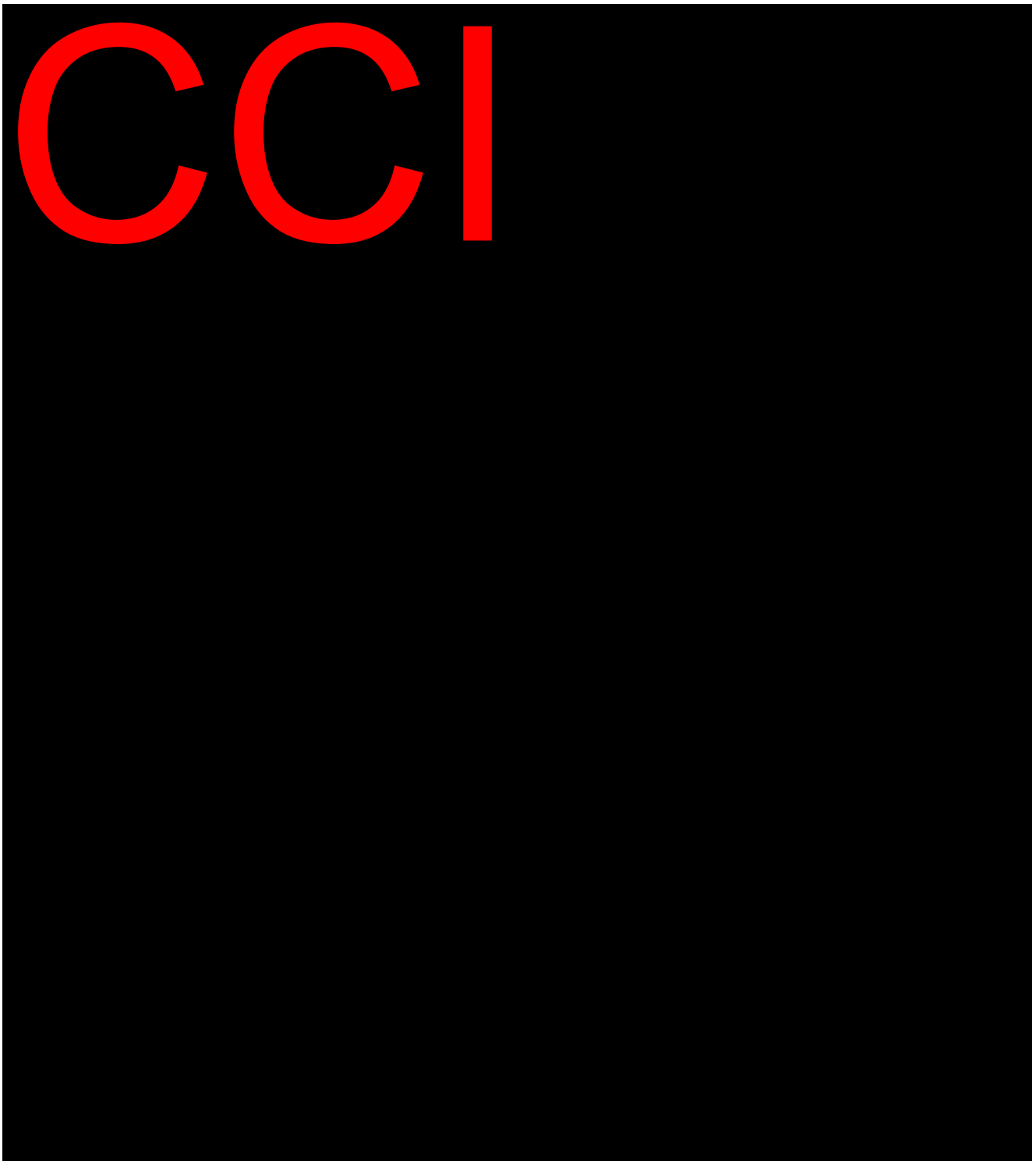
	Notes
Hepatitis Serology	
Hepatitis B virus (HBV) testing:	Assayed by Lilly-designated laboratory.
Hepatitis B virus (HBV) DNA	Performed only for participants who test positive for anti-HBc at screening.

	Notes
Pharmacokinetics (PK) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3454738 concentration	

	Notes
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3454738 antibodies	
anti-LY3454738 antibodies neutralization	

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

Abbreviations: DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; RNA = ribonucleic acid; WOCBP = women of childbearing potential.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10.2. Attachment 2: Contraceptive and Barrier Guidance

10.2.1. Definitions

See the master IMMB protocol.

10.2.2. Contraception Guidance

Females

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

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ postovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have pregnancy testing at initial screening: See the master IMMB protocol. Have subsequent pregnancy testing as described in the SoA (Section 1.3) of this ISA.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. Note: These forms of contraception must be used during the study and after the study for at least 18 weeks after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide
	Note: Male and female condoms should not be used in combination.

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

Males

No male contraception is required except in compliance with specific local government study requirements.

10.2.3. Pregnancy Testing Guidance

See Sections 1.3 and 8.2.7 of the master IMMB protocol, and Section 1.3 and Section 8.2.7 of this ISA.

10.3. Attachment 3: ISA-Specific Stopping Rules

The IAC will convene periodically but also when the accumulated safety data triggers one of the stopping rules specified in this ISA. Further enrollment in this ISA, or further dosing in this ISA, or both may be stopped, pending a decision of the IAC.

Stopping rules for Study FR01

The IAC will evaluate unblinded safety data from Study FR01 if

- 5 or more participants experience TEAEs in the same system organ class
- these TEAEs are serious (meeting at least 1 criterion which defines SAEs) or are assessed by the investigator as severe, or both, and
- these TEAEs are considered related to the blinded study intervention in the opinion of the investigator.

10.4. Attachment 4: Country-specific Requirements

For sites in EU Member States

This attachment is not applicable at this time.

For sites outside of EU Member States

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

10.5. Attachment 5: Provisions for Changes in Study Conduct During Exceptional Circumstances

Appendix 12, Section 10.12, of the master IMMB protocol, which describes provisions for changes in study conducting during exception circumstances, is applicable to this ISA.

In addition, the changes described in this attachment are applicable. These are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

See Appendix 12, Section 10.12, of the master IMMB protocol for these topics:

- exceptional circumstances
- implementing changes under exceptional circumstances
- considerations for making a change, and
- informed consent.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in Appendix 12, Section 10.12, of the master IMMB protocol or in this attachment, or not consistent with applicable local regulations, are not allowed. The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits for Visit 0 and thereafter

> **Telemedicine:** Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner may include, but are not limited to, concomitant medications, Aes, participant diary education and compliance check, and PROs via a tablet and/or a web-based collection system.
>
> **Mobile health care:** Health care visits may be performed by a mobile health care provider at locations other than the study site when participants cannot travel to the site if written approval is provided by the sponsor. Procedures performed at such visits may include, but are not limited to, vital signs, concomitant medications, Aes, participant diary education and compliance check, symptom-directed physical assessments, ECGs, collection of blood and urine samples for clinical safety laboratory testing, C-SSRS Since Last Assessed, PROs via a tablet and/or a web-based collection system.
>
> **Other alternative locations:** Procedures which could be done at an alternate location may include, but are not limited to, ECGs, biopsy sample collections, and collection of blood and urine samples for clinical safety laboratory testing.

See Appendix 12, Section 10.12, of the master IMMB protocol for additional information on data capture, safety reporting, and return to on-site visits.

Local laboratory testing option for Visit 0 (Week 0) and thereafter

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for samples listed in this table:

At…	Central laboratory testing must be retained for these samples…
Week 0 (Visit 0)	All samples, unless local testing is specified in the SoA (Section 1.3) and Attachment 1, Section 10.1.
Week 16	Hematology, clinical chemistry, and urinalysis.
All weeks/visits	CCI

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

Study intervention and ancillary supplies (including participant diaries)

See Appendix 12, Section 10.12, of the master IMMB protocol.

In addition, if study intervention will be administered to the participant during a mobile health care visit or at an alternate location, there must be resuscitation equipment, emergency drugs, and appropriately trained staff available during the CCI and until completion of all required postdosing activities.

Screening period guidance

See Appendix 12, Section 10.12, of the master IMMB protocol.

Adjustments to visit windows for Visit 0 (Week 0) and thereafter

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

This table describes the allowed adjustments to visit windows.

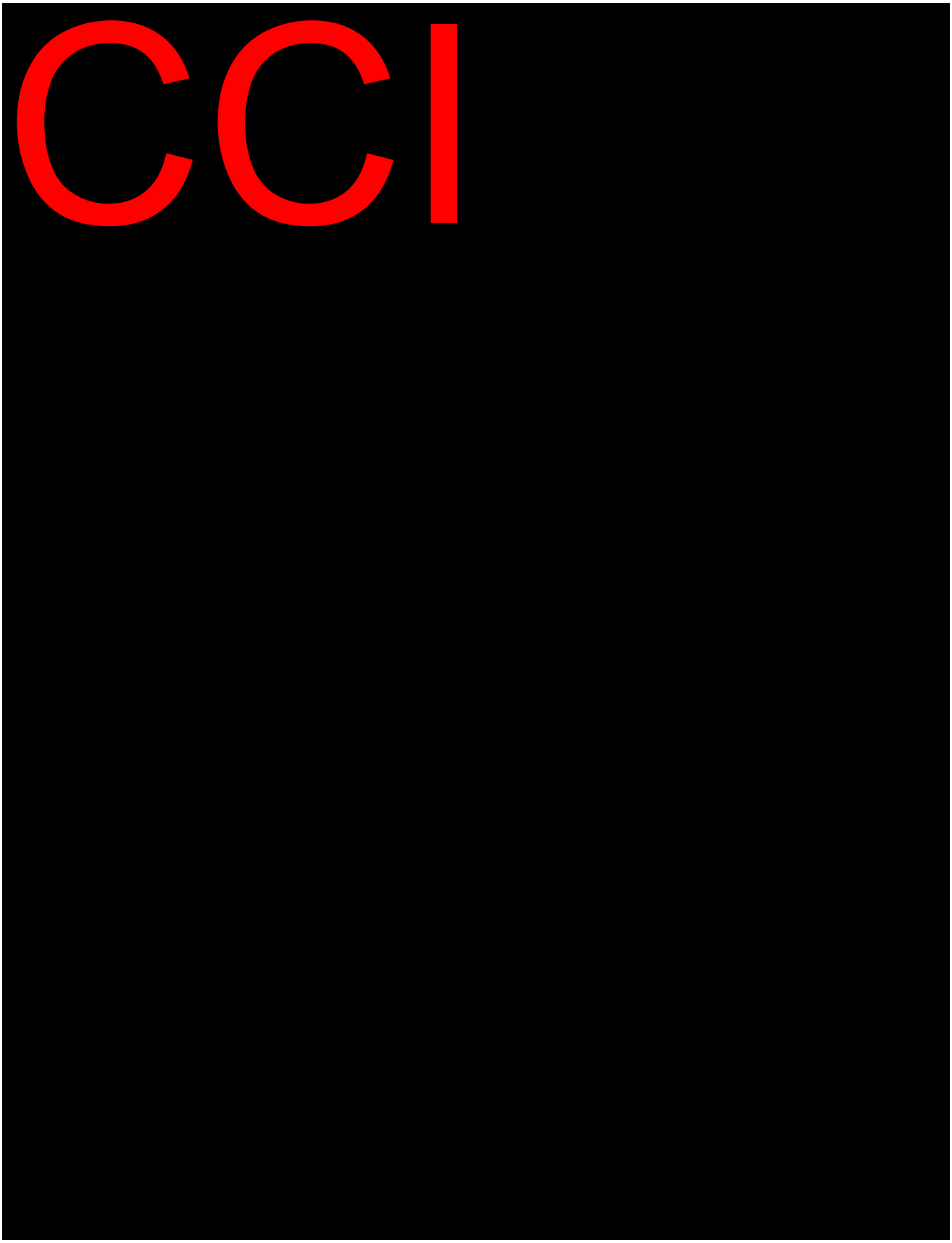
For this week or type of visit…	the permitted visit type is…	and the visit interval tolerance[a] is…
Week 0	on-site only	same as shown in the SoA
Weeks 1 though 14	remote	same as shown in the SoA
Week 16	combination of on-site and remote	on-site: EASI, vIGA-AD, SCORAD (clinical portion) within 7 days before or within 7 days after the targeted visit date (inclusive) remote: other procedures, same tolerance as shown in the SoA
CCI	remote	same as shown in the SoA
	combination of on-site and remote	on-site: EASI, vIGA-AD, SCORAD (clinical portion) within 7 days before or within 7 days after the targeted visit date (inclusive) remote: other procedures, same tolerance as shown in the SoA
Unscheduled	remote	not applicable

For this week or type of visit…	the permitted visit type is…	and the visit interval tolerance[a] is…
Early discontinuation	combination of on-site and remote	on-site: EASI, vIGA-AD, SCORAD (clinical portion) within 7 days after the early discontinuation decision remote: other procedures, same tolerance as shown in the SoA
Posttreatment follow-up 8 weeks after ED or final treatment period visit	remote	same as shown in the SoA
Posttreatment follow-up 12 weeks after ED or final treatment period visit	remote	same as shown in the SoA

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

Documentation

See Appendix 12, Section 10.12, of the master IMMB protocol.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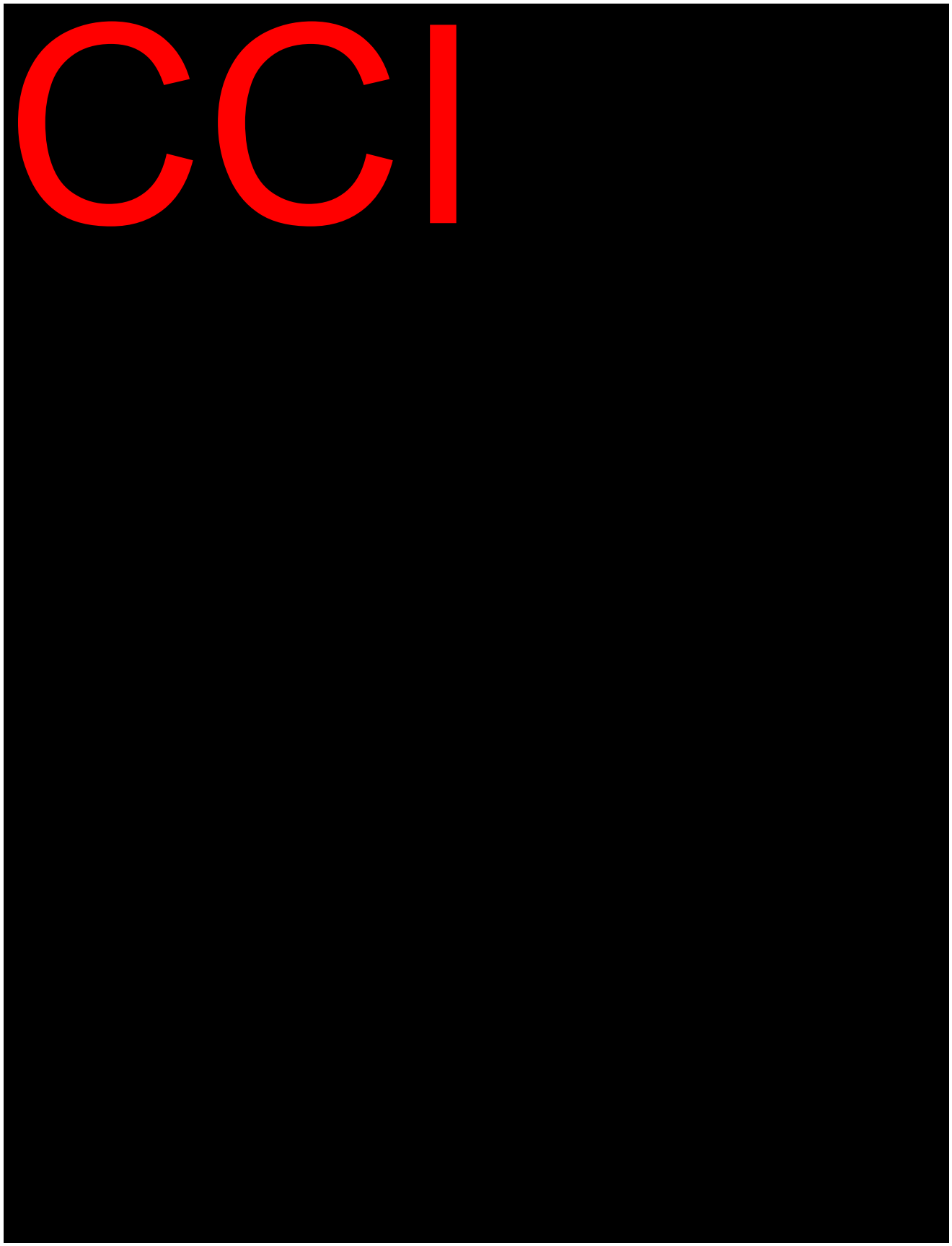
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10.8. Attachment 8: Abbreviations and Definitions

Term	Definition
ACQ-5	Asthma Control Questionnaire-5
AD	atopic dermatitis
ADA	anti-drug antibodies
ADCT	Atopic Dermatitis Control Tool
ADSS	Atopic Dermatitis Sleep Scale
AE	adverse event
AESI	adverse event of special interest
CCI	
anti-HBc	hepatitis B core antibody
AxMP	auxiliary medicinal product. See further definition in the master IMMB protocol
BCG	Bacillus Calmette-Guerin
BSA	body surface area
CBD	cannabidiol
CI	confidence interval
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
CCI **EASI-75** CCI	Participant's EASI score is reduced by at least CCI 75% CCI relative to their baseline score
ECG	electrocardiogram
ED	early discontinuation

EU	European Union
HADS	Hospital Anxiety Depression Scale
HBV	hepatitis B virus
hr	hour or hours
IAC	Internal Assessment Committee
IB	investigator brochure
ICE	intercurrent event
ICF	informed consent form
IEC	independent ethics committee
IGA	Investigator's Global Assessment
CCI	
IND	Investigational New Drug application
IRB	institutional review board
ISA	intervention-specific appendix
ISA-SAP	statistical analysis plan for the ISA
CCI	
IWRS	interactive web-response system
JAK	Janus kinase
LS	least squares
mAb	monoclonal antibody
MAD	multiple-ascending dose
MCMC-MI	Markov Chain Monte Carlo – multiple imputation
CCI	
min	minute or minutes
MP-SAP	statistical analysis plan for the master protocol

NRS	Numeric Rating Scale
PC	product complaint
PD	pharmacodynamic
PDE4	phosphodiesterase type 4
PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PRO	patient-reported outcome
CCI	
RNA	ribonucleic acid
CCI	
SAD	single-ascending dose
SAE	serious adverse event
CCI	
SCORAD	SCORing Atopic Dermatitis
SCORAD-75 **SCORAD-90**	Participant's SCORAD score is reduced by at least 75% or 90% relative to their baseline score
SoA	schedule of activities
CCI	
TB	tuberculosis
CCI	
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TE ADA	treatment-emergent anti-drug antibodies
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
US or USA	United States of America

UV	unscheduled visit
V	case report form visit
WOCBP	women of childbearing potential; see further definition in the master IMMB protocol

10.9. Attachment 9: ISA Amendment History

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

Amendment [a]: (13-Mar-2023)

Overall Rationale for the Amendment:

The purpose of this amendment is to classify the ACQ-5 as a paper instrument, to add a secondary objective for safety, to clarify dosing instructions, and to obtain additional information about CCI Minor editorial corrections and formatting errors are not represented in this table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added safety objective and endpoints as secondary objective	To improve alignment between objectives and title and rationale for study
1.3. Schedule of Activities (SoA)	In the Aes rows of Tables 1 and 2, added an instruction that information about CCI CCI events will be solicited at each visit	To improve awareness of the need to obtain additional information about these events
1.3. Schedule of Activities (SoA)	In Tables 1 and 2, listed ACQ-5 as a paper patient-reported outcomes instrument	To reflect the fact that the instrument will be provided to participants on paper, not electronically
1.3. Schedule of Activities (SoA)	In Table 1, added a CCI CCI at Week 16	To have additional data for understanding responder data at later time points
3. Objectives, Endpoints, and Estimands	Moved safety objective from exploratory to secondary, and added safety endpoints	To improve alignment between objectives and title and rationale for study
3.1. Estimands	Added the word “efficacy” in the phrase “secondary efficacy endpoints”	To align estimands text with changes made in Section 3
6. Study Intervention(s) and Concomitant Therapy	Reworded the definition of study intervention	To improve alignment with regulatory definitions
6.1. Study Intervention(s) Administered	Corrected the instructions about CCI CCI	To clarify and correct the instructions to more easily evaluate any CCI if they occur
8.3.1. Adverse Events of Special Interest	Added new text and a new subsection (Section 8.3.1.5) about the solicitation of comorbid CCI events	To obtain additional information about these CCI comorbidities

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Section # and Name	Description of Change	Brief Rationale
10.9. Attachment 9: ISA Amendment History	Revised statement about amendment history	To ensure internal document consistency

Amendment [b]: (12-Sep-2023)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the primary or major secondary analyses.

Overall Rationale for the Amendment:

The purpose of this amendment is to

- change the primary estimand and associated statistical methodology
- change the verbiage regarding the primary database interim analysis and populating language for another interim analysis based on enrollment of CCI [redacted] CCI [redacted] data, and
- remove the topical corticosteroid question.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis 3.1. Estimands	Primary estimand was changed from a CCI [redacted] estimand CCI [redacted] to a composite estimand for all intercurrent events (ICEs) of interest. The role of prohibited medications related to atopic dermatitis (AD) was clarified as an ICE of interest.	This change aligns the primary estimand and analysis CCI [redacted]
1.1. Synopsis (subsection Study Population and Number of Participants)	Added statement for 60 randomized participants who will CCI [redacted] added "up to" to the number of participants subsection to read as "Up to approximately 260 participants will be randomized…"	For better clarity
1.3. Schedule of Activities (SoA) 8.1. Efficacy Assessments	Removed TCS question	The TCS question was removed to reduce burden to sites and participants and to avoid duplicated data collection with the concomitant medication forms.
9.2. Analyses Sets	Added "at Week 0 and Week 16" in maintenance analysis set	For better clarity

Section # and Name	Description of Change	Brief Rationale
9.3.1. General considerations 9.3.2. Primary Endpoints/Estimands Analysis	The handling of missing data after accounting for ICEs of interest in the updated primary estimand will be specified in the statistical analysis plan for the ISA (ISA-SAP).	Missing data after accounting for ICEs of interest are expected to be uncommon in the updated primary estimand.
CCI		
9.3.1. General considerations	CCI	
9.3.1. General considerations 9.3.2. Primary Endpoints/Estimands Analysis		
CCI		
CCI		
9.5. Sample Size Determination	Updated the language and added number of participants	For better clarity
10.9. Attachment 9: ISA Amendment History	Inserted date, rationale, and summary of changes from ISA amendment (a).	To update document history
11. References	CCI	For reference

11. References

CCI

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