Protocol Addendum J4E-MC-IMMB (b)

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

NCT05911841

Approval Date: 12-Sep-2023

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

Master Protocol Amendment Number: b

Compound: Multi-molecule code LY900030

Master Protocol Brief 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

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

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

Document ID: VV-CLIN-080391

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

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

Amendment [b]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The purpose of this amendment is to remove topical corticosteroid (TCS) question.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Removed EU trial number	Correction
1.3. Schedule of Activities (SoA) 8.1. Efficacy Assessments 10.6. Appendix 6: Assessments of Disease Activity, Patient Reported Outcomes, and Quality of Life	Removed TCS question	The TCS question was removed to reduce burden to sites and to participants, and to avoid duplicated data collection with the concomitant medication forms.
10.3.6. Regulatory Reporting Requirements	Updated the language	To clarify for EU CTR compliance
10.5. Appendix 5: Contraceptive and Barrier Guidance	Removed “total” before hysterectomy in definition of Women not of childbearing potential (WNOCBP)	For better clarity
10.9. Appendix 9: Liver Safety: Suggested Action and Follow-up Assessments	Removed “segmented” after neutrophils	For better clarity
10.14. Appendix 14: Abbreviations and Definitions	Added definition of SUSARs	To clarify for EU CTR compliance
10.15. Appendix 15: Master Protocol Amendment History	Inserted date, rationale, and summary of changes from amendment (a).	To update document history

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1. Protocol Summary

1.1. Synopsis

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 Brief 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

Regulatory Agency Identifier Numbers:

IND: 163615

Rationale: Study J4E-MC-IMMB (IMMB) is designed as a platform trial to efficiently investigate the efficacy and safety of multiple investigational interventions for AD.

Objectives, Endpoints, and Estimands:

The purpose of this master protocol is to create a framework to evaluate the efficacy and safety of investigational interventions for AD as hypotheses emerge. In general, each ISA will assess at least 1 intervention relative to control with respect to

- efficacy as measured by assessments of disease activity (for example, EASI, SCORAD, and vIGA-AD®), patient-reported outcomes (for example, POEM), and quality of life (for example, DLQI), and
- safety, using standard assessments and measures, such as physical examinations, clinical safety laboratory tests, vital signs, and AEs.

The clinical research objectives, endpoints, and estimands for specific investigations are detailed in the relevant ISA.

Overall Design

This is a multinational, multicenter, randomized, double-blind, controlled, platform-type master protocol with ISAs to investigate multiple interventions for AD at the same time or serially over time.

The master protocol (IMMB) contains protocol elements common to every investigation in the platform, including but are not limited to, master protocol entry criteria, safety monitoring activities and criteria for discontinuation applicable to every ISA, and statistical analysis methods applicable to every ISA. It also contains administrative information applicable to all ISAs, such as an appendix describing standards for the design of ISAs to support use of a common clinical trial database.

The ISAs contain study elements specific to the interventions under study, such as dosing regimen, benefit/risk information, and intervention-specific eligibility criteria and assessments.

Brief Summary: Study participants will be adults with moderate-to-severe AD. Each ISA provides a brief summary of the health measurements/outcomes, study interventions, treatment durations, and overall study duration for that ISA**.**

Study Population: Individuals included in this study will be at least 18 years old and have a diagnosis of AD for at least 12 months before screening (Visit 401), have moderate-to-severe AD scores (EASI score ≥12; vIGA-AD score ≥3; and ≥10% of BSA involvement) at Visit 401; and be candidates for systemic therapy, having a documented history of inadequate response to existing topical medications within 6 months before screening or a history of intolerance to topical therapy.

Number of Participants: Each ISA specifies the planned number of participants for that ISA.

Intervention Groups and Duration: Each ISA specifies the intervention groups and study duration for that ISA.

Ethical Considerations of Benefit/Risk: Each ISA provides intervention-specific benefit/risk information for that ISA.

Data Monitoring Committee: Yes (Internal Assessment Committee).


CCI

1.3. Schedule of Activities (SoA)

Activities for the master protocol screening period can be conducted over more than 1 day as long as the activities are completed within the window. Decentralized capabilities, such as telephone, IT-assisted virtual visit, mobile health care, or a combination thereof, may be used for activities, if allowed by local regulations and if the sponsor provides written approval for such capabilities.

Table 1. Screening Period of the Master IMMB Protocol (Study J4E-MC-IMMB)		
		Comment
Visit interval tolerance (window) in days	≤90 before Study Day 1	Study Day 1 is the day of first dose of study intervention. The first dose is given to eligible participants after all screening and baseline evaluations of both the master IMMB protocol and the relevant ISA have been completed. See the relevant ISA for screening/baseline activities.
CRF Visit number	**V401**	
Consent and demographics		
Informed consent	X	Informed consent for the master IMMB protocol must be obtained before any master protocol-specific tests or procedures are performed. Informed consent must also be obtained before any ISA-specific tests or procedures are performed (Appendix 1, Section 10.1.3).
Inclusion and exclusion criteria: confirmation of eligibility	X	The inclusion and exclusion criteria of both the master IMMB protocol (Section 5) and the relevant ISA must be confirmed before the participant is randomized to a study intervention and receives a first dose. See the relevant ISA for ISA-specific inclusion and exclusion criteria.
Demographics	X	Includes year of birth, sex, ethnicity (where permissible), and race (Section 4.2.1).
Preexisting conditions and medical history	X	All conditions ongoing and relevant medical history should be collected.
Prespecified medical history	X	Prespecified medical history includes, but is not limited to, conjunctivitis, allergic rhinitis, allergies, asthma, depression, insomnia, and herpes infection, including herpes zoster.
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Concomitant medications	X	All ongoing medications at the time of consent should be collected. Background emollients are to be documented as concomitant medications.
Adverse events (AEs)	X	AE collection begins when the ICF for this master protocol is signed (Section 8.3.1). For AESIs, additional data may be collected per the ISA; see the relevant ISA for information about AESIs.
Physical evaluation		
Height	X	
Weight	X	

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CRF Visit number	**V401**	
Physical examination	X	The physical examination excludes pelvic, rectal, and breast examinations unless clinically indicated (Section 8.2.2). Assess for tuberculosis (TB) risk factors, and for signs and symptoms of active TB, including an assessment of peripheral lymph nodes (Sections 8.2.2 and 8.2.8).
Vital signs	X	Includes pulse rate, blood pressure, respiratory rate, and body temperature. Measured after the participant has been sitting at least 5 minutes (Section 8.2.1).
ECG 12-lead (single) (local)	X	A local ECG will be collected according to instructions in Section 8.2.4.
X-ray of chest	X	Posterior–anterior view and, if needed, lateral view. Locally performed. Interpreted and reported by a radiologist or pulmonologist. Chest x-ray is not required if one was performed within 90 days before Visit 401 and sufficient documentation exists for the TB evaluation (Sections 8.2.5 and 8.2.8). A chest CT scan can be used instead of a chest x-ray if the chest CT scan was performed within the same time window (Section 8.2.5).
Patient-reported outcomes (electronic)		Complete prior to any clinician-administered assessments.
Dermatology Life Quality Index (DLQI)	X	
Patient-Oriented Eczema Measure (POEM)	X	
SCORing Atopic Dermatitis (subjective) (SCORAD)	X	
Clinician-administered assessments (electronic)		
vIGA-AD	X	
Eczema Area and Severity Index (EASI)	X	
SCORing Atopic Dermatitis (objective) (SCORAD)	X	

Table 1. Screening Period of the Master IMMB Protocol (Study J4E-MC-IMMB)		
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CRF Visit number	**V401**	
Clinician-administered assessments (paper)		
Columbia-Suicide Severity Rating Scale Baseline/Screening (C-SSRS)	X	AE collection should occur prior to the collection of the C-SSRS. Adapted for the assessment of ideation and behavior categories only.
Participant diary (electronic)		
CCI		
Dispense diary	X	Diary contains the following assessments: Itch Numeric Rating Scale (Itch NRS), Atopic Dermatitis Sleep Scale (ADSS), and Skin Pain Numeric Rating Scale (Skin Pain NRS).
Participant education		
CCI		
Diary education	X	
Laboratory tests and sample collections		
Hematology	X	
Clinical chemistry	X	
Follicle-stimulating hormone (FSH)	X	Optional; performed as needed to confirm postmenopausal status (Section 8.2.7.1).
Serum pregnancy	X	Only for WOCBP (Section 8.2.7).
Urinalysis	X	
Hepatitis B virus (HBV) screening tests	X	Screening includes anti-HBc and HBsAg. If anti-HBc is positive, it will be followed by an HBV DNA test (Section 8.2.9).
Hepatitis B virus (HBV) DNA	X	Only for participants who are anti-HBc positive at Visit 401 (Section 8.2.9).
Hepatitis C virus (HCV) screening tests	X	If HCV antibody test is positive, an HCV RNA test will be run by the testing laboratory (Section 8.2.10).

Table 1. Screening Period of the Master IMMB Protocol (Study J4E-MC-IMMB)		
		Comment
Visit interval tolerance (window) in days	≤90 before Study Day 1	Study Day 1 is the day of first dose of study intervention. The first dose is given to eligible participants after all screening and baseline evaluations of both the master IMMB protocol and the relevant ISA have been completed. See the relevant ISA for screening/baseline activities.
CRF Visit number	**V401**	
Tuberculosis (TB) test	X	Participants who had a tuberculin skin test (TST) must have the test read 48 to 72 hr after placement. The TST test does not need to be read at the site but must be read by a trained professional and results must be presented to the site prior to first dose of study intervention in an ISA (Section 8.2.8).
HIV testing	X	
Estimated glomerular filtration rate (eGFR)	X	Calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2021).
Randomization and dosing-related activities		See the relevant ISA for randomization and dosing-related activities.
Register visit with IWRS	X	When this visit is registered in IWRS, the participant receives a unique participant number.
After confirming participant's eligibility for an ISA, register the participant in IWRS for the selected ISA	X	In IWRS, a participant can be registered for only 1 ISA at a time (Section 4.1). Before this activity is performed, review and confirm the participant's eligibility according to inclusion and exclusion criteria of both the master protocol and the selected ISA. See Section 5 of this document for inclusion and exclusion criteria of this master protocol. See the relevant ISA for ISA-specific inclusion and exclusion criteria.

Abbreviations: AESI = adverse event of special interest; anti-HBc = hepatitis B core antibody; CRF = case report form; CT = computed (or computerized) tomography; ECG = electrocardiogram; HBV = hepatitis B virus; HIV = human immunodeficiency virus; ICF(s) = informed consent form(s); ISA = intervention-specific appendix; IWRS = interactive web-response system; JAK = Janus kinase; RNA = ribonucleic acid; V = case report form visit; WOCBP = women of childbearing potential.

2. Introduction

AD, also called atopic eczema, is a common noncontagious, chronic, relapsing, pruritic inflammatory skin disease. Clinically AD is characterized by severe pruritus and eczematous dermatitis and can be distinguished from other skin diseases by such factors as age of onset, distribution on the body, xerosis, lichenification, and atopy (Barrett and Luu 2017; Bieber 2021). AD may present with dry itchy skin and may be complicated by rashes that blister or weep. This may lead to an unrelenting itch scratch cycle (Frazier and Bhardwaj 2020). Various factors have been implicated in the ongoing inflammation associated with AD, including genetics, environment, and pro-Th2 cytokines. Numerous cytokines, including IL-25, IL-33, IL-4, IL-13, IL-5, IL-31, and IL-10, have been shown to drive T helper response. Skin breakdown may be due to mutations in the filaggrin gene, leading to itch, and bacterial colonization may also contribute to the pro-inflammatory state (Brandt and Sivaprasad 2011).

Patients with AD have a high burden of disease, and their quality of life is significantly affected (Galli et al. 2020). In the Global Burden of Disease Study 1990-2017, AD had the highest disease burden among skin diseases as measured by disability-adjusted life years (Laughter et al. 2021). Because of pruritus and skin pain, patients with moderate-to-severe AD can experience severe and frequent disturbances of sleep, which can play a role in overall health (Silverberg et al. 2021a). In 1 study, AD was shown to have a greater negative effect on patient mental health than diabetes and hypertension (Kiebert et al. 2002). Symptoms of AD can impact a patient's self-esteem, social activities and relationships, and performance at work or school (Sibbald and Drucker 2017). The economic burden of AD can include increased sick leave, job changes, or job loss due to symptoms (Nørreslet et al. 2018).

Currently, there is no cure for AD. Common therapies for mild-to-moderate AD include avoidance of irritants; use of wet wraps, soaking baths, and emollients; and use of TCS and TCI. Topical medications provide some symptomatic relief for many patients but do not always adequately control the disease. In patients with persistent moderate-to-severe disease, step-up options include phototherapy and systemic immunosuppressives, such as oral glucocorticosteroids, azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil (Simpson et al. 2017; Wollenberg et al. 2018; Bieber 2021).

Recent advances in the understanding of the molecular pathogenesis of AD have led to the development and approval of more targeted therapies for AD (Worm et al. 2020). Some examples are listed in this table.

Therapy	Description	Indication	Citation
Dupilumab	Human anti-IL-4R alpha monoclonal antibody that inhibits signaling for both IL-4 and IL-13	Moderate-to-severe AD	Boguniewicz 2020 Dupixent package insert 2022 Dupixent summary of product characteristics
Tralokinumab	Human monoclonal antibody that binds to IL-13 and inhibits its interaction with IL-13Rα1 and IL-13Rα2	Moderate-to-severe AD	Adbry package insert 2021 Adtralza summary of product characteristics

Therapy	Description	Indication	Citation
Baricitinib	Oral JAK1/2 inhibitor	Moderate-to-severe AD	Olumiant summary of product characteristics
Upadacitinib	Oral JAK1 inhibitor	Moderate-to-severe AD	Rinvoq package insert 2022 Rinvoq summary of product characteristics Guttman-Yassky et al. 2021
Abrocitinib	Oral JAK1 inhibitor	Moderate-to-severe AD	Cibinqo package insert 2022 Cibinqo summary of product characteristics Simpson et al. 2020a Silverberg et al. 2020
Ruxolitinib	Topical JAK1/2 inhibitor	Mild-to-moderate AD	Opzelura package insert 2022

Nevertheless AD remains a major burden for patients and society. More efficacious and durable therapies with a favorable safety profile are needed.

2.1. Study Rationale

Variations in key parameters in the design and conduct of clinical trials for AD can have an impact on the interpretation of treatment efficacy and can complicate efforts to compare the trial outcomes, such that Silverberg et al. (2022) have called for efforts to "harmonize" trials for AD.

One approach to harmonizing a series of clinical trials is to implement a "platform" trial design. As described by Woodcock and LaVange (2017), a platform study uses a master protocol to establish an overarching structure for testing many interventions over time.

Studies employing master protocols have been used in many therapeutic areas, as shown in this table.

Therapeutic Area or Indication	Study Acronym (if available)	Citation
Oncology	I-SPY-2	Barker et al. 2009
Oncology	Lung-MAP	Herbst et al. 2015
Oncology	GBM AGILE	Alexander et al. 2018
Alzheimer's disease	EPAD	Ritchie et al. 2016
Alzheimer's disease	DIAN-TU	Bateman et al. 2017
COVID-19	ACTIV	LaVange et al. 2021
COVID-19	RECOVERY and REMAP-CAP	Goossens et al. 2022
Osteoarthritis	CPMP	NCT05080660
Hidradenitis suppurativa	—	NCT03827798
Sjogren's syndrome	—	NCT04988087
Systemic lupus erythematosus	WILLOW	NCT05162586
Systemic lupus erythematosus	IMMA	NCT05123586
Immune thrombocytopenia	—	NCT05086744
Crohn's disease	PRISM	NCT04102111
Chronic spontaneous urticaria	LIBERTY-CSU CUPID	NCT04180488

Studies of new treatments for AD could benefit from the harmonization that a platform design can bring. See the ISAs for rationales to investigate particular interventions in this platform.

2.2. Background

2.2.1. Intervention Selection: Adding or Stopping Intervention-Specific Investigations

This platform trial is designed to enable the investigation of many interventions for AD by means of the introduction of new ISAs over time.

At the inception of this platform trial, at least 1 ISA will be available.

Additional ISAs will be added to the platform trial over time based on

- availability of safety, tolerability, and PK data to support the clinical development of a particular intervention for AD, and
- regulatory and ERB approval to add the new ISAs to the platform trial.

An ISA may be stopped early for the reasons stated in Appendix 1, Section 10.1.9.

2.2.2. Governance

Selection of new interventions for investigation

Eli Lilly and Company will be responsible for the selection of interventions to be included in this platform trial.

Periodic assessment of data from intervention-specific investigations

An IAC will be established to make periodic assessments of ISA data and to make recommendations for protocol modifications or other actions. This internal committee will be independent of the Lilly study team responsible for the master protocol and its ISAs. The IAC is described in Appendix 1, Section 10.1.5.

Considerations for use of a common database in this platform trial

Data collected for the master protocol and for each ISA will be stored in a common database for the platform trial. To be included in this master protocol, investigations of new interventions must be amenable to trial designs that conform to the standard activity structure of the common database, as described in Appendix 13, Section 10.13.

2.3. Benefit/Risk Assessment

Study interventions are not administered during Visit 401. The screening procedures of Visit 401 generally present little risk. Participants may benefit by receiving personal health information from the physical examination and other safety assessments.

Intervention-specific benefit/risk information is provided in the relevant ISA. More detailed information about the known and expected benefits and risks and reasonably expected AEs of an intervention also may be found in the IB for the intervention.

3. Objectives, Endpoints, and Estimands

The purpose of this master protocol is to create a framework to evaluate the efficacy and safety of investigational interventions for AD as hypotheses emerge. In general, each ISA will assess at least 1 investigational intervention relative to control with respect to

- efficacy as measured by assessments of disease activity (for example, EASI, SCORAD, and vIGA-AD), patient-reported outcomes (for example, POEM), and quality of life (for example, DLQI), and
- safety, using standard assessments and measures, such as physical examinations, clinical safety laboratory tests, vital signs, and AEs.

The clinical research objectives, endpoints, and estimands for specific investigations are detailed in the relevant ISA.

4. Study Design

4.1. Overall Design

This is a multinational, multicenter, randomized, double-blind, controlled, platform-type master protocol with ISAs to investigate multiple interventions for AD at the same time or serially over time. The figure in Section 1.2 illustrates the schema.

The ISAs can begin independently of one another as interventions become available for clinical testing. The ISAs can also finish independently of one another, ending, for example, when the ISA has reached its full planned duration or when interim analyses show that an intervention's criteria for futility or success have been met.

Master protocol and ISAs

The overall design includes 2 components which, used together, constitute the complete protocol for study conduct:

- The master protocol (IMMB) document explains the platform and contains protocol elements common to every investigation in the platform. Common elements include, but are not limited to, the master protocol screening period and master protocol entry criteria; safety monitoring activities and criteria for discontinuation applicable to every ISA; and statistical analysis methods applicable to every ISA. The document also contains administrative information applicable to all ISAs, such as an appendix describing standards for the design of ISAs to support use of a common clinical trial database.
- The ISAs provide information on the interventions to be studied, for example, intervention-specific screening activities, background information, benefit/risk, and dose justification; intervention-specific study objectives, endpoints, and estimands; and intervention-specific outcomes measurements and statistical analysis methods. Each ISA includes an SoA listing study activities from Week 0 (Visit 0) through the last planned study visit.

Informed consent

Informed consent must be obtained from a potential study participant

- before any master protocol-specific tests or procedures are performed, and
- before any ISA-specific tests or procedures are performed.

The ICF(s) must meet the regulatory and ethical requirements stated in Appendix 1, Sections 10.1.1 and 10.1.3.

Screening periods

The master protocol and the ISAs each have screening periods. This approach to screening enables an ISA to have screening/baseline activities that are different from the screening/baseline activities of other ISAs.

The screening periods have windows that flexibly enable an investigator to begin screening a participant for an ISA either

- after screening the participant for the master protocol, or

- while still screening the participant for the master protocol

as long as

- the date of signing the master protocol ICF is earlier than or same as the date of signing the relevant ISA ICF, and
- the screening windows in the relevant SoAs are observed.

If a study site has more than 1 active ISA, the participant can be screened for multiple ISAs serially or in parallel, at the discretion of the investigator.

See Section 1.3 for procedures of the master protocol screening period. See the relevant ISAs for procedures of the ISA-specific screening/baseline period.

Participant assignment to an ISA

Before being randomized to a study intervention, a participant must be assigned to an ISA in IWRS. The assignment occurs in this manner.

Step 1	Assess the participant's eligibility according to all study entry criteria, including those of the master IMMB protocol and the available ISA(s).
Step 2	Determine which ISA the participant is to be assigned to, after confirming participant's eligibility for the applicable ISA.
Step 3	Interact with IWRS to register the participant's assignment to the selected ISA.

In IWRS, the participant can be registered for only 1 ISA at a time. The participant's assignment to an ISA is not blinded.

Treatment and posttreatment periods of ISAs

After being assigned to an ISA, eligible participants will be randomized to a study intervention within that ISA. Randomization to interventions within an ISA will be blinded (Section 6.4).

The duration of the treatment period depends on the design of the ISA. Some ISAs may have longer treatment periods than other ISAs, and some ISAs may have multiple treatment periods. Every ISA will include at least 1 posttreatment follow-up visit.

See the relevant ISA for procedures conducted during ISA-specific treatment and posttreatment study periods.

Early discontinuation of study intervention

Participants who permanently discontinue the study intervention early will have no additional treatment period visits but will remain in the study to complete procedures for an ED visit and the ISA-specified posttreatment follow-up visits (Section 7.1.2).

4.2. Scientific Rationale for Study Design

Platform trial design

A platform trial can enable harmonization of key elements of a series of related clinical trials, thereby easing the interpretation of treatment efficacy and aiding efforts to compare the trial outcomes.

This platform trial is intended to provide these and other clinical development efficiencies:

- using a common clinical trial database built on a standard visit structure that requires key assessments and procedures to be conducted at standard visits, while also flexibly enabling additional visits, assessments, and procedures if needed to support intervention-specific objectives and endpoints
- harmonizing certain elements study design by, for example, defining a core set of study entry criteria in the master protocol, and
- establishing a network of clinical study sites to enable a continuous stream of potential study participants over time, with sites potentially benefiting from streamlined and coordinated trial logistics.

Appropriateness of study population

The master protocol inclusion criteria will enable enrollment of patients who are representative of the general population with at least moderately severe AD at initial screening (Visit 401). Scores of EASI ≥12 and IGA ≥3, with AD involvement of ≥10% of BSA, at screening have been used among the inclusion criteria of other studies of AD (Thaçi et al. 2016; Wollenberg et al. 2021). An ISA, as part of its inclusion criteria, may specify criteria resulting in a population with greater disease severity.

Type of control group

To enable ISA designs in which use of placebo might not be necessary or appropriate, this master protocol does not specify what is to be used as control in every ISA. Each ISA will specify and justify the type of control (for example, placebo or an active intervention) used in that ISA.

4.2.1. Rationale for Collection of Race and Ethnicity

In this study, collection of demographic information includes ethnicity, where permissible according to local regulations, and race. The scientific rationale is based on the need to assess variable response in safety or efficacy, or both, based on race or ethnicity. Such a need can be addressed only if all the relevant data are collected.

4.2.2. Patient Input into Design

See the relevant ISA.

4.3. Justification for Dose

See the relevant ISA.

4.4. End of Study Definition

The end of the master protocol will occur when all ISAs are complete and no new ISAs are planned.

For each ISA, the end of the study is defined as the date of the last scheduled procedure of the last participant assigned to treatment in that ISA.

Consistent with local law and regulations, the competent authority and relevant ethics committees in each participating country will be notified about the completion or early termination of each ISA.

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 relevant ISA, 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.

Note: An ISA may have additional entry criteria that are more restrictive than the criteria listed in this master protocol. Review and confirm the participant's eligibility before interacting with IWRS for the purpose of registering the participant's ISA assignment.

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. Inclusion Criteria

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

Informed consent

[1] Are capable of giving, and have given, signed informed consent as described in Appendix 1, Section 10.1.3, which includes consent to compliance with the requirements and restrictions listed in the ICF(s) and in this protocol, including compliance with the use of contraceptives.

Note: Contraceptive use should be consistent with local regulations regarding the methods of contraception for persons participating in clinical studies. For contraception requirements, see the relevant ISA.

Participant characteristics

[2] Are male or female and at least 18 years of age at the time of signing the ICF(s).

Note: In some jurisdictions, the legal age of consent for study participation is greater than 18 years. For sites in such jurisdictions, the legal age of consent will be used for this criterion.

Disease-specific characteristics

[3] Present with a diagnosis of AD at least 12 months prior to screening (Visit 401), as defined by the American Academy of Dermatology "Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis" (Eichenfield et al. 2014), as well as the following, at Visit 401:

[3a] EASI score ≥12

[3b] vIGA-AD score ≥3

[3c] ≥10% of BSA involvement (per EASI BSA)

[4] Are candidates for systemic therapy, and have a history, documented by a physician and/or the investigator, of inadequate response to existing topical medications within 6 months preceding screening (Visit 401) or a history of intolerance to topical therapy, as defined by at least 1 of the following:

[4a] inability to achieve good disease control defined as mild disease or better, for example, IGA ≤2, after use of at least a medium-potency TCS for at least 4 weeks, or for the maximum duration recommended by the product prescribing information, for example, 14 days for super-potent TCS, whichever is shorter. Note: For the purpose of this criterion, a TCS may be used with or without TCI.

Note: Failing a systemic therapy intended to treat AD, for example, dupilumab, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or other small molecules, within 6 months before screening (Visit 401) will be considered a surrogate for inadequate response to existing topical medications.

[4b] a history of clinically significant adverse reaction with the use of TCS, for example, skin atrophy, allergic reaction, or systemic effects, that, in the opinion of the investigator, outweigh the benefits of retreatment

[5] Agree to daily use of at least 1 emollient continuously throughout the study.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply at screening (Visit 401):

Previous or current skin conditions

[6] Have a history of eczema herpeticum:

[6a] any episode within 12 months prior to screening (Visit 401), or

[6b] 2 or more episodes during lifetime

[7] Are currently experiencing or have a history of concomitant skin conditions other than AD, for example, psoriasis or cutaneous lupus, that, in the opinion of the investigator, would interfere with evaluations of the effect of study intervention on AD.

[8] Are currently experiencing or have a history of erythrodermic, refractory, or unstable skin disease which requires frequent hospitalizations or IV treatment and, in the opinion of the investigator, could interfere with study participation.

[9] Are currently experiencing a skin infection that requires treatment with, or is currently being treated with, topical or systemic antibiotics.

Note: Participants who fail screening due to this criterion should not be rescreened until at least 4 weeks after screen failure and at least 2 weeks after resolution of the infection.

Previous or current therapies

[10] Have a history of TCS use suggestive of a high risk for TCS withdrawal, for example, a history of prolonged or frequent use of moderate- to high-potency TCS, especially on the face (Hajar et al. 2015), such that, in the opinion of the investigator, the participant will be unable to withdraw and abstain from TCS for several weeks during the study.

Previous or current infections

[11] Have a current or recent acute, active infection. For at least 30 days before screening (Visit 401) and up to the first dosing visit of the ISA, participants must have no symptoms or signs of confirmed or suspected infection and must have completed any appropriate anti-infective treatment.

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

[12] Have had any of the following types of infection within 12 weeks before screening (Visit 401) or develop any of these infections before the first dosing visit of the ISA:

[12a] serious (requiring hospitalization, or IV or equivalent oral antibiotic treatment, or both)

[12b] opportunistic, as defined in Winthrop et al. 2015; see Appendix 8, Section 10.8 for examples

Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.

[12c] chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)

[12d] recurring, including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, and chronic osteomyelitis

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

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

[14] Have or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and the United States CDC, unless such treatment is underway (see Section 8.2.8).

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

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

[17] Have HIV infection.

Diagnostic assessments

[18] Have any of the following specific abnormalities on the Visit 401 screening laboratory tests:

[18a] serum creatinine, ALT, or AST ≥2 times ULN

[18b] ALP ≥2 times ULN

[18c] TBL ≥1.5 times ULN

[18d] hemoglobin <10.0 g/dL

[18e] neutropenia – ANC $<1.2 \times 10^3/\mu L$

[18f] lymphopenia – lymphocyte count $<0.75 \times 10^3/\mu L$

[18g] thrombocytopenia – platelets $<100 \times 10^3/\mu L$

[18h] eGFR <60 mL/min/1.73 m^2 (CKD-EPI Creatinine Equation [2021]) (FDA 2020; NKF [WWW]).

Note: For repeat testing of the Visit 401 screening laboratory tests, see Section 5.4.3 of this master protocol.

[19] Have other laboratory test results at screening (Visit 401) which are outside the normal reference range for the population or study site and, in the opinion of the investigator, indicate unacceptable risk for the participant's safety in the study.

[20] Have screening ECG abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the participant's safety in the study.

Other previous or current medical conditions

[21] Have a history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the participant to infection.

[22] Have a history of organ or bone marrow transplant, or will require such a transplant during the study.

[23] Have any serious concomitant illness that

[23a] requires treatment with systemic corticosteroids

[23b] requires active frequent monitoring, for example, unstable chronic asthma, or

[23c] would otherwise interfere with study participation, in the opinion of the investigator

[24] Have a history of any major surgery within 12 weeks before screening (Visit 401) or will require major surgery during the study.

[25] Have a history of a thrombotic event within 24 weeks before screening (Visit 401) or are on anticoagulants and in the opinion of the investigator are not well-controlled regarding management of hypercoagulable risk.

[26] Have a history of any of the following within 12 months before screening (Visit 401):

[26a] myocardial infarction

[26b] unstable ischemic heart disease

[26c] cerebrovascular accident

[26d] stroke, or

[26e] New York Heart Association Stage III or IV heart failure

[27] Have significant and uncontrolled disease, in the opinion of the investigator, such as

[27a] cardiovascular disease, for example, uncontrolled hypertension, angina, or congestive heart failure

[27b] endocrine disorder, for example, diabetes, or thyroid dysfunction

[27c] respiratory, hepatic, renal, gastrointestinal, hematologic, or neuropsychiatric disorder

[27d] any other serious or unstable illness that could constitute an unacceptable risk to the participant when taking an IMP or could interfere with the interpretation of study data

[28] Have a diagnosis or history of malignant disease within 5 years before screening (Visit 401), with the following exceptions:

- basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years, and
- cervical carcinoma in situ, with no evidence of recurrence within 5 years before screening (Visit 401).

[29] Are at risk for suicide, defined as at least 1 of the following:

[29a] are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide

[29b] have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS and the ideation occurred within the past month, **or**

have answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS, and the behavior occurred within the past month.

[30] Have a condition suggesting a possibly greater risk of clinically significant drug hypersensitivity reactions, for example:

[30a] clinically significant multiple or severe drug allergies, or

[30b] a history of severe posttreatment hypersensitivity reactions, including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis.

Previous or concurrent clinical study participation

[31] Have received an active study intervention in any clinical study within the last 30 days, including an active study intervention in any ISA of this master protocol.

Note: If the previous study intervention has a long half-life, at least 5 half-lives or 30 days (whichever is longer) should be used for this criterion.

Note: Participants are not excluded by this criterion if they received only placebo in a previous clinical investigation, whether that investigation was an ISA of Study IMMB or a separate clinical study.

[32] Were randomized to a study intervention in an ISA of this master protocol but prematurely stopped participating in that ISA for any reason, including but not limited to, early discontinuation from study intervention, early discontinuation (withdrawal) from the ISA, or being lost to follow-up.

[33] Are currently receiving a study intervention in any other clinical study, or are participating in any other type of medical research judged not to be scientifically or medically compatible with this study.

Other reasons for exclusion

[34] Are pregnant or are intending to become pregnant or breastfeed at any time during the study.

Note: WOCBP must test negative for pregnancy as indicated by a negative serum pregnancy test at screening (Visit 401) followed by a negative urine pregnancy test within 24 hours prior to the first exposure to study intervention in an ISA.

[35] Have evidence of current or a recent history (that is, within 6 months before Visit 401) of any substance use disorders, including but not limited to, cannabis use disorder, of any severity as defined by the DSM-V (APA 2013), in the opinion of the investigator, excepting disorders of nicotine or caffeine use.

Note: Participants are to be excluded by this criterion if there is evidence (per investigator or per participant's self-report) of use of marijuana, marijuana extract, or THC-containing products as self-medication for symptoms of AD or other conditions. See the relevant ISA for any prohibitions on the concomitant use of CBD products or medically prescribed marijuana, marijuana extract, or THC-containing products for the treatment of AD symptoms or other conditions during the study.

[36] Have received blood products within 6 months before screening (Visit 401).

[37] Have donated more than a single unit of blood within 4 weeks before screening (Visit 401) or intend to donate blood during the study.

[38] Are largely or wholly incapacitated, permitting little or no self-care, such as being bedridden or confined to wheelchair.

[39] Have insufficient venous access for the study-required blood sampling.

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

[41] Are employees of Eli Lilly and Company or are employees of a third-party organization that is involved in the study and requires exclusion of their employees.

[42] Are unable or unwilling to make themselves available for the required study visits or are unwilling to follow study restrictions and procedures.

[43] Are for any reason, in the opinion of the investigator or the sponsor's designated medical monitor, unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

See the relevant ISA for any applicable lifestyle considerations, such as restrictions on

- diet or meals
- exercise or activity, or
- use of caffeine, alcohol, or tobacco.

For some ISAs, there may be no such restrictions.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to a study intervention. A minimal set of screen failure information is

required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1. Rescreening of Individuals Who Failed Screening for the Master Protocol

Individuals who do not meet the criteria for participation in this master protocol according to Sections 5.1 and 5.2 of this master IMMB protocol (screen failure at the master protocol level) may be rescreened **2 times** after the reason for the screen failure has resolved.

At each rescreening for the master protocol, the individual will first sign an ICF for the master protocol (Appendix 1, Section 10.1.3), and the individual will receive a new participant number.

5.4.2. Rescreening of Individuals Who Failed Screening for an ISA

Individuals who do not meet the eligibility criteria for participation in a particular ISA cannot be rescreened for the same ISA using the same participant number.

However, if they are still within the master protocol screening window and if they still meet the master protocol eligibility criteria, they can be consented to, and screened for, participation in another ISA (Section 5.5).

Individuals will not be given a new participant number when they are consented to another ISA.

5.4.3. Allowed Retesting of Screening Laboratory Tests

Repeating laboratory tests 1 time during the screening period is permitted. Additional repeat testing of laboratory tests may be permitted in consultation with the sponsor's designated medical monitor. Repeating screening tests to comply with the protocol-designated screening period or for any other reason does not constitute rescreening.

Results of screening laboratory tests are valid for 60 days during the screening period. If a participant is still in screening after 60 days, the screening laboratory tests should be repeated (Section 8.2.6).

See Appendix 7, Section 10.7, for guidance on retesting for TB.

5.5. Criteria for Temporarily Delaying Randomization of a Participant

Not applicable for the master IMMB protocol.

A study site could experience a period of time in which no ISA is active at that site. During that time period, screening for the master protocol may continue, but the screening window of the master protocol, defined in Section 1.3, must still be observed. Participants who have not been assigned to an active ISA before the end of the master protocol screening window must undergo rescreening if they wish to continue their study participation.

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

Study interventions are described in the ISAs.

Supply and labeling of study interventions

The sponsor or its designee will supply study interventions in accordance with current Good Manufacturing Practice.

Study interventions will be labeled as appropriate for country requirements.

6.1.1. Medical Devices

See the relevant ISA for information about medical devices, if applicable.

All PCs, including malfunction, use error, and inadequate labeling, will be documented and reported by the investigator throughout the study and will be appropriately managed by the sponsor.

6.1.2. Background Therapy

At least 1 emollient should be used daily throughout the study as background therapy.

Moisturizers with additives such as antipruritics or antiseptics are not permitted.

Background therapies should be used according to their local product labeling.

On the days of study visits, emollients should not be applied until after the participant has undergone all study procedures and clinical evaluations. This is to allow adequate assessment of skin dryness at the visit.

Emollient therapy must be recorded as stated in Section 6.9.

6.2. Preparation, Handling, Storage, and Accountability

Sponsor responsibilities

The sponsor will provide instructions on the preparation, handling, and storage of the study interventions, including site responsibility and accountability for the administered study interventions.

Site responsibilities and accountability

Investigators and authorized site personnel will consult the information provided by the sponsor for information on the administration of study interventions, including warnings, precautions, contraindications, adverse reactions, and dose modifications.

The following are additional responsibilities of the investigator or the investigator's designee:

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

  Note: In some ISAs, enrolled participants may receive study intervention for self-administration during intervals between study visits. Such participants will receive appropriate instructions for the storage and use of study intervention, and, if applicable, for the return of unused of study intervention.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions will be provided by the sponsor.

The investigator or designee is also responsible for

- explaining the correct use of the study interventions
- verifying that instructions are followed properly
- maintaining accurate records of study intervention dispensing and collection, and
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Assignment to Study Intervention

For ISAs having multiple intervention groups and random assignment of participants to those groups, the randomization will be determined by a computer-generated random sequence using an IWRS. The randomization ratio and, if applicable, randomization stratification factors will be specified in the relevant ISA.

6.4. Blinding

Blinding will be maintained throughout the conduct of the study as described in the separate unblinding plan.

Method of assignment to an ISA

A participant's assignment to a particular ISA will not be blinded (Section 4.1).

Method of assignment to study intervention within an ISA

Within an ISA, a participant's assignment to a particular study intervention will be determined by a computer-generated random sequence using an IWRS. Unless otherwise specified in the ISA, this assignment will be blinded to participants, to investigators and other site personnel, and to sponsor staff who are involved in the treatment or clinical evaluation of the participants.

Emergency unblinding

Emergency unblinding for AEs may be performed through the IWRS. This option may be used **only** if the participant's well-being requires knowledge of the participant's intervention assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

The investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that the unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

If, because of emergency unblinding, a participant's study intervention assignment is unblinded to the participant or to blinded site personnel who are performing assessments, including the investigator, the participant must be discontinued from study drug (Section 7.1.2).

Additional measures to minimize bias

Additional measures to minimize bias may be described in the ISAs.

6.5. Study Intervention Compliance

Deviations from the prescribed dosage regimen should be recorded in the CRF. The investigator should verify that participants have the ability to understand and comply with study instructions. Before enrolling a participant, the investigator is responsible for discussing with the participant methods to attain high compliance with study procedures, including administration of study intervention.

If a participant is noncompliant with study procedures, with administration of study intervention, or both, the investigator should assess the participant for the cause of the noncompliance and to educate or manage the participant as appropriate to improve compliance.

If, in consultation with the sponsor or its designee, the noncompliance is deemed to be significant or further noncompliance occurs, the participant may be permanently discontinued from study intervention or from the study (Sections 7.1 and 7.2). If there are additional measures to assure or assess compliance or adherence, these measures will be described in the ISAs.

6.6. Dose Modification

Dose modifications, if allowed, are described in the relevant ISA.

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

If any study interventions are available after the participant's last visit in an ISA, those interventions will be described in the relevant ISA.

6.8. Treatment of Overdose

See the relevant ISA.

6.9. Prior and Concomitant Therapy

Prior therapy

Relevant prior therapies, as defined in the SoA (Section 1.3), are to be assessed and recorded according to the instructions of the CRF.

Concomitant therapy

Any vaccine, therapy, or medication, including over-the-counter medicines, prescription medicines, vitamins, and herbal supplements, that the participant receives during the study must be identified and at a minimum assessed and recorded at the visits specified in the SoA, along with

- reason for their use
- dates of administration, including start and end dates, and
- dosage information for concomitant therapies of special interest, including rescue medication.

The sponsor's designated medical monitor should be contacted if there are any questions regarding concomitant therapy.

6.9.1. Rescue Medication

See the relevant ISA.

6.9.2. Permitted Concomitant Therapy

See the relevant ISA.

6.9.3. Prohibited Concomitant Therapy

See the relevant ISA.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

This section describes reasons for a participant's

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

Discontinuation of specific sites or the study as a whole is handled as part of Appendix 1, Section 10.1.9.

7.1. Discontinuation of Study Intervention

7.1.1. Temporary Discontinuation of Study Intervention

A participant may need to have study drug temporarily interrupted (withheld) during the study. Except in an emergency, the investigator should consult the sponsor's designated medical monitor

- before temporarily interrupting study drug for reasons not specified in this protocol or the relevant ISA, and
- before resuming interrupted study drug, unless otherwise specified in this protocol or the relevant ISA.

This table lists some reasons for temporary interruption (withholding) of study drug and conditions necessary for resumption of study drug.

Temporarily interrupt study drug if the participant...	Conditions for resuming study drug
has an AE or abnormal laboratory value which, in the opinion of the investigator, may have an unclear relationship to study drug	The investigator and the sponsor's designated medical monitor agree that resumption of study drug is appropriate for the participant
has neutropenia – ANC $<1.0 - 0.5 \times 10^3/\mu L$	ANC $\geq 1.0 \times 10^3/\mu L$
has hepatic events or liver test abnormalities as described in Section 7.1.1.1	As described in Section 7.1.1.1, resumption of study drug can be considered only in consultation with the sponsor's designated medical monitor and only if the liver test results return to baseline or near baseline values and if a self-limited nondrug etiology is identified
is a candidate for LTBI treatment and is treated for LTBI	Withhold study drug for at least the first 4 wk of LTBI treatment. Study drug may be resumed ● after participant has received at least 4 wk of appropriate LTBI therapy as per WHO or US CDC guidelines, and ● if there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance. The participant must complete appropriate LTBI therapy to remain eligible to receive study drug

Temporarily interrupt study drug if the participant...	Conditions for resuming study drug
has a serious or opportunistic infection, as defined in Section 5.2 (for LTBI, see preceding row)	After resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment
has HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. In this situation, the sponsor's designated medical monitor should be contacted regarding the participant's status. HBV DNA testing is to be repeated as soon as is feasible	Negative for HBV DNA. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study drug (see Section 7.1.2)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDC = Centers for Disease Control and Prevention; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; LTBI = latent tuberculosis infection; ULN = upper limit of normal; US = United States; WHO = World Health Organization.

7.1.1.1. Elevated Liver Test Results

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

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

Elevation	Exception
ALT or AST >8 times ULN	
ALT or AST >5 times ULN for more than 2 wk	
ALT or AST >3 times ULN and either TBL >2 times ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2 times ULN
ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	
ALP >3 times ULN, when the source of increased ALP is the liver	
ALP >2.5 times ULN and TBL >2 times ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2 times ULN
ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	

Source: FDA 2009 and other consensus guidelines, with minor modifications.

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

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

Elevation	Exception
ALT or AST >4 times baseline	
ALT or AST >3 times baseline for more than 2 wk	
ALT or AST >2 times baseline and either TBL >2 times ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2 times ULN
ALT or AST >2 times baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	
ALP >2.5 times baseline, when the source of increased ALP is the liver	
ALP >2 times baseline and TBL >2 times ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2 times ULN
ALP >2 times baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	

Source: FDA 2009 and other consensus guidelines, with minor modifications.

Resuming study drug after elevated liver tests

Resumption of the study drug can be considered only in consultation with the sponsor's designated medical monitor and only if the liver test results return to baseline or near baseline values and if a self-limited nondrug etiology is identified. Otherwise, the study drug should be discontinued (Section 7.1.2).

7.1.2. Permanent Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for

- an ED visit, and
- posttreatment follow-up visits, if applicable, as shown in the SoA of the relevant ISA.

Possible reasons for permanent discontinuation of study drug include, but are not limited to, the reasons listed here:

Participant decision: The participant asks to stop receiving study drug.

Pregnancy: The participant becomes pregnant (Sections 8.2.7 and 8.3.2).

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

Suicidal ideation and behavior: The participant

- becomes actively suicidal, in the judgment of the investigator, or
- answers "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
- answers "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

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

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

HIV or AIDS: The participant develops HIV infection or AIDS.

Active TB or untreated LTBI: The participant develops active TB or has untreated LTBI (Section 8.2.8). For temporary discontinuation of study drug while the participant is being treated for LTBI, see Section 7.1.1.

HBV: The participant tests positive for HBV DNA (Section 8.2.9).

Note: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification (Section 7.1.1). Prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study drug, the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study drug relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

HCV: The participant tests positive for HCV RNA (Section 8.2.10).

Clinically significant ECG finding: Discontinuation of study drug may occur after consultation with the sponsor's designated medical monitor (see Section 8.2.4).

Liver test abnormality: Section 7.1.1.1 describes temporary interruption of study drug based on liver test abnormalities. If, after temporary interruption of study drug, liver test results fail to return to baseline or near baseline and a self-limited nondrug etiology is not identified, study drug is to be permanently discontinued.

Abnormal hematology laboratory values: The participant has any of the following results on 2 consecutive samples taken at least 48 hours, but no more than 1 week, apart:

- hemoglobin <8.0 g/dL

- neutropenia – ANC <0.5 × 10^3/µL
- lymphopenia – lymphocyte count <0.5 × 10^3/µL
- thrombocytopenia – platelets <50.0 × 10^3/µL
- eosinophil counts >5.0 × 10^3/µL with signs and/or symptoms of target organ involvement that are not consistent with the participant's AD and medical history, and
- eGFR <30 mL/min/1.73 m^2 (CKD-EPI Creatinine Equation [2021]) (FDA 2020; NKF [WWW]).

For laboratory values that meet permanent discontinuation thresholds, study intervention should be discontinued. However, if, in the opinion of the investigator, the laboratory abnormality is due to intercurrent illness, laboratory tests may be repeated. When the laboratory value returns to baseline and the intercurrent illness or other identified factor has resolved, then the investigator may restart study intervention after consultation with the sponsor's designated medical monitor.

Other AEs or changes in laboratory values: The participant has an AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits the permanent discontinuation of study drug and appropriate measures being taken.

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

Unblinding: If an investigator, blinded site personnel, or blinded designees who are performing assessments, or the participant is unblinded to the participant's intervention assignment because of an emergency unblinding as described in Section 6.4, the participant must be permanently discontinued from study drug. In cases where there are ethical reasons for the participant to continue in the study and continue to receive study drug, the investigator must obtain specific approval from the sponsor's designated medical monitor for the participant to continue.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation (withdrawal) from the study is expected to be uncommon.

A participant may withdraw from the study in these circumstances:

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

Data collection and follow-up for participants who discontinue the study

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit and posttreatment follow-up, as shown in the SoA of the relevant ISA. If the

participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

Withdrawal of consent for disclosure

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

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the IMMB SoA (Section 1.3) and in the SoA of the relevant ISA. Adherence to the study design requirements, including those specified in the SoAs, 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 relevant ISA, all blinded assessments and sample collections should be completed before a dose is administered at the dosing visits.

Patient-reported outcomes assessments should be completed prior to any clinician-administered assessments.

If multiple safety assessments are scheduled to occur at the same visit, the preferred order of completion is

1. ECGs and then vital signs
2. other safety assessments, including physical examinations and nonleading (spontaneous) AE collection, followed by C-SSRS, if the C-SSRS is applicable (Sections 8.2.12 and 8.3.1.1), and finally
3. sample collections for clinical safety laboratory testing, PK, immunogenicity, biomarkers, and other sample testing specified in the applicable SoA.

8.1. Efficacy Assessments

Efficacy-related assessments occur at visits specified in the IMMB SoA (Section 1.3) and in the relevant ISA.

Efficacy endpoints

Efficacy endpoints are described in the relevant ISA.

Participant diary

The diary contains the following assessments:

- Itch NRS
- ADSS, and
- Skin Pain NRS.

Descriptions of efficacy-related assessments

See Appendix 6, Section 10.6, for descriptions of efficacy-related assessments, including assessments of

- disease activity
- patient-reported outcomes, and
- quality of life.

8.2. Safety Assessments

Visits and order of safety assessments

Safety assessments occur at visits specified in the IMMB SoA (Section 1.3) and in the relevant ISA.

Safety monitoring

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

The sponsor will monitor the trial safety data, including AEs, SAEs, discontinuations, vital signs, and clinical laboratory results by means of periodic blinded reviews and other appropriate methods. These methods include reviews by a functionally independent safety physician and/or clinical research scientist who regularly reviews SAE reports in real time and across studies, and who reviews applicable clinical safety and epidemiological publications from the literature. If this safety monitoring uncovers an issue that needs to be addressed by unblinding at the individual or group level, the IAC can conduct additional analyses of the safety data. The IAC is an advisory group for this study formed to protect the integrity of the study in unblinded safety data reviews. See Appendix 1, Section 10.1.5.

Safety data collection and reporting

The AE data collection and reporting requirements are described in Section 8.3 and Appendix 3, Section 10.3.

For some interventions studied under this master protocol, there may be predefined AESIs. If so, any additional sample or data collections for AESIs will be specified in the relevant ISAs.

Appropriateness of safety assessments

The safety assessments used in this study are routine elements of clinical health assessment and Phase 2 drug development.

Safety assessments described in this master protocol and in ISAs

The following sections describe safety assessments applicable to all ISAs. See the relevant ISAs for any additional safety assessments that may be applicable.

8.2.1. Vital Signs

Vital signs, including pulse rate, blood pressure, respiratory rate, and body temperature, will be measured as specified in the IMMB SoA (Section 1.3) and in the relevant ISA, and as well as whenever clinically indicated. Additional vital signs may be measured whenever warranted, as determined by the investigator.

Timing of collection of vital signs

Vital signs should be measured after the participant has been sitting for at least 5 minutes. When possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point. See the relevant ISA for additional timings, if any.

Unscheduled orthostatic vital signs

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If the participant feels unable to stand, sitting or supine vital signs will be recorded. See the relevant ISA for any additional orthostatic vital signs requirements.

8.2.2. Physical Examinations

Complete physical examinations and symptom-directed physical examinations will be conducted as specified in the IMMB SoA (Section 1.3) and in the relevant ISA.

Symptom-directed physical assessments may also be conducted at other visits, as specified in the ISA and as determined by the investigator, if a participant presents with complaints or as needed based on participant status and local standard of care.

TB assessments

At screening and approximately every 3 to 4 months thereafter, the specified physical evaluation, whether complete or symptom-directed, will include a documented assessment of TB risk factors and symptoms or signs of active TB, including an assessment of peripheral lymph nodes and body temperature (see Section 8.2.8).

Complete physical examination

The complete physical examination should include the following regions and body systems:

- general appearance
- skin
- head, ears, eyes, nose, and throat
- lymph nodes
- cardiovascular
- respiratory
- abdominal
- genitourinary (only as clinically indicated)
- extremities, and
- neurologic.

Pelvic, rectal, and breast examinations are not required unless clinically indicated.

Symptom-directed physical assessments

After screening, physical assessments should include

- a symptom-directed evaluation
- evaluation of eyes, heart, lungs, and abdomen
- visual evaluation of the skin, other than area covered by clothing or other material, and
- examination for signs of active TB, including assessment of peripheral lymph nodes.

Height and weight

Height and weight will be measured and recorded as specified in the IMMB SoA (Section 1.3) and, if applicable, in the relevant ISA.

8.2.3. Skin Assessment with Fitzpatrick Scale of Skin Phototypes

The skin type of each participant will be assessed using the Fitzpatrick Scale of Skin Phototypes, as specified in the relevant ISA.

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

8.2.4. Electrocardiograms

A single, local 12-lead ECG will be collected for each participant as specified in the IMMB SoA (Section 1.3). ECGs may also be collected at visits specified in the relevant ISA and at additional visits or time points when deemed clinically necessary.

Timing of collection of ECGs

The ECGs should be collected before any blood or tissue samples are collected. Participants must be supine for at least approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

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

Interpretation of collected ECGs

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

Actions to be taken after a clinically significant finding on an ECG

Any new clinically relevant finding should be reported as an AE (Section 8.3).

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT/QTc interval) after enrollment, the investigator or qualified designee, in conjunction with the sponsor's designated medical monitor, will determine if the participant can continue on study intervention and if any change in participant management is needed (Section 7.1.2).

Documentation of review of ECGs

The review of the ECG printed at the time of collection must be documented. All ECGs recorded should be stored at the investigational site.

8.2.5. Chest Imaging

A high-quality, locally performed chest x-ray (posterior–anterior view and, if needed, a lateral view), interpreted and reported by a radiologist or pulmonologist, will be obtained as specified in the IMMB SoA (Section 1.3) and, if applicable, in the relevant ISA.

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

Conditions for using a previous chest x-ray at screening

Participants do not need to have a chest x-ray at screening if, in the opinion of the investigator, both of these conditions are met and, in the opinion of the investigator, there is no clinical indication for a repeated chest x-ray:

- the chest x-ray was performed within 90 days before starting the initial screening period of this master protocol (Visit 401), and
- documentation of that chest x-ray, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

  Note: In some jurisdictions, the interval between x-rays must be greater than 90 days. If so, a chest x-ray performed within 6 months before Visit 401 can be used.

Alternatives to chest x-ray

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

8.2.6. Clinical Safety Laboratory Tests

In this master protocol, Appendix 2 (Section 10.2) and the SoA (Section 1.3) provide a list of clinical laboratory tests to be performed during the screening period of this master protocol. See the relevant ISA for clinical laboratory tests to be performed during the study periods of an ISA.

All protocol-required laboratory assessments, as defined in the ISAs and in this master protocol, must be conducted in accordance with the SoAs, standard collection requirements, and the laboratory manuals.

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

Reviewing and recording test results

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

Duration of validity of screening tests

Results of screening laboratory tests are valid for 60 days during the screening period. If a participant is still in screening after 60 days, the screening laboratory tests should be repeated. Repeating screening laboratory tests does not by itself constitute rescreening (Section 5.4.3).

Additional information

See the relevant ISA for instructions about

- repeat testing after a clinically significant abnormal finding
- fasting visits
- laboratory samples to be collected after a systemic hypersensitivity event, and
- allowance for additional laboratory testing.

8.2.7. Pregnancy Testing

Pregnancy testing is to be performed for WOCBP, as defined in Appendix 5, Section 10.5.

Pregnancy testing at Visit 401

Serum pregnancy testing will be performed centrally during the screening period of this master protocol (Section 1.3 and Appendix 2, Section 10.2).

Pregnancy testing after Visit 401

Urine pregnancy testing after Visit 401 will be performed locally according to the SoA of the relevant ISA. If the specified visit includes administration of study intervention, the pregnancy test must be "negative" within 24 hours before the study intervention is administered.

If a urine pregnancy test is not available, a local serum pregnancy test is an acceptable alternative.

If a urine pregnancy test is inconclusive at any visit, an additional serum pregnancy test should be performed.

Pregnancy testing at any time during the study

Additional pregnancy testing may be performed at any time in the study, at the discretion of the investigator, if the participant's menstrual period is missed or there is clinical suspicion of pregnancy, or as required by local law or regulation.

Discontinuation of participants who are pregnant

Participants who are pregnant will be permanently discontinued from the study intervention (Section 7.1.2).

8.2.7.1. Optional FSH Testing

A participant's FSH level can be measured centrally at the discretion of the investigator at the Visit 401 screening (Section 1.3 and Appendix 2, Section 10.2). The FSH level can also be measured locally after screening at the discretion of the investigator. The purpose of this optional FSH testing is to assist the investigator in determining whether a participant can be considered "postmenopausal" for the purposes of pregnancy testing and contraception requirements.

8.2.8. Tuberculosis Testing and Monitoring

Screening

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

- thorough history to determine the lifetime risk factors for TB infection, for TB progression, and for symptoms and/or signs of active TB, and
- signs of previous or active TB by means of
  - thorough physical examination for signs of active TB, including measurement of body temperature (Section 8.2.1) and assessment of peripheral lymph nodes (Section 8.2.2), and
  - a high-quality chest x-ray (posterior–anterior view, including a lateral view if needed) interpreted and reported by a radiologist or pulmonologist (Section 8.2.5).

All participants with no history of LTBI or active TB, and no history of positive Mantoux TST using PPD or positive *Mycobacterium tuberculosis* IGRA must have 1 of the following tests:

- PPD TST, or
- IGRA for *M tuberculosis.*

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

Diagnosed LTBI

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

- After receiving at least 4 weeks of appropriate LTBI therapy, as per WHO or the United States CDC guidelines, there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance. In this case, the participant may be rescreened (Section 5.4.1) and is not excluded due to LTBI.
- The participant must continue and complete appropriate LTBI therapy to remain eligible to continue to receive study intervention (Sections 7.1.1 and 7.1.2).

Monitoring during the study

For all participants, monitoring for TB is to be continuous throughout the study. At a minimum, each participant is to have the following documented approximately every 3 to 4 months:

- Thorough history to determine any risk factors for TB infection and for TB progression, symptoms or signs of active TB (Section 8.2.2), and
- Thorough physical examination for signs of active TB, including measurement of body temperature (Section 8.2.1) and assessment of peripheral lymph nodes (Section 8.2.2).

8.2.9. Hepatitis B Testing and Monitoring

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

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
- If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required:
  - If the screening HBV DNA is positive, the participant is excluded.
  - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least approximately every 3 to 4 months during the study, as specified in the relevant ISA.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected, study intervention will be temporarily withheld or permanently discontinued, as described in Sections 7.1.1 and 7.1.2, and the participant should receive appropriate follow-up medical care.

8.2.10. Hepatitis C Testing

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

- If anti-HCV is positive, a test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded (Section 5.2).

Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study intervention will be discontinued, as described in Section 7.1.2, and the participant should receive appropriate follow-up medical care.

8.2.11. Hepatic Safety Testing and Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 9, Section 10.9), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN
ALP <1.5 times ULN	ALP ≥2 times ULN
TBL <1.5 times ULN	TBL ≥2 times ULN, except for patients with Gilbert's syndrome
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline
TBL ≥1.5 times ULN	TBL ≥1.5 times baseline, except for patients with Gilbert's syndrome

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, a history of concomitant medications (including over-the-counter), herbal and dietary supplements, a history of alcohol drinking, and other substance abuse.

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

Comprehensive hepatic evaluation

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

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

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

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

Based on the patient's history and initial results, further testing should be considered in consultation with the sponsor's designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

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

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

- elevation of serum ALT to ≥5 times ULN on 2 or more consecutive blood tests, if baseline ALT <1.5 times ULN
    - In participants with baseline ALT ≥1.5 times ULN, the threshold is ALT ≥3 times baseline on 2 or more consecutive tests
- elevated TBL to ≥2 times ULN, if baseline TBL <1.5 times ULN (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5 times ULN, the threshold should be TBL ≥2 times baseline
- elevation of serum ALP to ≥2 times ULN on 2 or more consecutive blood tests, if baseline ALP <1.5 times ULN
    - In participants with baseline ALP ≥1.5 times ULN, the threshold is ALP ≥2 times baseline on 2 or more consecutive blood tests
- hepatic event considered to be an SAE, and
- discontinuation of study drug due to a hepatic event.

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

8.2.12. Suicidal Ideation and Behavior Risk Screening and Monitoring

Screening for suicidal ideation or behavior

As specified in the IMMB SoA (Section 1.3), screening for suicidal ideation or behavior includes the C-SSRS.

Monitoring for suicidal ideation and behavior and depressive symptomatology

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

During the treatment and posttreatment periods of the ISAs, suicidal ideation and behavior and depressive symptomatology may be assessed; see the relevant ISA for details.

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).

8.2.12.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

See Section 8.3.1.1 for the collection of the C-SSRS relative to nonleading (spontaneous) AE collection.

8.2.13. Systemic Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

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

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in the relevant ISA. Laboratory results are provided to the sponsor via the central laboratory.

8.2.14. Additional Safety Data and Sample Collections

For some interventions, some additional data or sample collections may be necessary for the assessment of safety. See the relevant ISA for any additional instructions.

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

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

- AEs
- SAEs, and
- PCs.

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and, if applicable, all AESIs as defined in the ISAs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality, or both. Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hr of awareness	SAE CRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hr of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	End of period equal to at least 5 terminal half-lives after last dose of study intervention; consult the IB or the sponsor's medical monitor	Within 24 hr (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hr of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; CRF = case report form; IB = investigator's brochure; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

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

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading (spontaneous) AE collection should occur before the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS collection but was not captured during the nonleading AE collection, sites should not change the AE form.

However, if an AE is serious or leads to discontinuation, the AE should be included on the AE form, and the process for reporting SAEs should be followed.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

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

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

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

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the

appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

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

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

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

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

Any female participant who becomes pregnant while participating in the study will permanently discontinue study intervention (Section 7.1.2). When discontinued, the participant will follow the standard discontinuation process and continue directly to the posttreatment follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

See the relevant ISA for

- a list of intervention-specific AESIs, if any, and
- additional actions to take, if any, when a listed AESI occurs.

8.4. Pharmacokinetics

If specified in the relevant ISA, blood samples will be collected for the purpose of determining the plasma or serum concentrations of the study intervention.

Collection visits and times

The visits and times for collecting PK samples will be specified in the relevant ISA, if applicable. The actual date and time (24-hour clock time) of dosing and PK sample collections must be recorded accurately on the appropriate forms. See the ISA for instructions about when to record the date and time of dosing relative to PK sample collections.

Handling and analysis of samples

Instructions for the collection and handling of blood samples will be provided by the sponsor. Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of the study intervention will be assayed using a validated PK assay.

Additional and excess samples

A maximum of 3 extra samples may be collected at additional time points during an ISA's treatment and posttreatment follow-up periods, if the collection of additional samples is warranted and agreed upon between both the investigator and sponsor.

In the case of systemic hypersensitivity reactions, additional blood samples may be obtained for PK analyses (see Section 8.2.13 and the relevant ISA).

All unused excess samples collected for PK testing may be used for exploratory analyses such as

- bioanalytical methods development
- assay validation or cross-validation exercises
- protein binding
- additional biomarker analysis, and/or
- metabolism work.

Blinding

Drug concentration information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

Sample retention

The purpose of retention and maximum duration of retention for long-term storage of samples is described in Appendix 1, Section 10.1.12.

8.5. Pharmacodynamics

If specified in the relevant ISA, blood samples will be collected for the purpose of determining PD, and the visits and times for collecting these samples will be specified in the relevant ISA, if applicable. See the ISA for statements about sample use, if PD samples are collected. The duration of sample retention is specified in Appendix 1, Section 10.1.12.

Any PD results which could unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

8.6. Genetics

Where local regulations and the IRB or IEC allow, a whole blood sample will be collected from consenting participants for pharmacogenetic/DNA analysis. This sample collection may occur at the randomization visit or at any later visit, as specified in the SoA of the relevant ISA.

Sample use

Samples may be used for research related to the study intervention and its mechanism of action, the drug target, genetic variants thought to play a role in AD, on the disease process and pathways associated with the disease or related diseases. The samples may also be used to develop tests or diagnostic tools or assays related to AD or to the study intervention. The samples may also be used to investigate variable exposure or response to study intervention. The assessment of variable response may include evaluation of AEs or differences in efficacy. Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Genetic variation may impact a participant's response to the study

intervention (as specified in the individual ISA), susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to

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

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

Sample confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel. The sponsor will store the blood and/or DNA samples in a secure storage space with adequate measures to protect confidentiality.

Sample retention

Samples will be retained at a facility selected by the sponsor or its designee. Samples will be retained while research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified in Appendix 1, Section 10.1.12.

8.7. Exploratory Biomarkers

If specified in the relevant ISA, samples will be collected for exploratory non-pharmacogenetic biomarker research.

Collection visits and times

The visits and times for collecting samples for non-pharmacogenetic biomarker research will be specified in the relevant ISA, if applicable.

Sample use

Samples may be used for research on the

- drug target
- disease state
- variable response to treatment with the study intervention, as specified in the individual ISA
- pathways associated with AD

- mechanism of action of the study intervention, and/or
- development and/or validation of diagnostic tools or assays related to AD or the study intervention.

Sample confidentiality

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

Sample retention

Samples will be retained at a facility selected by the sponsor or its designee. Samples will be retained while research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified in Appendix 1, Section 10.1.12.

8.8. Immunogenicity Assessments

Immunogenicity may be evaluated in an ISA. Information on immunogenicity sample collection and assessment will be described in the ISA, as applicable. See Appendix 1, Section 10.1.12 for details on sample retention.

If specified in the relevant ISA, 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 will be specified in the relevant ISA, if applicable. The actual date and time (24-hour clock time) of each sample collection will be recorded.

To aid interpretation of these results, a predose blood sample for PK analysis will be collected at time points after baseline.

Handling and analysis of samples

Instructions for the collection and handling of blood samples will be provided by the sponsor. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the study intervention at a laboratory approved by the sponsor. If applicable, antibodies may be further characterized for cross-reactive binding, as well as their ability to neutralize the activity of the study intervention and/or a relevant native cytokine.

Additional samples

If specified in the ISA, when the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE ADA positive and, if applicable, the ADA cross-reactively bind an endogenous counterpart, then additional samples may be taken every 3 months for up to 1 year from last dose or until the ADA signal returns to baseline (that is, no longer TE ADA positive), whichever is less.

In the case of systemic hypersensitivity reactions, additional blood samples may be obtained for ADA analyses (see Section 8.2.13 and the relevant ISA).

Sample retention

Samples will be retained at a facility selected by the sponsor or its designee. Samples will be retained while research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified in Appendix 1, Section 10.1.12.

8.9. Medical Resource Utilization and Health Economics

See the relevant ISA.

9. Statistical Considerations

The SAP for this master protocol (MP-SAP) will be finalized prior to the first unblinding. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of key aspects of the planned analyses.

9.1. Statistical Hypotheses

For each ISA of this master protocol, the primary null hypothesis is that there is no difference between the intervention and the control on the primary endpoint. Intervention-specific details regarding hypotheses and statistical testing are in its respective ISA.

9.1.1. Multiplicity Adjustment

No adjustments for multiplicity will be performed.

9.2. Analyses Sets

This table describes analysis sets defined for all ISAs unless otherwise specified in the ISA:

Participant Analysis Set	Description	Used to Analyze Endpoints Related to...
Modified intent-to-treat (mITT)	All randomized participants receiving at least 1 dose of study intervention. Participants will be included in the analysis set according to their randomly assigned intervention.	● efficacy objectives, and ● patient-reported outcomes, if applicable
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.	● safety
Pharmacokinetics (PK)	All randomized participants receiving at least 1 dose of study intervention and have PK data available.	● PK

Additional intervention-specific analyses sets may be described in respective ISAs.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Unless otherwise indicated in ISA-specific analyses, the following general considerations apply to the analyses:

- Primary and secondary endpoint analyses will be tested at a 2-sided α level of 0.05 for frequentist analyses and a probability threshold of 97.5% for Bayesian Analyses.
- Baseline values will be defined as the last available value before the first dose of study intervention.
- Efficacy and PRO analysis models may contain independent variables. These variables may include, but are not limited to, treatment group, baseline disease activity, and geographic region.
- Estimands and the corresponding imputation methods will be specified in the ISAs.

Changes to the data analysis methods

An ISA can change any data analysis method described in this master protocol without necessitating an amendment to this master protocol. Any change to the data analysis methods described in this master protocol and not further clarified in the ISA will require an amendment to this master protocol only if (a) the change affects a principal feature of the protocol, and (b) the ISA(s) are not amended to clarify the change. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the

CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate. Complete details of the planned analyses will be documented in the MP-SAP and ISA-SAP.

Handling of missing, unused, and spurious data

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

9.3.2. Primary Endpoint/Estimand Analysis

See the relevant ISA.

9.3.3. Secondary Endpoints/Estimands Analysis

See the relevant ISA.

9.3.4. Exploratory Endpoints Analysis

See the relevant ISA.

9.3.5. Safety Analyses

Safety analyses will include, but not be limited to, evaluation of all reported AEs, AESIs, C-SSRS, ECGs, vital signs, and laboratory analytes. Unless otherwise specified in the ISA, safety analyses will compare the intervention to all available control data at time of analysis. Exposure to each study intervention will be calculated for each participant and summarized by treatment group for each ISA. Categorical safety measures will be summarized by treatment for each ISA with incidence rates. The mean change of the continuous safety measures will be summarized for each ISA by visit.

Safety analyses will be summarized overall and separately for the induction period, maintenance period (if applicable to the ISA), and posttreatment follow-up period. If applicable to the ISA, safety analyses during the maintenance period will use the last available value before the first dose of study intervention during the maintenance period. Safety analyses during the posttreatment follow-up period will use the last nonmissing assessment on or prior to entering the posttreatment period. Additionally, some ISAs may combine the maintenance period and the posttreatment follow-up period for safety analyses, and these analyses will use the last available value before the first dose of study intervention during the maintenance period.

9.3.5.1. Adverse Events

AEs will be coded according to MedDRA and summarized by system organ class, preferred term, severity, and relationship to the study intervention. A TEAE is defined as an event that first occurs or worsens in severity after baseline, with baseline defined as all preexisting conditions recorded at Visit 401 and any AEs recorded before the first dose of study intervention, that is, during Visit 401 and Visit 0 and recorded with the time of onset before the first dose of study intervention). The postbaseline period for the analysis will include the treatment period and the posttreatment follow-up period. For events that are sex specific, the denominator and computation of the percentage will only include participants of the given sex.

The number, percentage, and incidence rate of participants who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an AE, and AESIs will be summarized. TEAEs (all, by maximum severity), SAEs (including deaths), and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class and preferred term.

Treatment-related TEAEs (TEAEs related to study intervention) are defined as events that are indicated by the investigator on the CRF to be related to treatment.

In addition to general safety parameters, safety information on specific topics of AESIs may also be presented. Potential AESIs will be identified by a standardized MedDRA query or a Lilly-defined MedDRA preferred term listing.

Follow-up emergent AEs, SAEs (including deaths), and AEs that lead to a participant's discontinuation from study intervention or discontinuation from study will be summarized. All AEs, including preexisting conditions, will be listed by participant, preferred term, treatment group, severity (intensity), and relationship to the study intervention.

9.3.5.2. Columbia–Suicide Severity Rating Scale

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (CSSRS WWW). Suicidal ideation and/or behavior and self-injurious behavior with no suicidal intent, on the basis of the C-SSRS, will be listed by participant.

9.3.6. Other Analyses

9.3.6.1. Participant Disposition

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete the study or discontinue, both overall and by reason for discontinuation for each ISA at the end of the study. Intervention-specific analyses are described in the respective ISAs. A summary of important protocol deviations will be provided for each ISA.

9.3.6.2. Participant Characteristics

Participant characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include sex assigned at birth, age, age category, weight, race, geographic region, country, and baseline disease activity, including vIGA-AD, EASI, SCORAD, and Itch NRS. Intervention-specific analyses are described in the respective ISAs.

Demographic data are collected and summarized to demonstrate that the study population represents the target patient population. A summary of baseline participant characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by treatment group using descriptive statistics. Other participant characteristics will be summarized by treatment group as deemed appropriate within each ISA.

9.3.6.3. Concomitant Therapy

Previous and concomitant medications will be summarized by treatment for each ISA and will be presented by Anatomical Therapeutic Chemical drug classes using the latest version of the WHO drug dictionary.

9.3.6.4. Treatment Compliance

Treatment compliance with investigational product will be summarized by treatment for each ISA. Intervention-specific analyses are described in the relevant ISA.

9.3.6.5. Pharmacokinetic/Pharmacodynamic Analyses

When applicable, sample concentrations of the active study intervention, that is, other than placebo or other control, will be listed by time point and dosing regimen using descriptive statistics. The PK of the study drug may CCI [redacted]

Analyses of exposure-response relationships may be conducted CCI [redacted]. Evaluations may be performed for PD, efficacy, and/or safety endpoints contingent on review of the data.

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

9.3.6.6. Immunogenicity Analyses

Immunogenicity analyses will be described in the ISAs as applicable.

9.3.6.7. Patient-Reported Outcomes

Intervention-specific analyses of PROs, if applicable, are described in the relevant ISA.

9.3.6.8. Subgroup Analyses

Subgroup analyses may be conducted for endpoints of interest. Subgroups that may be evaluated include, but are not limited to, sex, race, geographic region, weight, baseline disease severity, duration since AD onset, and previous therapies.

Additional intervention-specific analyses of subgroups may be described in the relevant ISA or ISA-SAP.

9.3.6.9. Sensitivity Analyses

Sensitivity analyses may be performed for alternative approaches to, for example, nonresponder criteria, prohibited medication use, or other intercurrent events of interest. CCI [redacted] Details of sensitivity analyses and alternative models are specified in the ISA and/or ISA-SAP.

9.4. Interim Analyses

Interim analyses of the master protocol

Master protocol interim analyses may occur when an ISA has a primary database lock, an efficacy interim database lock (if applicable), and/or a final database lock as specified in its respective ISA. These analyses will be conducted to assess ISA objectives and to compare the intervention data to placebo data and may include placebo data collected for more than 1 ISA. Analysis details will be provided in the ISA and its SAP.

Interim analyses of the ISAs

Prior to the primary analysis for each ISA, there may be planned interim analyses to assess drug safety, PK, and/or efficacy. If so, details for the planned interim analysis will be provided in the respective ISAs or in the respective ISA-SAPs.

CCI

Futility or efficacy stopping rules

See the relevant ISA and/or ISA-SAP for information about interim analyses and about stopping rules for futility or efficacy, if applicable.

Unblinding plan

Intervention-specific unblinding details are provided in the respective ISA-SAP or in a separate unblinding plan document.

Evaluation of unblinded interim analyses

Only the IAC is authorized to evaluate unblinded interim efficacy and safety analyses (Section 10.1.5).

9.5. Sample Size Determination

Details of sample size and power assumptions and calculations for each intervention are in respective ISAs.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- applicable ICH GCP guidelines
- for ISAs having a device: International Organization for Standardization (ISO) 14155, and
- applicable laws and regulations.

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

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

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

The investigator will be responsible for the following:

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

Investigator sites are compensated for participation in the study as detailed in the CTA.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests for the master protocol and each ISA in which the investigator participates, and for 1 year after completion.

10.1.3. Informed Consent Process

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

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

The medical record must include a statement that written informed consent was obtained before the participant was entered into the master protocol and into any ISA, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

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

Participants who are rescreened are required to sign a new ICF (Section 5.4).

10.1.4. Data Protection

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

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

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

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address the management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration, or the loss of information or personal data. These processes include appropriate contingency plans for appropriate and timely response in the event of a data security breach. The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The

sponsor's processes are compliant with local privacy laws and relevant legislations, including General Data Protection Regulation and the EU CTR.

10.1.5. Committees Structure

Internal assessment committee

In addition to the safety reviews routinely performed by the blinded study team as described in Section 8.2, an IAC will exist for the purpose of reviewing safety data in an unblinded fashion periodically or on an ad hoc basis. The IAC will determine whether any changes to the study, for example, dose reductions or other protocol modifications, should be made (Section 10.1.5.1).

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

If an efficacy interim analysis is considered necessary, the IAC will be responsible for review of the efficacy data. See Section 9.4 for general information about interim analyses. Details of interim analyses will be provided in the SAP.

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

10.1.5.1. Stopping Rules

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

10.1.6. Dissemination of Clinical Study Data

CSRs

A CSR will be provided for each ISA.

Reports

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

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

Data

The sponsor provides access to all individual participant data collected during the study, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication

acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, SAP, CSR, and blank or annotated CRFs, will be provided in a secure data-sharing environment for up to 2 years per proposal.

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

10.1.7. Data Quality Assurance

Investigator responsibilities

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

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

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

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

Data monitoring and management

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

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

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

The sponsor assumes accountability for actions delegated to other individuals, for example, CROs.

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

Records retention and audits

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

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

Data capture system

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

Electronic data capture system

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

Clinical outcome assessments

Additionally, COA data (participant-focused outcome instrument) and other data will be collected by authorized study personnel via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

Additionally, eCOA data per the SoA (participant-focused outcome instrument, and clinician assessments) will be directly recorded by the participant or investigator site personnel into an instrument, for example, handheld smart phone or tablet). The eCOA data will serve as the source documentation, and the investigator does not maintain a separate written or electronic record of these data. Therefore, the data must be recorded contemporaneously.

Data storage and access

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

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

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

10.1.8. Source Documents

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

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

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

10.1.9. Study and Site Start and Closure

First act of recruitment

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

Study or site termination

The sponsor or sponsor's designee reserves the right to close a study site, or to terminate either the master protocol as a whole or only 1 particular ISA, at any time for any reason at the sole discretion of the sponsor.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- For study termination:
  - discontinuation of further study intervention development, and
  - decision of the IAC (Section 10.1.5.1).
- For site termination:
  - failure of the investigator to comply with the protocol, the requirements of the IRB or IEC or local health authorities, the sponsor's procedures, or GCP guidelines
  - inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and
  - total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs or IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The

investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of the ISAs conducted as part of this master protocol will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

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

10.1.12. Sample Retention

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

This table lists the maximum retention period for sample types. The retention period begins after the last participant's last visit for the ISA.

Sample Type	Custodian	Maximum Retention Period after the Last Participant Visit
PK	Sponsor or designee	2 years for radiolabeled PK samples 1 year for all other PK samples
Exploratory biomarkers, including but not limited to PD and genetics samples	Sponsor or designee	Up to 15 years
Immunogenicity	Sponsor or designee	Up to 15 years

Any samples remaining after the retention period will be destroyed.

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

10.2. Appendix 2: Clinical Laboratory Tests

Use of central or local laboratories

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

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 or exclusion of potential study participants

See Section 5 of this master protocol for laboratory tests that are part of the master protocol eligibility criteria. See Section 5 of the relevant ISA for any additional laboratory testing 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.

10.2.1. Clinical Laboratory Tests Performed at Visit 401

This section lists the clinical laboratory tests performed at Visit 401.

	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)	
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory at Visit 401 screening. See Section 8.2.7.1.
Serum pregnancy	Assayed by Lilly-designated laboratory at Visit 401 screening. For WOCBP only. See Section 8.2.7.

	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
TB, HIV, and Hepatitis Serology	
Tuberculosis (TB) testing:	TB test based on local standard of care.
QuantiFERON®-TB Gold	Assayed by Lilly-designated laboratory.
T-SPOT®.TB	May be tested and evaluated locally. Local laboratory must be qualified by local regulations.
Tuberculin skin test (TST)	Tested and evaluated locally. Local staff must be qualified to administer and interpret the test.
Human immunodeficiency virus (HIV)	Assayed by Lilly-designated laboratory.
Hepatitis C virus (HCV) testing:	Assayed by Lilly-designated laboratory.
HCV antibody	
HCV RNA	Performed only for participants who test positive for hepatitis C antibody.
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.
Hepatitis B core antibody (anti-HBc)	
Hepatitis B surface antigen (HBsAg)	

	Notes
Calculations	Generated by Lilly-designated laboratory.
Estimated glomerular filtration rate (eGFR)	CKD-EPI Creatinine Equation (2021).

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DNA = deoxyribonucleic acid; RNA = ribonucleic acid; WOCBP = women of childbearing potential.

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

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

If an ISA involves a medical device, both the investigator and the sponsor will comply with all local medical device reporting requirements. The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See the relevant ISA for the list of sponsor medical devices, if any.

10.3.1. Definition of AE

AE Definition
● For drug-only clinical studies: An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. ● For clinical studies that include a medical device: An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events Meeting the AE Definition
● Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease. ● Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition. ● New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. ● Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. ● Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability or incapacity

- The term *disability* means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly or birth defect

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

f. Other situations

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. For studies that include a medical device:

Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

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

- use errors for device or drug-device combination products due to ergonomic design elements of the product.

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

Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.

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

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

AE, SAE, and Product Complaint Recording

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

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

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

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

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

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

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

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB in their assessment.

For each AE/SAE, the investigator **must** document in the medical notes that the investigator has reviewed the AE/SAE and has provided an assessment of causality.

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

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

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

Follow-Up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on an SAE paper form (see next section) or to the sponsor or designee by telephone.

Contacts for SAE reporting can be found in the Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

SAE Reporting via Paper Form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee.

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

Contacts for SAE reporting can be found in the Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will

comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB or IEC, and investigators.

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

10.4. Appendix 4: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs), and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

See Appendix 3, Section 10.3, for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman • at any age at least 6 wk postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note, or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with an FSH >40 mIU/mL, or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women **should not** be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.5.2. Contraception Guidance

See the ISA to which the participant is assigned.

10.5.3. Pregnancy Testing Guidance

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

10.6. Appendix 6: Assessments of Disease Activity, Patient-Reported Outcomes, and Quality of Life

This appendix describes efficacy-related assessments which may appear in the IMMB SoA or in the SoA of an ISA. Additional efficacy-related assessments may be described in an ISA.

10.6.1. Eczema Area and Severity Index (EASI)

The EASI is an investigator-reported, 20-item scale that evaluates 2 dimensions of AD in participants:

- extent of disease at 4 body regions (head/neck, trunk, upper and lower extremities), and
- 4 clinical signs (erythema, induration/papulation, excoriation, and lichenification).

The clinical signs are assessed for severity on a scale of 0 (absent) to 3 (severe).

The scores are added up for each of the 4 body regions. The assigned percentages of BSA for each section of the body are

- 10% for head/neck
- 20% for upper extremities
- 30% for trunk, and
- 40% for lower extremities.

Each subtotal score is multiplied by the BSA represented by that region.

In addition, an area score of 0 to 6 is assigned for each body region, depending on the percentage of AD-affected skin in that area:

- 0 (none)
- 1 (1% to 9%)
- 2 (10% to 29%)
- 3 (30% to 49%)
- 4 (50% to 69%)
- 5 (70% to 89%), or
- 6 (90% to 100%).

Each of the body area scores is multiplied by the area affected. The resulting EASI score ranges from 0 to 72 points, with the highest score indicating worse severity of AD (Hanifin et al. 2001). The recall period of this scale is present time.

10.6.2. vIGA-AD

The vIGA-AD® measures the investigator's global assessment of the participant's overall severity of their AD, based on a single-item, numeric, 5-point scale from 0 (clear skin) to 4 (severe disease) (Simpson et al. 2020b). The score is based on an overall assessment of the degree of erythema, papulation or induration, oozing or crusting, and lichenification. The recall period of this assessment is present time.

10.6.3. SCORing Atopic Dermatitis (SCORAD)

The SCORAD index is an investigator- and participant-reported, 9-item assessment that assesses 3 aspects as provided below:

- The **extent** (1-item) of AD is assessed as a percentage of each defined body area and reported as the sum of all areas. The maximum score is 100%.
- The **severity** of 6 specific symptoms of AD: erythema, edema or papulation, oozing or crusts, excoriation, lichenification, and dryness (6-items) is assessed by the investigator using a 4-point scale, that is, none = 0, mild = 1, moderate = 2, severe = 3, with a maximum possible total of 18 points.
- The **subjective symptoms** of pruritus and sleep loss (2 items) is assessed by the participant via a 10-cm VAS. The symptoms (itch and sleeplessness) are recorded by the participant on a visual analog scale, where 0 is no symptoms and 10 is the worst imaginable symptom, with a maximum possible score of 20.

The maximum possible SCORAD score calculated based on the above 3 aspects is 103. The higher scores indicate poorer or more severe condition (Stalder and Taïeb 1993; Kunz et al. 1997; Oranje et al. 2007; Schram et al. 2012). The recall period is present time for extent and intensity, and average for the last 3 days/nights for subjective symptoms of AD.

10.6.4. Patient-Oriented Eczema Measure (POEM)

The POEM is a simple, participant-reported, 7-item scale that assesses disease severity in adults. Participants respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping or oozing, cracking, flaking, and dryness or roughness) over the past week. Response categories include “No days,” “1-2 days,” “3-4 days,” “5-6 days,” and “Every day” with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0 to 28, with higher total scores indicating greater disease severity (Charman et al. 2004).

10.6.5. Dermatology Life Quality Index (DLQI)

The DLQI is a participant-reported, 10-item, QoL questionnaire in those ≥16 years of age that covers 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment). The recall period of this scale is over the “last week.” Response categories include “not at all,” “a little,” “a lot,” and “very much,” with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered (or “not relevant”) responses scored as 0.

Scores range from 0 to 30 with higher scores indicating greater impairment of QoL. A DLQI total score of 0 to 1 is considered as having no effect on a participant’s HRQoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

10.6.6. Atopic Dermatitis Control Tool (ADCT)

The ADCT is a participant-reported, simple, brief tool for adults and adolescents, which evaluates 6 symptoms and effects associated with AD over the past week:

- overall severity of symptoms
- days with intense episodes of itching

- intensity of bother
- problem with sleep
- impact on daily activities, and
- impact on mood or emotions.

Each of the 6 ADCT items has a score range from 0 (no problem) to 4 (worst), rating the severity of each concept. The total score ranges from 0 to 24, which is the summation of the responses to all the items. A score of ≥7 points was derived as the threshold to identify participants "not in control." The threshold for meaningful within-person change was estimated to be 5 points (Simpson et al. 2019; Pariser et al. 2020).

10.6.7. Itch Numeric Rating Scale (Itch NRS)

The Itch NRS is a participant-reported, single-item, 11-point scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable" in adults. Overall severity of a participant's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016; Newton et al. 2019; Silverberg et al. 2021b).

10.6.8. Atopic Dermatitis Sleep Scale (ADSS)

The ADSS is a participant-reported, 3-item questionnaire in adults developed to assess the impact of itch on sleep, including difficulty falling asleep, frequency of waking, and difficulty getting back to sleep last night. Participants rate their difficulty falling asleep and difficulty getting back to sleep, Items 1 and 3, respectively, using a 5-point Likert-type scale. Response options include "Not at all," "A little bit," "Somewhat," "Quite a bit," and "Very difficult," with corresponding scores of 0, 1, 2, 3, and 4, respectively. Participants report their frequency of waking last night, Item 2, by selecting the number of times they woke up each night, ranging from 0 to 29 times. The ADSS is designed to be completed each day with respondents thinking about sleep "last night." Each item is scored individually (Silverberg et al. 2021b).

10.6.9. Skin Pain Numeric Rating Scale (Skin Pain NRS)

The Skin Pain NRS is a participant-reported, 11-point scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a participant's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours (Newton et al. 2019; Silverberg et al. 2021b).

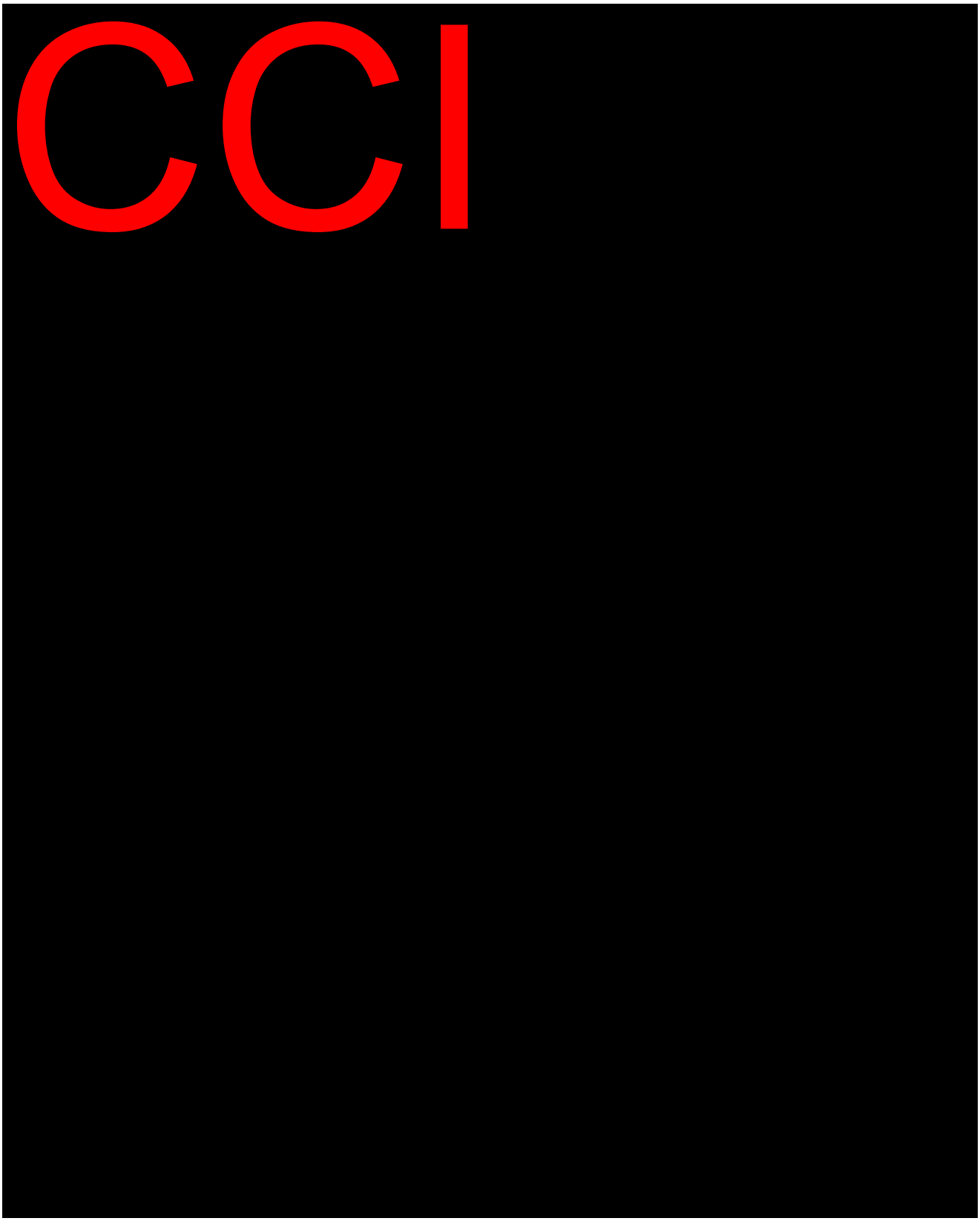
10.7. Appendix 7: Tuberculosis Testing

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

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

TB test type	How to perform the test	How to interpret the test	When to retest
IGRA for *M tuberculosis*	Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.	Results are provided by the laboratory assaying the test.	The investigator may discuss retesting with the sponsor's designated medical monitor if ● the investigator suspects a false-positive IGRA result in a participant with no increased risk of TB infection during lifetime, and ● there is no evidence of prior or current TB on physical examination and/or on chest x-ray interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and with documented chest x-ray report).

Abbreviations: IGRA = interferon gamma release assay; PPD = purified protein derivative; TB = tuberculosis; TNF = tumor necrosis factor; TST = tuberculin skin test.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10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic evaluation testing

See Section 8.2.11 for guidance on appropriate test selection.

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

In circumstances where required in accordance with local regulations, local laboratory testing may be performed in lieu of Lilly-designated central laboratory testing (in the table below).

Local testing may be performed in addition to central testing when necessary for immediate participant management.

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

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[a]
Basophils	**Hepatis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	**Hepatitis E virus (HEV) testing:**
Direct bilirubin	HEV IgG antibody
Alkaline phosphatase (ALP)	HEV IgM antibody
Alanine aminotransferase (ALT)	HEV RNA[a]
Aspartate aminotransferase (AST)	**Anti-nuclear antibody (ANA)**
Gamma-glutamyl transferase (GGT)	**Anti-smooth muscle antibody (ASMA)**[b]
Creatine kinase (CK)	**Anti-actin antibody**[c]
Hepatic Coagulation Panel	**Immunoglobulin IgA (quantitative)**
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgG (quantitative)**
Urine Chemistry	**Immunoglobulin IgM (quantitative)**
Drug screen	**Epstein-Barr virus (EBV) testing:**
Haptoglobin	EBV antibody

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

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

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

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[a]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[a]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology**
Ethyl glucuronide (EtG)	Culture:
Epstein-Barr virus (EBV) testing:	Blood
EBV DNA[a]	Urine

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

10.10. Appendix 10: Genetics

See Section 8.6.

10.11. Appendix 11: Country-specific Requirements

For sites in EU Member States

This appendix 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.

10.12. Appendix 12: Provisions for Changes in Study Conduct During Exceptional Circumstances

The following provisions are applicable to all ISAs unless otherwise specified.

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

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

See the relevant ISA for the additional informed consent requirements specific to that ISA.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix or in an ISA, 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 401 (master protocol screening period)

> **Telemedicine:** Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Procedures to be completed in this manner may include, but are not limited to, concomitant medication, 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 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 Baseline/Screening, and PROs via a tablet and/or a web-based collection system.
>
> **Other alternative locations:** Procedures that could be done at an alternate location may include, but are not limited to, ECGs and collection of blood and urine samples for clinical safety laboratory testing.

Types of remote visits for ISA screening period and thereafter

> See the relevant ISA.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option for Visit 401 (master protocol screening period)

Central laboratory testing must be used for all samples collected at Visit 401 unless local testing is specified by the SoA (Section 1.3) and by Appendix 2, Section 10.2.1.

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

See the relevant ISA. A local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements, if applicable, must be met before action is taken:

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

If study intervention will be administered to the participant during a mobile health care visit or at an alternate location, these additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer study intervention.
- See the relevant ISA for any intervention-specific instructions, for example, about having resuscitation equipment, emergency drugs, and appropriately trained medical staff available both during an infusion and for a designated number of hours after the completion of the infusion or in cases of hypersensitivity or infusion site reactions.

Guidance for the screening periods of the master protocol and ISAs

The following rules will be applied for active, nonrandomized participants whose participation in screening activities (in the master protocol or in an ISA, or both) must be paused due to exceptional circumstances:

- If screening is paused for a brief period of time, such that a participant's screening activities can still be conducted within the allowed screening windows, and if the

participant is found to be eligible to participate in the master protocol and an ISA, the participant can continue in the study as usual. Due to the pause in screening, however, sites should reconfirm the participant's consent and document this confirmation in the source documentation.

- If screening is paused for a long period of time, such that a participant's screening activities cannot be conducted within the allowed screening windows, the participant must be discontinued from the study because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can be reconsented and be rescreened as a new participant. This rescreen is in addition to the number of rescreenings already allowed by the main protocol. The screening procedures per the usual SoAs of the master protocol and the relevant ISA should be followed to ensure eligibility before the rescreened participant is randomized to study intervention.

Adjustments to visit windows

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.

Visit Number	Tolerance
Visit 401	No adjustment to the visit window described in the master protocol SoA
Visit 0 (Week 0) through the last posttreatment follow-up visit	See "Provisions for Changes in Study Conduct During Exceptional Circumstances" in the relevant ISA

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

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.13. Appendix 13: Requirements for ISA Design

The ISAs of this master protocol will use a common clinical trial database. The common database is built on a standard visit structure, and certain activities are expected to occur at the standard visits.

This appendix describes these standards. A study team developing an SoA for a new ISA will adhere to the sponsor's usual data collection requirements, for example, AE data collection at every visit, and may add visits and activities to the SoA as needed to support intervention-specific objectives and endpoints. However, the required standards described in this appendix must also be incorporated into the SoA to support use of the common database.

Investigators are to refer to the relevant ISA for ISA-specific details and actual assessments and procedures to perform in an ISA.

10.13.1. Activities During the Induction Period

The visit structure of the induction period must include a screening/baseline/randomization visit (Visit 0/Day 1/Week 0) as well as visits at 4-week intervals thereafter, for example, visits at Week 4, Week 8, and so on, until the end of the period.

An ISA may include additional visits in this period to support ISA-specific objectives and endpoints. It is anticipated, but not required, that this period will end at either the Week 12 visit or the Week 16 visit.

This table lists the timing and/or frequency of the required standard activities for this period.

Activity	Timing or Frequency in an Induction Period of an ISA
Patient-reported outcomes (electronic)	
Dermatology Life Quality Index	At first visit and at visits every 4 wk thereafter
Patient-Oriented Eczema Measure	At first visit and at visits every 4 wk thereafter
SCORing Atopic Dermatitis (subjective)	At first visit and at visits every 4 wk thereafter
Atopic Dermatitis Control Tool	At first visit and end of induction period Note: Atopic Dermatitis Control Tool is required only of ISAs having a maintenance period.
Clinician-administered assessments (electronic)	
vIGA-AD	At first visit and at visits every 4 wk thereafter
Eczema Area and Severity Index	At first visit and at visits every 4 wk thereafter
SCORing Atopic Dermatitis (objective)	At first visit and at visits every 4 wk thereafter
Fitzpatrick Scale of Skin Phototypes	At first visit
Laboratory tests and sample collections	
Hematology	At first visit and at visits every 4 wk thereafter
Clinical chemistry	At first visit and at visits every 4 wk thereafter
Urine pregnancy test (local)	At first visit and at visits every 4 wk thereafter
HBV DNA	At a visit corresponding to an interval of approximately 12 to 16 wk from the last HBV DNA test. Only for participants who are anti-HBc positive at Visit 401 of the master protocol [IMMB] and are enrolled in the ISA.
CCI	

Activity	Timing or Frequency in an Induction Period of an ISA
CCI	

10.13.2. Activities During a Maintenance Period

An ISA is not required to have a maintenance period. If an ISA does have such a period, the ISA visit structure must include visits at Week 16 and at 12-week intervals thereafter until the end of the period. An ISA may include additional visits in this period to support ISA-specific objective and endpoints.

This table lists the timing and/or frequency of the required standard activities for this period.

Activity	Timing or Frequency in a Maintenance Period of an ISA
Patient-reported outcomes (electronic)	
Dermatology Life Quality Index	At the Week 16 visit, and at visits every 12 wk thereafter
Patient-Oriented Eczema Measure	At the Week 16 visit, and at visits every 12 wk thereafter
SCORing Atopic Dermatitis (subjective)	At the Week 16 visit, and at visits every 12 wk thereafter
Atopic Dermatitis Control Tool	At the Week 16 visit, and at visits every 12 wk thereafter
Clinician-administered assessments (electronic)	
vIGA-AD	At the Week 16 visit, and at visits every 12 wk thereafter
Eczema Area and Severity Index	At the Week 16 visit, and at visits every 12 wk thereafter
SCORing Atopic Dermatitis (objective)	At the Week 16 visit, and at visits every 12 wk thereafter
Laboratory tests and sample collections	
Hematology	At the Week 16 visit, and at visits every 12 wk thereafter
Clinical chemistry	At the Week 16 visit, and at visits every 12 wk thereafter
Urine pregnancy test (local)	At the Week 16 visit, and at a minimum every 4 to 12 wk thereafter, depending on the frequency of dosing in an ISA
HBV DNA	At a visit corresponding to an interval of approximately 12 to 16 wk from the last HBV DNA test. Only for participants who are anti-HBc positive at Visit 401 of the master protocol [IMMB] and are enrolled in the ISA.

10.13.3. Activities During a Posttreatment Follow-up Period

An ISA is required to have a posttreatment follow-up period consisting of at least 1 visit. The duration of posttreatment follow-up is typically equal to, or greater than, 5 half-lives of a study intervention. Thus, the timing of this visit relative to the last administered dose of study intervention will vary across the ISAs. An ISA may include additional visits within this period. The number of added visits and the intervals between them will be determined by the ISA team.

This table lists the timing and/or frequency of the required standard activities for this period.

Activity	Timing or Frequency in a Posttreatment Follow-up Period of an ISA
Patient-reported outcomes (electronic)	
Dermatology Life Quality Index	At the final visit
Patient-Oriented Eczema Measure	At the final visit
SCORing Atopic Dermatitis (subjective)	At the final visit
Atopic Dermatitis Control Tool	At the final visit

Activity	Timing or Frequency in a Posttreatment Follow-up Period of an ISA
Clinician-administered assessments (electronic)	
vIGA-AD	At the final visit
Eczema Area and Severity Index	At the final visit
SCORing Atopic Dermatitis (objective)	At the final visit
Laboratory tests and sample collections	
Hematology	At the final visit
Clinical chemistry	At the final visit
Urine pregnancy test (local)	At the final visit
HBV DNA	At intervals of approximately 12 to 16 wk during this period. Only for participants who are anti-HBc positive at Visit 401 of the master protocol [IMMB] and are enrolled in the ISA.

10.13.4. Activities During an Early Discontinuation Visit

An ISA must specify which activities are to be performed at an ED visit. Some ED activities will be standard for all ISAs, but an ISA may include additional activities. This table lists the required standard activities for an ED visit.

Activity	Instruction
Patient-reported outcomes (electronic)	
Dermatology Life Quality Index	
Patient-Oriented Eczema Measure	
SCORing Atopic Dermatitis (subjective)	
Atopic Dermatitis Control Tool	
Clinician-administered assessments (electronic)	
vIGA-AD	
Eczema Area and Severity Index	
SCORing Atopic Dermatitis (objective)	
Laboratory tests and sample collections	
Hematology	
Clinical chemistry	
Urine pregnancy test (local)	
HBV DNA	Only for participants who are anti-HBc positive at Visit 401 of the master protocol (IMMB) and are enrolled in the ISA. Perform only if HBV DNA test has not been performed within 16 wk or participant will not complete a posttreatment follow-up visit.

10.14. Appendix 14: Abbreviations and Definitions

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
AD	atopic dermatitis
ADA	anti-drug antibodies
ADCT	Atopic Dermatitis Control Tool
ADSS	Atopic Dermatitis Sleep Scale
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HCV	antibodies to HCV
AST	aspartate aminotransferase
authorized IMP	*applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
authorized AxMP	*applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an auxiliary medicinal product
AxMP	auxiliary medicinal product. See also NIMP. a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial

BSA	body surface area
blinding	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
CBD	cannabidiol
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system
compliance	adherence to all study-related requirements, GCP requirements, and applicable regulatory requirements
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed (or computerized) tomography
CTA	clinical trial agreement
CTR	Clinical Trial Regulation
device deficiencies	equivalent to product complaint
DLQI	Dermatology Life Quality Index

DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DNA	deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders. 5th ed.
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
EDC	electronic data capture
ED	early discontinuation
eGFR	estimated glomerular filtration rate
enroll	the act of assigning a participant to a treatment (study intervention). Participants who are enrolled in the study are those who have been assigned to a treatment
enter	Participants entered into a study are those who have signed the ICF directly or through their legally acceptable representative
ERB	ethics (or ethical) review board. An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human participants involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial participants
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr	hour, or hours

HRQoL	health-related quality of life
IAC	Internal Assessment Committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee; see "ERB"
IgA	immunoglobulin A
IGA	Investigator's Global Assessment
IGRA	interferon gamma release assay
IL	interleukin
IMP	investigational medicinal product (see also "investigational product") a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial
IND	Investigational New Drug application
informed consent	a process by which participants voluntarily confirm their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF
INR	international normalized ratio
interim analysis	an analysis of clinical trial data by intervention group that is conducted before the primary outcome database lock. Also, an analysis comparing intervention groups at any time before the final reporting database is locked
investigational product (IP)	a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP"
IRB	institutional review board; see "ERB"
ISA	intervention-specific appendix
ISA-SAP	statistical analysis plan for an intervention-specific appendix (ISA)

ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to an intervention group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment
CCI	
IWRS	interactive web-response system
JAK	Janus kinase
LTBI	latent tuberculosis infection
MedDRA	Medical Dictionary for Regulatory Activities
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling, for example, Summary of Product Characteristics, IB, local label, protocol, or • shared use of cartridges or prefilled pens, or both.
misuse	use of a study intervention for self-treatment that is inconsistent with either the prescribed dosing regimen or indication, or both, or is obtained without a prescription
MP-SAP	statistical analysis plan for the master protocol
N/A	not applicable
NIMP	noninvestigational medicinal product. See AxMP. a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment
NRS	numeric rating scale
participant	equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint

PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PPD	purified protein derivative
PRO(s)	patient-reported outcome(s)
PT-INR	prothrombin time, international normalized ratio
QoL	quality of life
QTc	corrected QT interval
QTLs	quality tolerance limits
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
screen	the act of determining whether an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study
SERMs	selective estrogen receptor modulators
SoA	Schedule of Activities
study drug	See “study intervention”
study intervention	any medicinal product or medical device intended to be administered to a study participant according to the study protocol
SUSARs	suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid

TE ADA	treatment-emergent anti-drug antibodies
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have a causal relationship with this treatment
THC	tetrahydrocannabinol
TST	tuberculin skin test
ULN	upper limit of normal
US or USA	United States of America
VAS	visual analog scale
wk	week, or weeks
WHO	World Health Organization
WOCBP	women of childbearing potential

10.15. Appendix 15: Master Protocol Amendment History

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

Amendment [a]: 13 Mar 2023

Overall Rationale for the Amendment:

The purpose of this amendment is to include language to address regulatory expectations. Minor editorial or formatting corrections are not represented in this table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Removed anti-HBs from the description of HBV screening tests	Anti-HBs testing is not required for eligibility
6. Study Intervention(s) and Concomitant Therapy	Reworded the definition of study intervention	To improve alignment with regulatory definitions
8.2.9. Hepatitis B Testing and Monitoring	Removed anti-HBs from the description of HBV screening tests	To align with Section 1.3.
8.7. Exploratory Biomarkers	Removed the phrase “where local regulations allow”	To simplify the text and reduce implicit redundancy
10.1.4. Data Protection	Added statements to clarify methods for protection of personal data and handling of data security breach	To address an EU CTR (536/2014) requirement
10.2. Appendix 2: Clinical Laboratory Tests	Removed anti-HBs from the list of HBV screening tests	To align with Section 1.3
10.3.6. Regulatory Reporting Requirements	Added a statement on the reporting SUSARs	To address an EU CTR (536/2014) requirement
10.13. Appendix 13: Requirements for ISA Design	Removed requirement for ISAs to have sample collections for CCI [redacted]	CCI [redacted]
10.14. Appendix 14: Abbreviations and Definitions	Reworded the definition of study intervention	To improve alignment with regulatory definitions
10.15. Appendix 15: Master Protocol Amendment History	Revised statement about amendment history	To ensure internal document consistency

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Approval	PPD Statistician 12-Sep-2023 12:08:44 GMT+0000

Approval	PPD Medical Director 12-Sep-2023 16:50:29 GMT+0000

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