Protocol Amendment J1A-MC-KDAF (e)

A Phase 2b, Double-blinded, Placebo-Controlled Study to Evaluate Peresolimab in Adult Participants with Moderately-to-Severely Active Rheumatoid Arthritis

NCT05516758

Approval Date: 31-May-2023

Title Page

Protocol Title: A Phase 2b, Double-Blind, Placebo-Controlled Study to Evaluate Peresolimab in Adult Participants with Moderately-to-Severely Active Rheumatoid Arthritis

Protocol Number: J1A-MC-KDAF

Amendment Number: e

Compound: Peresolimab (LY3462817)

Brief Title: A Phase 2b Study to Evaluate Peresolimab in Adult Participants with Moderately-to-Severely Active Rheumatoid Arthritis

Study Phase: 2b

Acronym: RESOLUTION-1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number:

IND: 150710

EU trial number: 2022-501425-20-00

Document ID: VV-CLIN-116958

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

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment d	07 March 2023
Amendment c	31 January 2023
Amendment b	07 October 2022
Amendment a	11 August 2022
Original Protocol	19 July 2022

Amendment [e]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to address regulatory feedback. Changes and rationale are summarized in this table. Editorial or formatting changes to maintain document consistency are not shown in this table.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 2b, Double-Blind, Placebo-Controlled Study to Evaluate Peresolimab in Adult Participants with Moderately-to-Severely Active Rheumatoid Arthritis

Brief Title:

A Phase 2b Study to Evaluate Peresolimab in Adult Participants with Moderately-to-Severely Active Rheumatoid Arthritis

Regulatory Agency Identifier Number:

IND: 150710

EU trial number: 2022-501425-20-00

Rationale:

This study aims to find the appropriately CCI for peresolimab in adults with moderately-to-severely active rheumatoid arthritis (RA) for further clinical development.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To evaluate the efficacy of peresolimab compared to placebo in achieving ACR20	• Proportion of participants achieving ACR20 at Week 12
Secondary	
To evaluate the effect of peresolimab compared to placebo for measures of disease activity	• Proportion of participants achieving ACR50 or ACR70 at Week 12 • Proportion of participants achieving LDA or remission at Week 12 for ○ DAS28-hsCRP CCI • Change from baseline at Week 12 for mean ○ DAS28-hsCRP CCI

	CCI
To evaluate the effect of peresolimab compared to placebo for patient-reported outcome measures	CCI ○ Patient's Assessment of Arthritis Pain (VAS), and ○ patient's assessment of physical function using HAQ-DI.
To evaluate the effect of peresolimab for measures of disease activity	CCI

	CCI
To characterize the pharmacokinetics of peresolimab	

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Primary estimand

The primary clinical question of interest is

> What is the difference between peresolimab and placebo in the target patient population, in achieving a successful response at CCI

The estimand is described by the following attributes:

- Population: Participants with moderately-to-severely active RA.
- Endpoint: CCI
- Intercurrent events (ICEs) related to study intervention include the use of rescue or prohibited medication and early discontinuation from the study or study intervention. A composite strategy will be used for ICEs. Specifically, participants with an ICE will be considered as a nonresponder after the first occurrence of the ICE.
- Population-level summary: Difference in proportion of participants achieving response at CCI between intervention conditions.
- Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will be considered as treatment failures and categorized as nonresponder since it is assumed the participant was not receiving benefit from the intervention.

Overall Design:

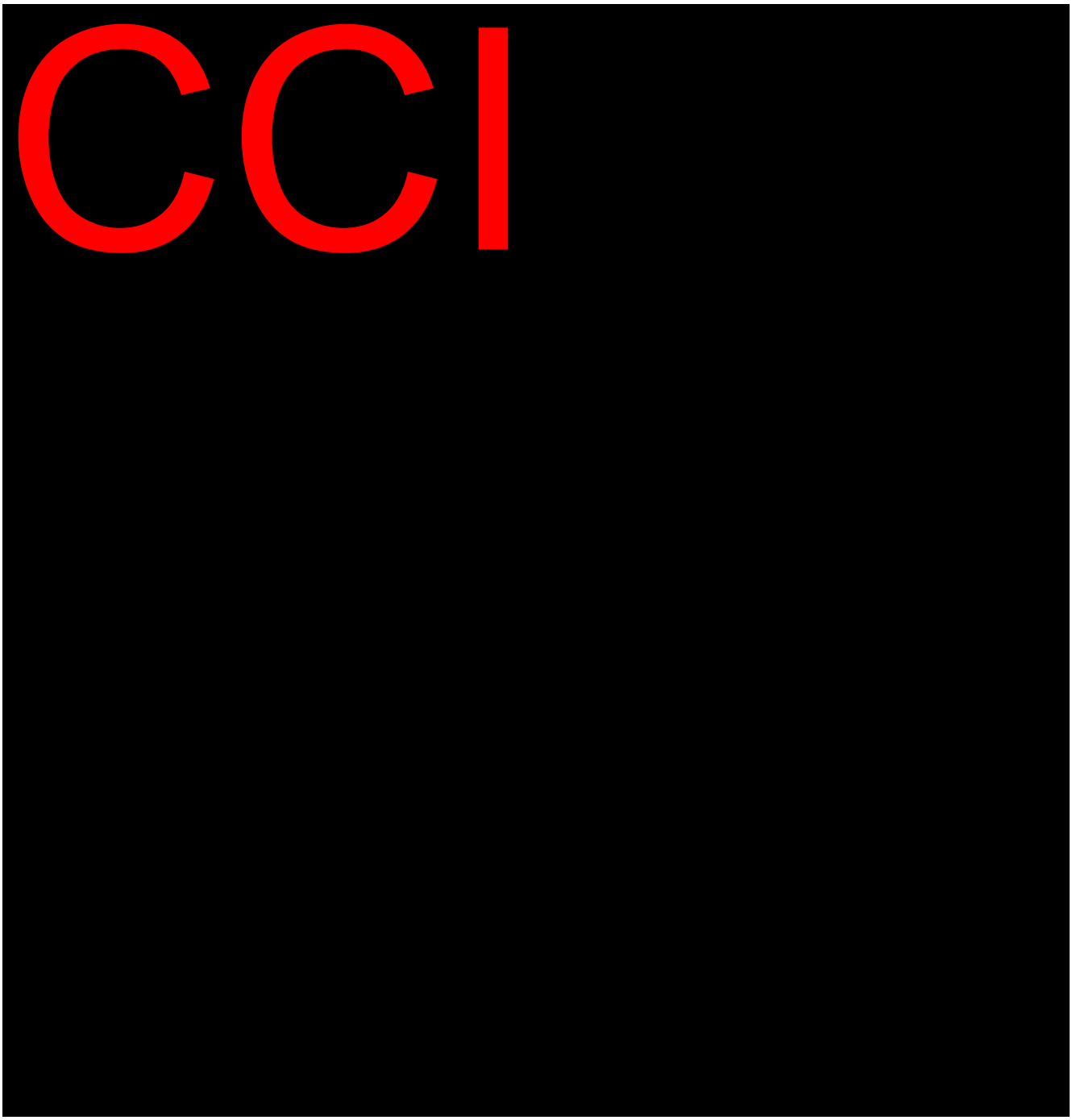
Study J1A-MC-KDAF is a Phase 2b, randomized, double-blind, placebo-controlled study to determine the appropriate dose and dosing frequency of peresolimab in adult participants with moderately-to-severely active RA.

This study includes a

- screening period
- CCI

- CCI
- post-treatment follow-up.

Treatment period design



Study Population:

In general, an individual may take part in this study if they

- Are 18 years of age or older at the time of signing the informed consent.

- Were diagnosed with RA as an adult, at least 3 months prior to screening, as defined by the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria.
- Currently have moderately-to-severely active RA.
- Have positive test results for rheumatoid factor or anti-cyclic citrullinated peptide antibodies at screening **OR** previous radiographs that show images of the hands or feet consistent with RA.
- Have C-reactive protein (CRP) >1.2 times upper limit of normal (ULN).
- CCI
- Have up to date vaccinations per regional and national guidelines, specifically influenza, pneumonia, and zoster.

In general, an individual may not take part in this study if they

- Have 1 or more of these medical conditions
    - poorly controlled diabetes or hypertension
    - chronic kidney disease stage IIIb, IV, or V
    - symptomatic heart failure according to New York Heart Association Class II, III, or IV
    - heart attack, poor blood flow to the heart, stroke or temporary symptoms of a stroke, within the past 12 months before randomization
    - severe chronic lung disease
    - major chronic inflammatory disease or connective tissue disease other than RA, or
    - multiple sclerosis.
- Have had any of these types of infections within 3 months of screening or develop any of these infections before the randomization visit
    - Serious - requires hospitalization or IV or equivalent oral antibiotic treatment
    - Opportunistic – infections caused by bacteria, viruses, fungus, or parasites that occur more often or are more severe in people with weakened immune systems
    - Chronic – duration of symptoms, signs, or treatment of 6 weeks or longer
    - Recurring – including, but not limited to, herpes simplex, herpes zoster, recurring bacterial skin infections (cellulitis), or chronic bone infections

    - Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over
    - Exception: If the investigator determines that a participant with recurrent nonserious infections such as cellulitis and uncomplicated orolabial or genital herpes, is not at an increased risk of complications.

- Have any of these infections
    - human immunodeficiency virus (HIV) infection
    - current infection with hepatitis B virus (HBV), for example, positive for hepatitis B surface antigen or polymerase chain reaction (PCR) positive for HBV DNA
    - current infection with hepatitis C virus (HCV), for example, positive for HCV RNA, or
    - active tuberculosis (TB).
- Have a current or recent acute active infection, or fever of 100.5°F (38°C) or above, at screening or baseline. For at least 30 days prior to screening, participants must have no symptoms or signs of confirmed or suspected infection and must have completed any appropriate treatment for the infection.

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Approximately 70% of the participants randomly assigned to study intervention will have a history of inadequate response to bDMARDs or tsDMARDs, while approximately 30% of participants will have a history of inadequate response to only conventional synthetic DMARDs.

Number of Participants:

Approximately 420 participants will be randomly assigned to study intervention.

Intervention Groups and Duration:

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Ethical Considerations of Benefit/Risk:

The safety data available to date suggest that there is no increased risk to participant safety with peresolimab compared to other approved humanized monoclonal antibody or immunomodulatory therapy.

Considering the measures taken to minimize risk to participants in this study, the potential benefit risk balance for this study is acceptable for testing in Phase 2 and justified by the potential benefits for participants with moderately-to-severely active RA.

Data Monitoring Committee: No

An internal assessment committee will review the interim efficacy and safety data in an unblinded fashion.

1.2. Schema

1.3. Schedule of Activities (SoA)

Two tables describe the SoA.

Table 1 (Section 1.3.1) describes Period I Screening, Period II Double-blind, Placebo-controlled Treatment, and Period III Double-blind Treatment visits.

Table 2 (Section 1.3.2) describes the ED Visit and Period IV Post-treatment Follow-up Visits 801 and 802.

Period I – Screening

Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.

Periods II and III – Double-blind Treatment periods

If an ED occurs before the last visit in the Period III treatment period, see the activities listed for the ED visit in Table 2.


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2. Introduction

Rheumatoid arthritis

RA is a common, systemic autoimmune inflammatory disease, characterized by synovial inflammation leading to pain, swelling, stiffness, and progressive destruction and deformity of small and large joints. Patients experience impaired physical function, social participation, and health-related quality of life. Patients also have increased risk of significant comorbidities that are not musculoskeletal (Picerno et al. 2015; Simon et al. 2015; Ogdie et al. 2018).

Current treatment of rheumatoid arthritis

Current treatment of RA includes timely initiation and modification of DMARD therapy to bring patients to a target of sustained LDA or remission (Smolen et al. 2020). Achievement of these targets improves short- and long-term patient health outcomes, including prevention of progressive, irreversible structural joint damage (Smolen et al. 2020).

The treatment target can be met in most patients with the therapeutic options currently available, which include csDMARDs, bDMARDs, and tsDMARDs. However, 20% to 30% of the patients with RA fail to respond to current therapies. For these patients, new treatment options are needed (Smolen et al. 2020).

Peresolimab (otherwise known as LY3462817)

Peresolimab is a CCI [redacted] Peresolimab binding to CCI is expected to trigger the physiological immune inhibitory pathway to restore immune regulation, which is a novel treatment approach for patients with autoimmune or auto-inflammatory diseases.

CCI ***target and autoimmune disease***

The CCI and its ligands, CCI, are important elements of the CCI pathway involved in immune homeostasis. There is evidence of the PD-1 pathway having a significant pathophysiologic role in autoimmune diseases such as psoriasis (Gulati et al. 2015), psoriatic arthritis (Bommarito et al. 2017), giant cell vasculitis (Zhang et al. 2017), multiple sclerosis (Trabattoni et al. 2009), systemic sclerosis (Fukasawa et al. 2017) and RA (Canavan et al. 2021).

In RA patients, reported biomarker changes that reflect disruption of the PD-1 pathway included significant increases in PD-1 expression and decreases in PD-L1 expression (Guo et al. 2018). Additionally, auto-antibodies to PD-L1 (Dong et al. 2003) and increases in soluble PD-1 in the synovium, which can bind PD-L1 (Bommarito et al. 2017), were reported in RA patients, that may reflect disrupted signaling through the PD-1 receptor and defects in immune inactivation pathways.

2.1. Study Rationale

This study aims to find the appropriately CCI [redacted] for peresolimab in adults with moderately-to-severely active RA for further clinical development.

2.2. Background

Peresolimab

Information on the safety, tolerability, PK, and PD of peresolimab comes from completed study J1A-MC-KDAB (KDAB) and from the ongoing studies J1A-MC-KDAC (KDAC) and J1A-MC-KDAD (KDAD). This table summarizes the clinical studies for peresolimab as of June 2022.

Study	Study design	Population	Number of Participants Randomly Assigned to Intervention	Study Interventions	Study Status
KDAB	Phase 1, single ascending dose, first in human study	Healthy participants	64	CCI	Completed
KDAC	Phase 1b, randomized, placebo-controlled, multiple ascending dose study	Participants with psoriasis (BSA ≥2)	27		Ongoing
KDAD	Phase 2, proof-of-concept, placebo-controlled, double-blind, randomized study	Participants with moderately-to-severely active RA with CCI	98		Ongoing

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Overview of clinical data

Safety

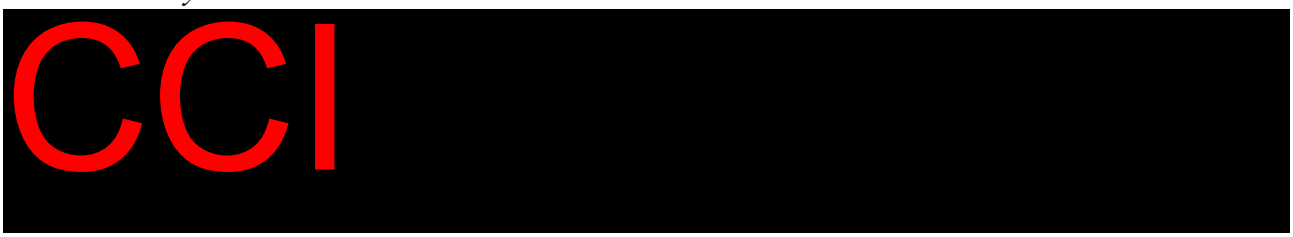
Phase 1 Studies KDAB and KDAC

In Studies KDAB and KDAC, there were no reports of

- deaths or SAEs
- discontinuations because of an AE
- infusion reactions
- injection site reactions
- malignancy
- serious infection
- reactivation of latent infection, or
- opportunistic infections.

The most frequently reported TEAEs related to treatment overall were in the Nervous System Disorders system organ class. The most frequently reported TEAE following dosing with peresolimab was headache.

Phase 2 Study KDAD



Efficacy

Pharmacokinetics

Pharmacodynamics

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2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of peresolimab may be found in the IB.

2.3.1. Risk Assessment

Potential risks for this study

The risks associated with peresolimab are similar to risks generally expected with approved humanized monoclonal antibodies or immunomodulatory therapies, such as

- hypersensitivity and cytokine release reaction
- injection site reactions, for example, injection site rash, erythema, or pruritus or lipohypertrophy
- risk of developing infection or of an infection becoming more serious
- immunogenicity, and
- malignancy.

In participants who received peresolimab, there are no apparent trends in any AE.

All AEs from the 3 clinical studies were mild or moderate in severity with only 1 SAE observed during the treatment in Study KDAD. See Section 2.2 and the IB for clinical safety results.

Management of risks

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

2.3.2. Benefit Assessment

Study KDAD established the efficacy of peresolimab (Section 2.2).

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

2.3.3. Overall Benefit Risk Conclusion

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3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To evaluate the efficacy of peresolimab compared to placebo in achieving ACR20	• Proportion of participants achieving ACR20 at Week 12
Secondary	
To evaluate the effect of peresolimab compared to placebo for measures of disease activity	• Proportion of participants achieving ACR50 or ACR70 at Week 12 • Proportion of participants achieving LDA or remission at Week 12 for o DAS28-hsCRP CCI • Change from baseline at Week 12 for mean o DAS28-hsCRP CCI
To evaluate the effect of peresolimab compared to placebo for patient-reported outcome measures	CCI o patient's assessment of physical function using HAQ-DI. CCI

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To evaluate the effect of peresolimab for measures of disease activity	
To characterize the pharmacokinetics of peresolimab	
Exploratory	
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Primary estimand

The primary clinical question of interest is:

> What is the difference between peresolimab and placebo in the target patient population, in achieving a successful response at CCI without use of rescue medication or discontinuing the study intervention?

The estimand is described by the following attributes:

- Population: Participants with moderately-to-severely active RA (see Section 5).
- Endpoint: CCI
- ICEs related to study intervention include the use of rescue or prohibited medication and ED from the study or study intervention. A composite strategy will be used for ICEs. Specifically, participants with an ICE will be considered as a nonresponder after the first occurrence of the ICE.
- Population-level summary: Difference in proportion of participants achieving response at CCI
- Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will be considered as treatment failures and categorized as nonresponder since it is assumed the participant was not receiving benefit from the intervention.

Secondary estimands for categorical endpoints

For secondary objectives that have categorical endpoints analyzed up to CCI the clinical question of interest is:

> What is the difference between peresolimab and placebo in the target patient population, in achieving a successful response at CCI without use of rescue medication or discontinuing the study intervention?

The estimand is described by the following attributes:

- Population: Participants with moderately-to-severely active RA (see Section 5).
- CCI
- ICE will be accounted using the same estimand strategy as for the primary estimand.

- Population-level summary:

  Difference in proportion of participants achieving response at CCI between intervention conditions.

- Rationale for estimand is described above for the primary estimand.

Secondary estimands for continuous endpoints

For secondary objectives that have continuous endpoints analyzed up to CCI the clinical question of interest is:

> What is the difference between peresolimab and placebo in the target patient population, in average at CCI without use of rescue medication or discontinuing the study intervention?

The estimand is described by the following attributes:

- Population: Participants with moderately-to-severely active RA (see Section 5).
- Endpoint: change from baseline for

- How to account for ICEs: A hypothetical estimand strategy will be used. That is, data collected after the first occurrence of ICE will be excluded from an analysis and what the treatment effect would have been if rescued medication was not used.
- Population-level summary:

  Difference in mean change from baseline to CCI between intervention conditions.

Supportive estimands

Additional details on supportive estimands for primary and secondary objectives will be provided in the SAP.

4. Study Design

4.1. Overall Design

Study J1A-MC-KDAF (KDAF) is a Phase 2b, randomized, double-blind, placebo-controlled study to determine the appropriate dose and dosing frequency of peresolimab in adult participants with moderately-to-severely active RA.

This study includes a

- screening period
- CCI double-blind, placebo-controlled treatment period
- CCI double-blind treatment period, and
- post-treatment follow-up.

See the SoA for visit schedule, procedural and assessment details (Section 1.3).

Participant population

CCI of the participants randomly assigned to study intervention will have a history of CCI of participants will have a history of CCI

Treatment period design

Follow-up period

Two follow-up visits occur at CCI after the final treatment period visit.

Participation in an open-label extension study

If an open-label extension study is enrolling at the time the participant completes CCI they will be given the opportunity to enroll in that study.

4.2. Scientific Rationale for Study Design

Primary endpoint

Clinical CCI in disease activity is the main target for participants with RA. The CCI are an accepted measure of reduction in RA disease activity per FDA, guidance (FDA 2013).

Independent Joint and Safety Assessors

To prevent potential bias from observed efficacy or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety (see Section 8).

Overall design

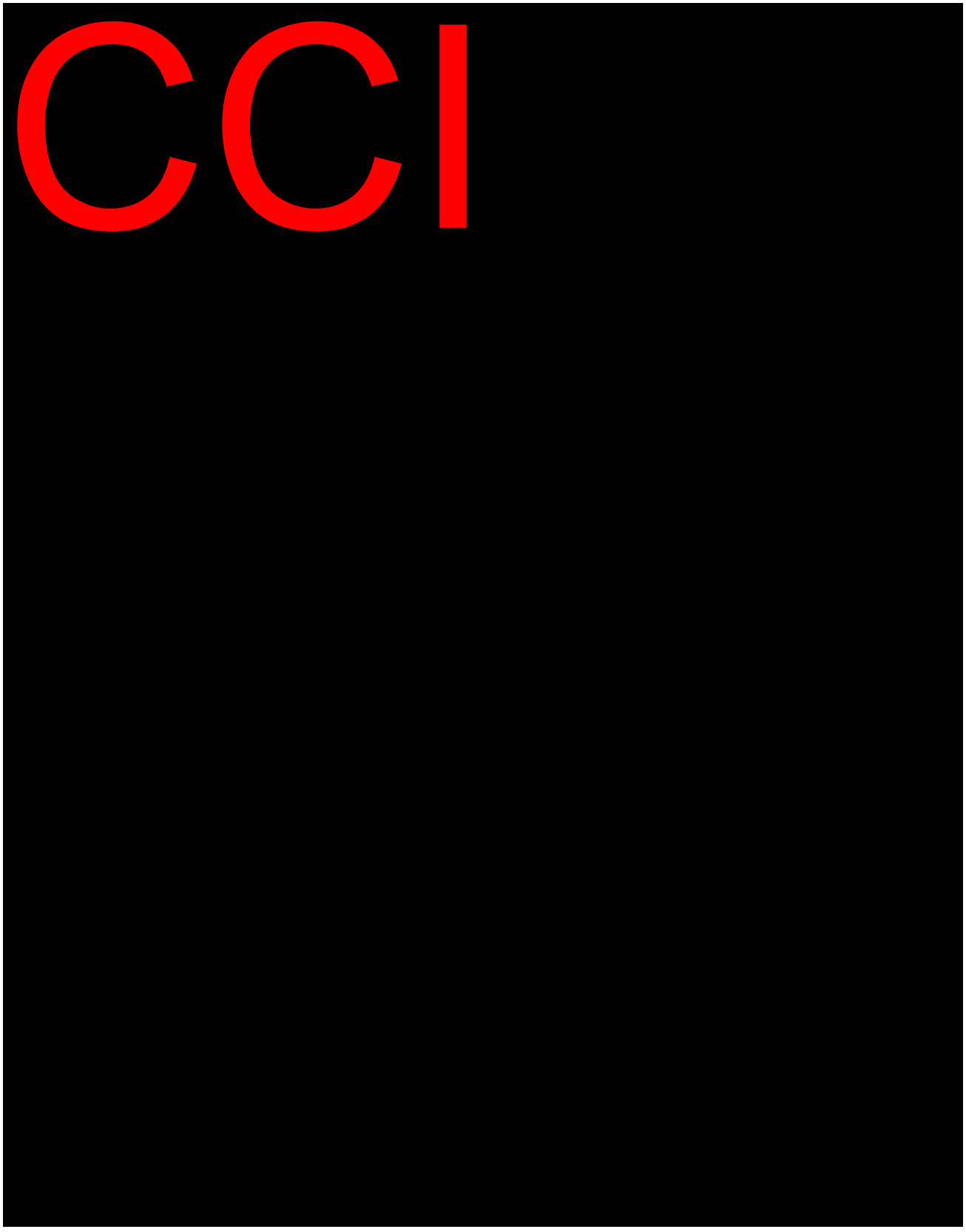
Follow-up period duration

The CCI follow-up duration is considered acceptable to evaluate safety and to explore the durability of biomarker and clinical disease activity changes achieved during the treatment period.

Collection of race and ethnicity data

In this study, collection of demographic information includes race and ethnicity as allowed per local regulations. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose



4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Are ≥18 years of age at the time of signing the informed consent.

Type of participant and disease characteristics

2. Have a diagnosis of adult onset RA for at least 3 months prior to screening, as defined by the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria (Aletaha et al. 2010).
3. Have moderately-to-severely active RA, at **screening and baseline**, defined by the presence of
   - ≥6 swollen joints based on 66 joint count, and
   - ≥6 tender joints based on 68 joint count.

   Notes:

   The distal interphalangeal joints should be evaluated but not included in the total count to determine eligibility.

   If a participant has received corticosteroid treatment per Criterion 27, the treated joint should be excluded from the joint count.
4. Have positive test results for rheumatoid factor or anti-cyclic citrullinated peptide antibodies at screening **OR** previous radiographs documenting bony erosions in hands or feet consistent with RA.
5. Have C-reactive protein (CRP) >1.2 times ULN per the central laboratory at screening.

CCI [redacted]

7. Have up to date vaccinations per regional and national guidelines, specifically influenza, pneumonia, and zoster.
   - Live vaccines should be administered >3 months before randomization.
   - All vaccinations should be administered ≥30 days before randomization.
8. Have clinical laboratory test results within normal reference range or results with acceptable deviations that are judged as not clinically significant by the investigator at screening. This table outlines laboratory test results with required ranges for inclusion in this study.

Test	Result
Hematology	
Absolute neutrophil count	≥1.5 x 10^9/L (≥1.5 x 10^3/µL or ≥1.5 GI/L)
Platelet count	≥100 x 10^9/L (≥100 x 10^3/µL or ≥100 GI/L)
Hemoglobin level	≥10.0 g/dL
Lymphocyte count	>500 cells/µL (>0.50 x 10^3/µL or >0.50 GI/L)
Total leukocyte count	≥3.0 × 10^9/L (≥3.0 x 10^3/µL or ≥3.0 GI/L)
Clinical Chemistry	
Serum creatinine, ALT, and AST	levels ≤ 2x upper limit of normal (ULN)
TBL and ALP	<1.5 x ULN. Participants with Gilbert's syndrome must have serum direct bilirubin <1.5 mg/dL

See Section 6.8 for allowed treatments during the study if the dose is stable for ≥4 weeks
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Note to sites in EU Member States: See Section 10.9.1 for country-specific modifications to Criterion 9.

Sex and contraceptive/barrier requirements

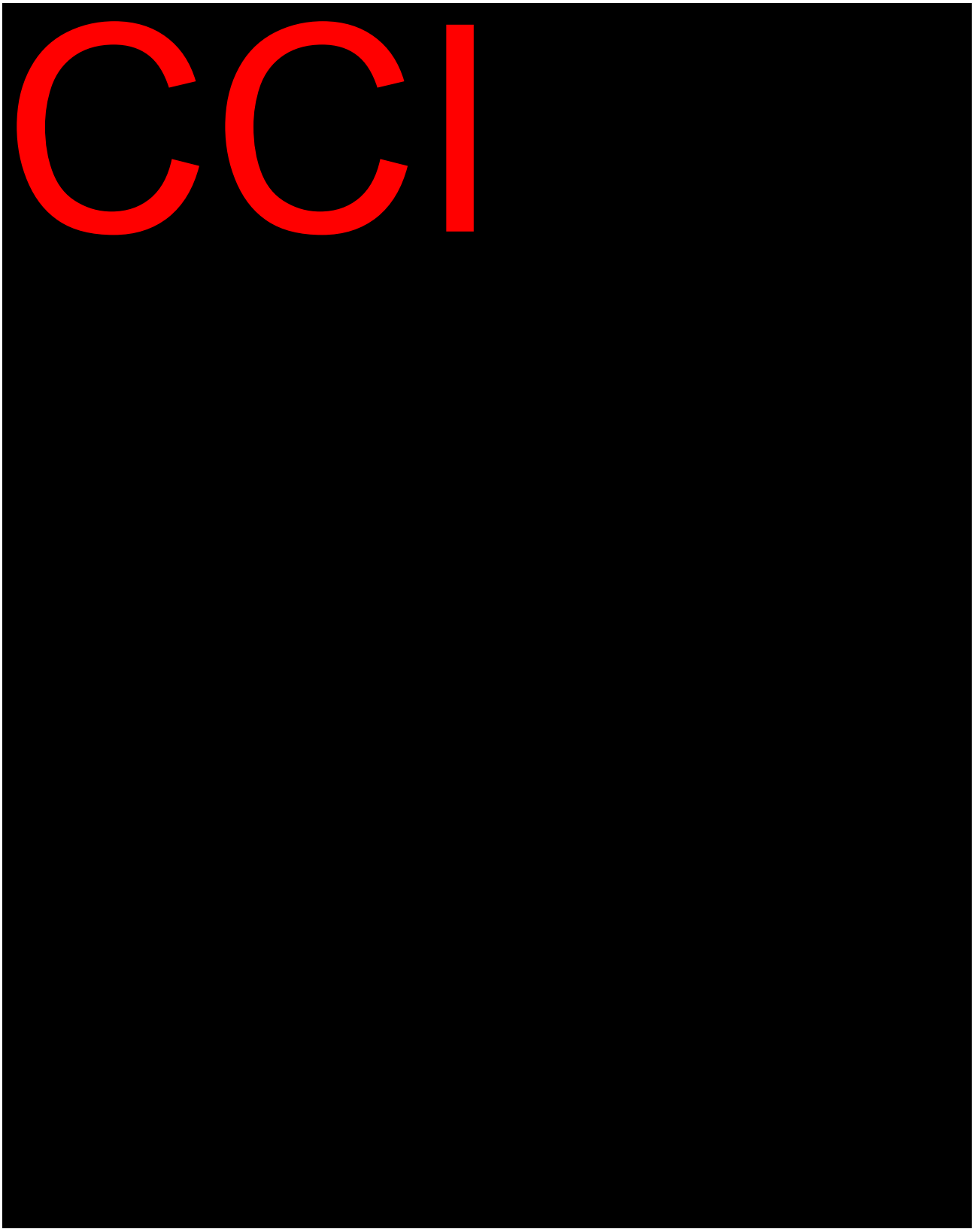
10. Male or female
    Women of childbearing potential (WOCBP) and women not of childbearing potential (WNOCBP) may participate in this study.
    Males who agree to use highly effective methods of contraception may participate in this study.
    See Section 10.4 for definitions and additional requirements related to contraception.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

Informed consent

11. Are capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria



20. Have had any surgical procedure, within 12 weeks prior to screening, or any planned surgical procedure scheduled to occur during the study, with the exception of minor surgery requiring local or no anesthesia and without any complications or sequelae.
21. Have had any of the following types of infections within 3 months of screening or develops any of these infections before the randomization visit
    - Serious - requires hospitalization or IV or equivalent oral antibiotic treatment
    - Opportunistic - as defined in Section 10.7
    - Chronic - duration of symptoms, signs, or treatment of 6 weeks or longer
    - Recurring - including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, or chronic osteomyelitis
        - Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over
        - Exception: If the investigator determines that a participant with recurrent nonserious infections such as cellulitis and uncomplicated orolabial or genital herpes, is not at an increased risk of complications.
22. Have any of these infections
    - HIV infection
    - current infection with HBV, for example, positive for hepatitis B surface antigen (HBsAg) or polymerase chain reaction (PCR) positive for HBV DNA
    - current infection with HCV, for example, positive for HCV RNA, or
    - active TB.
23. Have or had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO or the United States CDC, unless such treatment is underway, as per Section 8.2.8.
24. Have a current or recent acute active infection, or fever of 100.5°F (38°C) or above, at screening or baseline. For at least 30 days prior to screening, participants must have no symptoms or signs of confirmed or suspected infection and must have completed any appropriate anti-infective treatment.
25. Are women who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study intervention.

Prior/concomitant therapy

26. Have failed more than [redacted]
27. Are currently receiving or have received any of these therapies within 28 days [redacted]

Therapy	Notes
[redacted]	

28. Have received these treatments [redacted] or plan on receiving any of these biologic immunosuppressive treatments during the study

[redacted]

30. Have received a Bacillus Calmette-Guérin (BCG) vaccination or BCG treatment within 12 months of screening.

Prior/concurrent clinical study experience

31. Were previously enrolled in a clinical study investigating peresolimab (LY3462817) or any other molecule targeting PD-1 for the treatment of auto-immune or auto-inflammatory conditions.
32. Are currently enrolled in any other clinical study involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study.
33. Have participated, within the last 30 days, in a clinical study involving study intervention. If the previous study intervention has a long half-life, 3 months or CCI whichever is longer, should have passed prior to screening.
34. Have previously completed or withdrawn from this study.

Diagnostic assessments

Other exclusions

36. Have donated more than a single unit of blood within 4 weeks before randomization or plan on donating blood during the study.
37. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
38. Are Lilly employees or employees of third-party organizations involved with the study that require exclusion of their employees.
39. Are not willing to receive CCI

40. Are unsuitable for inclusion in the study, in the opinion of the investigator or sponsor, for any reason that may compromise the participant's safety or confound data interpretation.
41. Have experienced allergic/hypersensitivity reaction to any component of peresolimab (LY3462817), including excipients.

5.3. Lifestyle Considerations

All study participants should not donate blood or blood products during the study or for CCI after the last dose of the study intervention.

Reproductive and contraceptive guidance is provided in Section 10.4.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

A possible reason for rescreening may be a status change such that the eligibility criterion that caused the participant to screen fail would not cause the participant to screen fail again.

If an individual is rescreened, a new participant number is assigned, and the individual must sign a new ICF.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study. All entry criteria must be met within the specified visit intervals in the SoA.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Study intervention will be administered at the study sites, at visits summarized in the SoA.

This table provides information for the interventions used in this clinical study.

Study intervention dosing information

Each dose of study intervention is planned to be CCI The sponsor will provide detailed instructions for study intervention administration in a separate document.

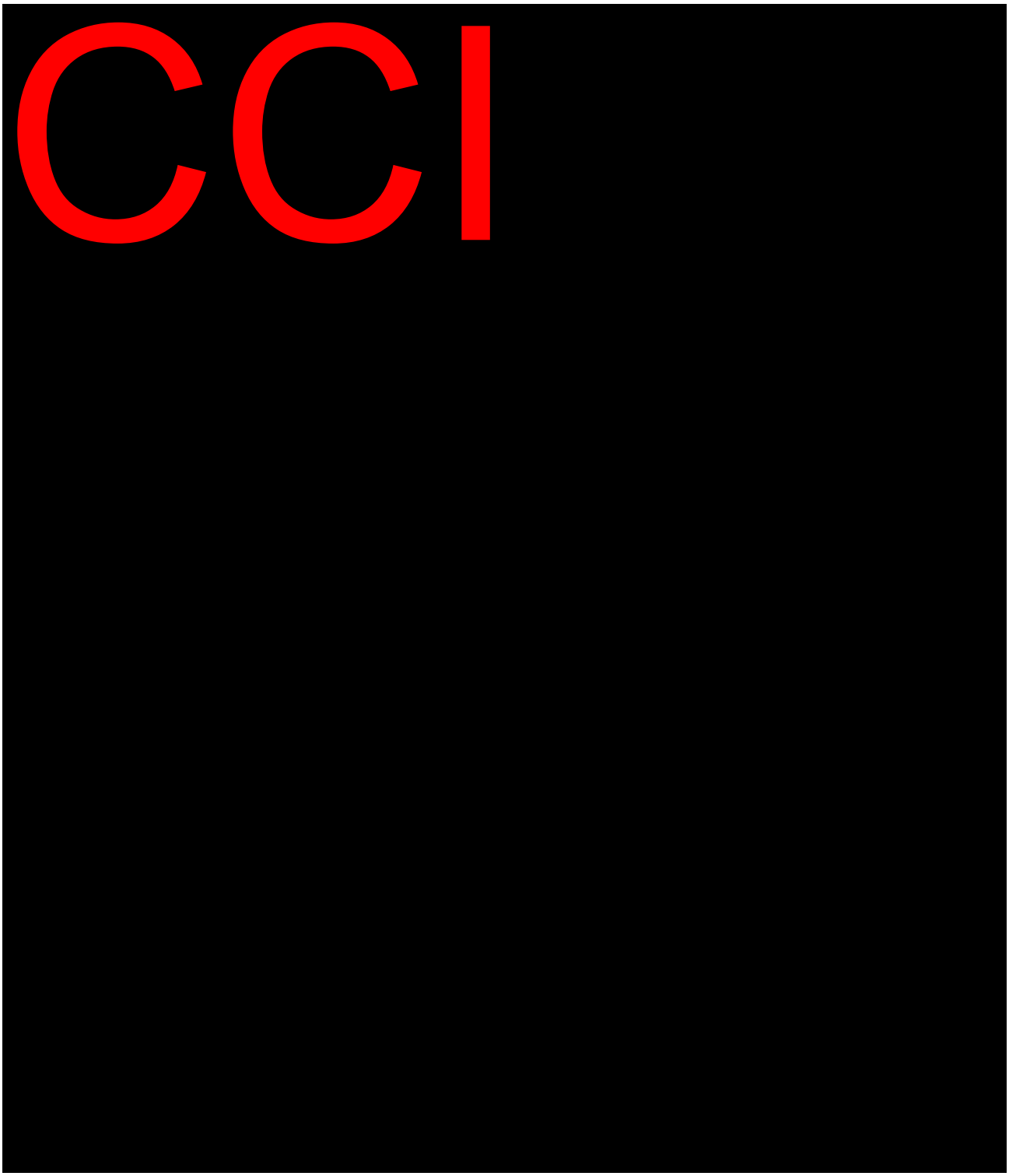
After dosing, the investigator should monitor all participants for 1 hour or longer according to investigator practice or local standard of care.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Rescue Medicine

Guidance for starting rescue therapy



6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

Blinding

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

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

Emergency unblinding

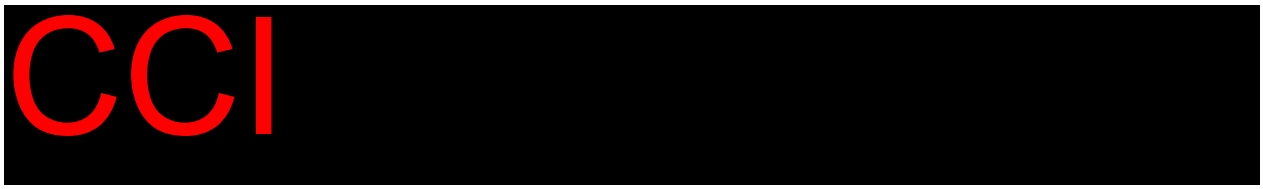
The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the sponsor must be notified immediately within 24 hours of this occurrence. The date and reason that the blind was broken must be recorded.

Discontinuation from the study in case of unblinding

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

6.4. Study Intervention Compliance



6.5. Dose Modification

This protocol does not allow dose adjustments.

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

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

If an open-label extension study is enrolling at the time the participant completes Visit 18 (Week 60), they will be given the opportunity to enroll in that study.

6.7. Treatment of Overdose

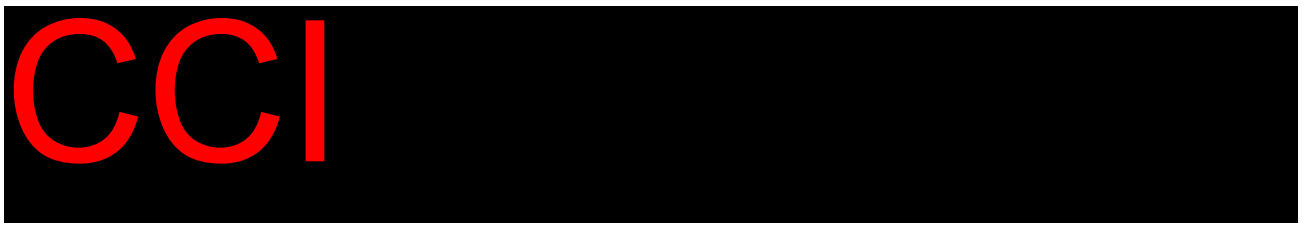
The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted
- closely monitor the participant for any AE/SAE and laboratory abnormalities

6.8. Concomitant Therapy

General considerations



Concomitant therapy data collection

For therapy that the participant is receiving at the time of enrollment or receives during the study, whether prescription or over-the-counter, authorized study personnel should collect

- the name of medication, vaccine or therapy
- the reason for use
- route of administration, and
- dates of administration, including start and end dates.

For RA background therapy and rescue therapy, study personnel should collect additional dosing information, including dose and frequency.

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

This section outlines

- Permanent discontinuation of study intervention
- Temporary interruption of study intervention
- Discontinuation from the study, and
- Participants lost to follow-up.

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

7.1. Discontinuation of Study Intervention

Permanent discontinuation of study intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will be encouraged to remain in the study and follow procedures for all remaining study visits, as shown in the SoA.

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

- requests to discontinue the study intervention
- becomes pregnant during the study
- is diagnosed with an active or untreated malignancy, except for successfully treated basal or squamous cell carcinoma
- is diagnosed with HIV infection
- is diagnosed with active TB
- is diagnosed with LTBI and are not a candidate for treatment as described in Section 8.2.8
- tests positive for HBV DNA or HCV RNA (see Sections 8.2.9 and 8.2.10 for details)
- answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS
- answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS
  A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.
- has a systemic hypersensitivity reaction related to study intervention administration, or
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons.

Additional guidance

Escape criteria

A participant not achieving CCI [redacted] or example, if a participant meets rescue criteria at Week 16 and does not achieve a 20% improvement from baseline in both TJC and SJC at Weeks 20 and 24, then they should be permanently discontinued from study intervention. Participants may continue in the study and receive additional standard of care therapies at the investigator's discretion.

Systemic hypersensitivity reactions

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, 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.

HBV DNA

Prior to discontinuation of any immunomodulatory or immunosuppressive therapy, including study intervention, the participant should be referred to, evaluated, and managed by a physician with expertise in evaluation and management of viral hepatitis.

The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis should be based on the recommendation of the consulting physician with expertise in hepatology, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study intervention based on elevated liver tests

The study intervention should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.7), if 1 or more of the conditions in this table occur.

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

ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

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

Resuming study intervention after elevated liver tests

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

7.1.2. QTc Stopping Criteria

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

7.1.3. Temporary Discontinuation of Study Intervention

Infection-related criteria for temporary discontinuation of study intervention

This table describes the required criteria for temporarily discontinuing study intervention and the next steps the site staff should follow.

If a participant develops…	Then follow this guidance…
serious or opportunistic infections, as defined in the exclusion criteria (Section 5.2)	Withhold study intervention until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment. The investigator should consult with the sponsor-designated medical monitor to determine when it is appropriate to restart study intervention.
any acute infection or illness	At the discretion of the investigator and sponsor or its designee, withhold intervention until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.
positive HBV DNA results or results detecting HBV DNA, but the HBV DNA is below the level of quantification	• Contact the sponsor-designated medical monitor. • Repeat HBV DNA testing as soon as possible. • If HBV DNA is confirmed as positive, then permanently discontinue intervention.
LTBI and the participant is a candidate for LTBI treatment	• Withhold study intervention for at least the first 4 weeks of LTBI treatment. • If there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance after receiving at least 4 weeks of appropriate LTBI therapy, per WHO or CDC guidelines, then restart study intervention. • The participant must complete appropriate LTBI therapy before restarting study intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

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

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Joint and safety assessors

To prevent potential bias from observed efficacy or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety.

The same assessor should perform the joint assessments of a participant, whenever possible, throughout the study to minimize interobserver variation.

A back-up independent joint assessor should be identified.

The independent joint assessors should be a CCI [redacted] Any other joint assessor must be trained and competent in performing such assessments.

8.1. Efficacy Assessments

Order of assessments

The patient-reported and clinician-reported efficacy assessments should be completed in the following order

Additional calculations and assessments

Efficacy measurements also include calculations and assessments by


CCI


CCI


CCI


CCI

8.1.8. Clinician Administered Tender or Swollen Joint Count (TSJC) (68/66)

The clinician administered TSJC (68/66) will be performed at visits according to the SoA.

Data will be captured on an electronic tablet collected at site visits.

The same assessor should perform the joint assessments of a participant, whenever possible, throughout the study to minimize interobserver variation.

Tender Joint Counts

The number of tender joints will be determined by examination of 68 joints, 34 joints on each side of the participant's body.

The 68 joints to be assessed and classified as tender or not tender include

- 2 temporomandibular joints
- 2 acromioclavicular joints
- 2 elbow joints
- 2 hip joints
- 2 ankle joints
- hands
  - 10 metacarpophalangeal joints
  - 2 interphalangeal joints of the thumb
  - 8 proximal interphalangeal joints, and
  - 8 distal interphalangeal joints.
- 2 sternoclavicular joints
- 2 shoulder joints
- 2 wrist joints
- 2 knee joints
- 2 tarsal joints, and
- feet
  - 10 metatarsophalangeal joints
  - 2 first proximal interphalangeal joints, and
  - 8 proximal interphalangeal joints.

The investigator will identify any joints to be excluded from evaluation at each visit. Replaced, synovectomized, ankylosed, or arthrodesed joints should be excluded from evaluation.

Any joint that has had an intra-articular corticosteroid injection within 4 weeks prior to baseline should be excluded from evaluation during the study. The locations or a listing of these previous procedures should be documented in the participant's source documents or CRF.

The joint count will be assessed by scoring aspects of tenderness on pressure and passive movement of the particular joint. The participant will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement or both will be translated into a single tender-versus nontender dichotomy.

CCI

CCI

The 28 joints examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC include 14 joints on each side of the participant's body (Smolen et al. 1995):

- 2 shoulders
- 2 elbows
- 2 wrists
- 10 metacarpophalangeal joints
- 2 interphalangeal joints of the thumb
- 8 proximal interphalangeal joints, and
- 2 knees.

CCI


CCI


CCI

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of these system

- cardiovascular
- respiratory
- gastrointestinal, and
- neurological.

The physical examination will determine if there are symptoms of active TB, including measurement of body temperature and assessment of peripheral lymph nodes.

A complete physical examination may be repeated at the investigator's discretion at any time a participant presents with physical complaints.

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

Symptom-directed physical assessments after screening

These assessments are performed based on participant status and standard of care.

8.2.2. Vital Signs

For each participant, conduct vital signs measurements according to the SoA (Section 1.3).

Measure vital signs after the participant has been sitting at least 5 minutes, and before obtaining an ECG tracing, or collection of blood samples for laboratory testing.

8.2.3. Electrocardiograms

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

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the study 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 findings be identified.

If a clinically significant finding is identified after enrollment, the investigator in conjunction with the sponsor will determine if the participant can continue in the study and if any change in participant management is needed.

8.2.4. Clinical Safety Laboratory Tests

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

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within approximately 50 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.5. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected as outlined in Sections 8.3.1 and 8.3.2.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Participants who experience signs of suicidal ideation and behavior should undergo a risk assessment. All factors contributing to suicidal

ideation and behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

Baseline assessment of suicidal ideation and behavior and intervention emergent suicidal ideation and behavior will be monitored during the study using the C-SSRS.

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 (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) 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.

Nonleading AE collection should occur prior to the collection of the C-SSRS.

If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form, except if a serious AE occurs or an AE leading to discontinuation occurs.

If a serious AE occurs, then capture the AE on the AE form and follow the process for reporting SAEs.

If an AE leads to discontinuation, then capture the AE on the AE form and record the reason for discontinuation.

8.2.7. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests, 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 the conditions in this table occur.

If a participant with baseline results of...	Develops the following elevations…
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

What to do if the abnormal condition persists or worsens

If the abnormality persists or worsens, the investigator, in consultation with the Lilly-designated medical monitor, should initiate clinical and laboratory monitoring, and evaluation for possible

causes of abnormal liver tests. At a minimum, this evaluation should include physical examination and a thorough medical history, including

- symptoms
- recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- history of concomitant medications including over-the-counter, herbal and dietary supplements, and
- history of alcohol drinking and other substance abuse.

Frequency of monitoring

Initially, monitoring of symptoms and hepatic biochemical tests should be done 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 lab results stabilize.

Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in this table occur.

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

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

What a comprehensive evaluation should include

At a minimum, this evaluation should include

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

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- 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.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Collect additional hepatic safety data in hepatic safety CRFs if a study participant develops a hepatic event considered to be an SAE or discontinues study intervention due to a hepatic event or meets 1 of the conditions described in this table.

If a participant with baseline results of...	Develops the following elevations…
ALT <1.5x ULN	ALT to ≥5x ULN on 2 or more consecutive blood tests
ALT ≥1.5x ULN	ALT ≥3x baseline on 2 or more consecutive blood tests
TBL <1.5x ULN	TBL ≥2x ULN, except for participants with Gilbert's syndrome
TBL ≥1.5x ULN	TBL ≥2x baseline
ALP <1.5x ULN	ALP ≥2x ULN on 2 or more consecutive blood tests
ALP ≥1.5x ULN	ALP to ≥2x baseline on 2 or more consecutive blood tests

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

8.2.8. Tuberculosis Testing and Monitoring

Tuberculosis testing at screening Visit 1

Medical history will determine the lifetime risk factors for TB infection, for TB progression, and for symptoms or signs of active TB.

A physical examination will determine symptoms of active TB, including measurement of body temperature and assessment of peripheral lymph nodes.

A chest x-ray will be interpreted and reported by a radiologist or pulmonologist, as specified in the SoA (Section 1.3). Participants do not need to have a chest x-ray at screening if results from a chest x-ray within 3 months prior to the study are available.

All participants with no history of LTBI or active TB, and no history of positive Mantoux tuberculin skin test (TST) using purified protein derivative (PPD) or positive *Mycobacterium tuberculosis* interferon gamma release assay (IGRA), must have either a PPD, TST or IGRA for *M. tuberculosis*.

PPD TST

An induration of 5 or more millimeters is considered positive in persons

- with HIV-infection
- with a recent contact with a person with TB disease
- with fibrotic changes on chest radiograph consistent with prior TB
- with organ transplants, or
- who are immunosuppressed for other reasons, for example, taking the equivalent of >15 mg/day of prednisone for 1 month or longer, or taking tumor necrosis factor -α antagonists.

An induration of 10 or more millimeters is considered positive in all other potential study participants.

Two-step testing, repeating TST from 1 to 3 weeks after the first TST, is recommended for certain participant groups, including persons

- receiving immunosuppressant treatment
- with a history of temporally remote increased risk of TB infection, or
- for whom the first test is negative, as per local public health or professional medical society recommendations.

IGRA for M. tuberculosis

Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.

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 LTBI therapy, per the WHO or the United States CDC guidelines, there is no evidence of hepatotoxicity, defined as ALT/AST ≤2 times ULN, or other treatment intolerance.
- The participant completes appropriate LTBI therapy.

Monitoring during the study

At a minimum, each participant will have the following documented at least every 3 months

- thorough history to determine any risk factors for TB infection and for TB progression, symptoms, or signs of active TB, and
- thorough physical examination that includes assessment for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes.

8.2.9. Hepatitis B Testing and Monitoring

The following actions should be taken in response to HBV DNA test results during the study.

If…	Then…
a single result is obtained with a value "below limit of quantitation"	the test should be repeated within approximately 2 weeks
the repeat test result is "target not detected"	monitoring may resume according to the study schedule
the participant has 2 or more test results with a value "below limit of quantitation" during the study	HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended
a result is obtained with a value "above limit of quantitation" at any time during the study	the participant will be permanently discontinued from the study intervention (see Section 7.1) and should be referred to a hepatologist immediately.

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 and 7.1.3, and the participant should receive appropriate follow-up medical care.

8.2.10. Hepatitis C Testing and Monitoring

Initial testing for HCV infection includes testing for antibodies to HCV.

If…	Then…
anti-HCV is positive	HCV RNA testing is required.
HCV RNA test is negative	the participant is not excluded.
HCV RNA test is positive	the participant is excluded.

Participants who have had HCV infection and have been successfully treated must also have a negative HCV RNA test at screening to remain eligible for the study. Successful treatment is defined as a sustained virologic response of HCV RNA by PCR negative for at least 24 weeks following treatment completion.

If HCV RNA is detected during the study, the study intervention will be permanently discontinued (Section 7.1), and the participant should receive appropriate follow-up medical care.

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

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

- AEs
- SAEs, and
- PCs.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up 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 AEs of special interest 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. Further information on follow-up procedures is provided in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

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

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 hours of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	at least 5 terminal half-lives after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	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
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

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

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

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

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

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 12 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.

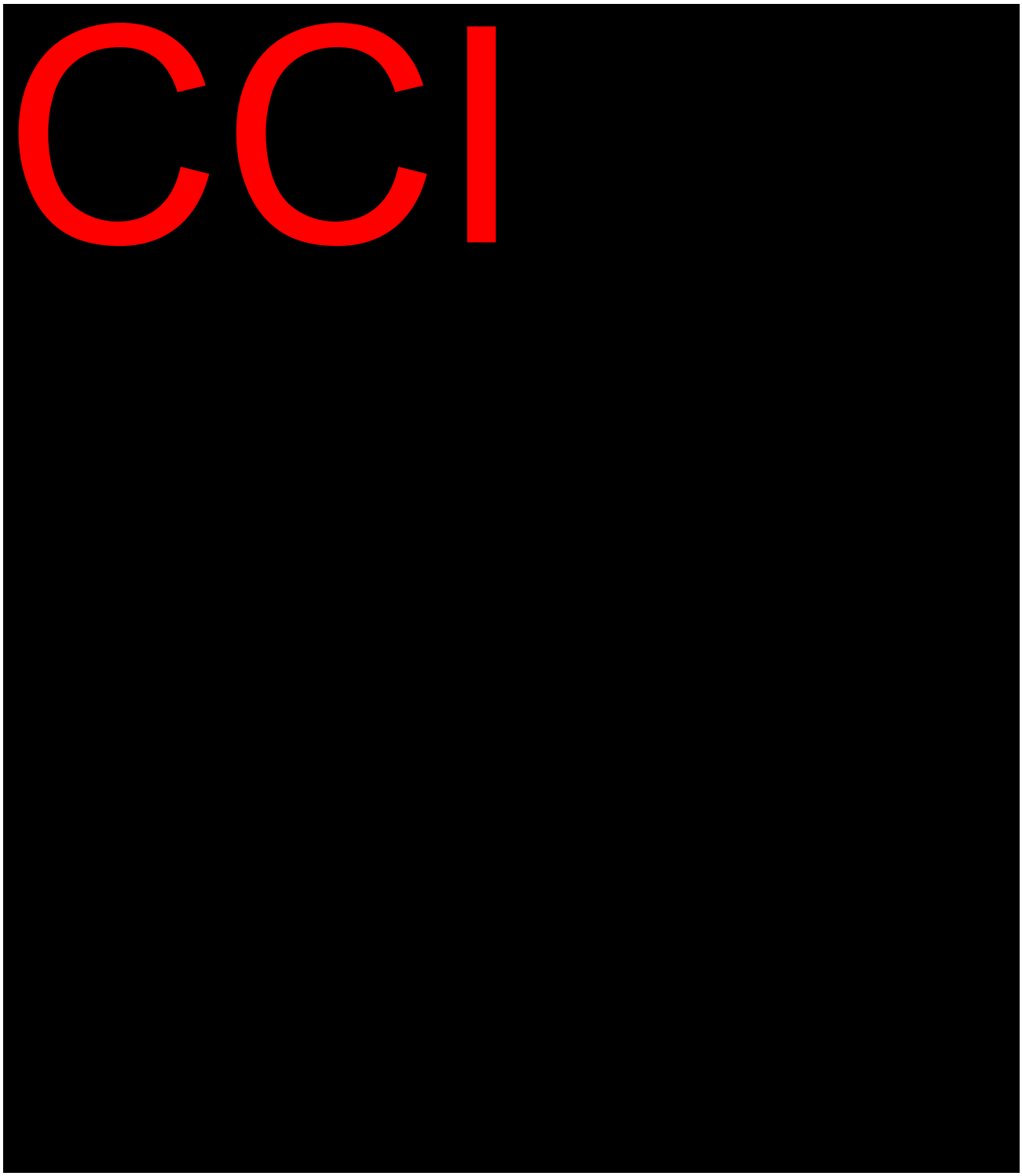
The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 12 weeks beyond the estimated 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, they may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.



8.4. Pharmacokinetics

8.5. Pharmacodynamics

Immunogenicity will be assessed by a validated assay designed to detect and characterize ADA in the presence of peresolimab at a laboratory approved by the sponsor.

Antidrug antibodies may be further characterized for their ability to neutralize the activity of peresolimab.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Treatment-emergent ADAs are defined in Section 9.3.7.

Sample retention is described in Section 10.1.12.

8.9. Health Economics

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

9. Statistical Considerations

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

9.1. Statistical Hypotheses

9.1.1. Multiplicity Adjustment

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

9.2. Analyses Sets

9.3. Statistical Analyses

9.3.1. General Considerations

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

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.

Efficacy analyses will be conducted on the mITT population, unless otherwise specified. Safety analyses will be conducted on the safety population. Placebo participants will be pooled for CCI

This study includes

- Period I - screening period
- Period II - CCI double-blind, placebo-controlled treatment period
- Period III - CCI double-blind treatment period, and
- Period IV - post-treatment follow-up.

Efficacy and safety data will be analyzed and summarized by these treatment periods if appropriate

- Period II - double-blind, placebo-controlled treatment period CCI
- Period III – double-blind treatment period. CCI
  - CCI
  - CCI

Baseline for the Treatment Period is defined as the last non-missing assessment on or prior to the date of the CCI of study treatment. Any assessment collected after the CCI is defined as post-baseline for the Treatment Period. Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline value or the value at the visit is missing for a particular variable, then the change from baseline is defined as missing.

Summary statistics for continuous variables may include mean, standard deviation, median, and minimum and maximum values.

Categorical variables will be presented as counts and percentages. Variables will be analyzed in the original scale on which they are measured, unless otherwise specified.

The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, is more fitting.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

Dichotomous responder endpoints including the primary endpoint will be analyzed using a CCI The odd ratio and p-value based on odd ratio will be reported. CCI of mean difference will also be reported without being adjusted by covariates. Missing data will be imputed using the nonresponder imputation method.

Treatment comparisons of continuous efficacy endpoints with multiple postbaseline timepoints will be analyzed using CCI will include

- treatment
- stratification factors
- baseline value
- visit, and treatment-by-visit interaction in the model as fixed factors, and
- participant as a random factor.

The covariance structure to model the within-participant errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the CCI will be used.

The CCI will be used to estimate the denominator degrees of freedom. Type III sums of squares for the LS means will be used for the statistical comparison. The 95% CI will also be reported. Missing data will be handled with the missing at random assumption. No additional imputation methods will be applied to the CCI

Where appropriate, treatment comparisons of continuous efficacy endpoints will be analyzed using CCI modeled with treatment group, stratification factors, and baseline value as covariates. Type III sums of squares for the LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and CCI unless otherwise specified, will also be reported. Missing data imputation method for the CCI model will the last observation carried forward.

Dose response modeling will be performed on the primary objective to assist in dose selection decisions. More details will be provided in the SAP.

Any change to the data analysis methods or imputation methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data may be conducted as deemed appropriate.

9.3.2. Primary Endpoint/Estimand Analysis

9.3.3. Secondary Endpoints Analysis

The secondary efficacy and health outcome endpoints at CCI will use the statistical analysis methods described in Section 9.3.1.

For the secondary efficacy endpoints at CCI summary statistics will be provided as described in Section 9.3.1.

Additional details will be provided in the SAP.

9.3.4. Exploratory Analysis

Exploratory analyses will be further described in the SAP that is finalized before database lock.

9.3.5. Safety Analyses

Safety analyses will be assessed by evaluating exposure, AEs, laboratory analytes, vital signs, and adverse events of special interests.

Duration of exposure to therapy during the treatment periods will be calculated for each participant and summarized by treatment group.

The AEs will be coded according to the MedDRA and summarized by system organ class, preferred term, severity, and relationship to the study intervention. All AEs, including pre-existing conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

A TEAE is defined as an event that first occurred or worsened in severity after baseline, with baseline defined as all pre-existing conditions recorded at Visit 1 and any AEs recorded before the first dose of study intervention (that is, during the interval between Visits 1 and 2, and recorded with the time of onset before the first dose of study intervention). The treatment period will be used as the postbaseline period for the analysis. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

The number and percentage of participants who reported TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an AE, and adverse events of special interests 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.

Adverse events of special interest or special safety topics 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 study discontinuation will be summarized. All AEs, including pre-existing conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

9.3.6. Pharmacokinetic Analyses

Peresolimab concentrations will be illustrated graphically and summarized descriptively.

A model-based approach using nonlinear mixed effects modeling or other appropriate software may be conducted. If appropriate, data from this study may be combined with data from other studies in model-based analyses. The impact of extrinsic and intrinsic patient factors, such as age, weight, and sex, on PK may be examined as needed. Estimates of PK model parameters and covariate effects will be reported. If ADA titers are detected from immunogenicity testing, then the impact of immunogenicity titers on peresolimab PK parameters may also be examined.

If data warrant, analyses of exposure-response relationships may be conducted using both exploratory graphical approaches and model-based approaches.

Exploratory graphical analysis approaches for categorical clinical endpoints may consist of graphs showing the percentage of participants that achieve the clinical endpoint at different

percentiles, for example, quartiles, of exposure of peresolimab at CCI Measures of exposure may include population PK estimated average concentrations at steady state ($C_{avg, ss}$) or observed trough concentrations at the time of the clinical endpoint.

Model-based analyses of the categorical clinical endpoints may use population exposure-response logistic regression models, where maximum effect (E_{max}) or other model structures may be used to relate exposure to the probability of achieving the endpoint. These models may be used to evaluate participant factors that may impact the relationship between exposure and the probability of achieving the endpoint. Longitudinal exposure-response models for ACR scores or response rates may be developed, which relate the time course and magnitude of peresolimab exposure to the time course and magnitude of ACR response.

Exploratory PK/PD analyses may be conducted to evaluate the relationship between peresolimab exposure and select measures of response, such as, receptor occupancy. Additional analyses may be conducted if they are deemed appropriate.

Further details on PK/PD analyses will be provided in the PK/PD analysis plan.

9.3.7. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting ADA and with treatment-emergent ADA to peresolimab may be tabulated.

Treatment-emergent ADAs are defined as participants

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For the treatment-emergent ADA + patients, the distribution of maximum titers will be described by peresolimab dose. The frequency of neutralizing antibodies to peresolimab may be tabulated in treatment-emergent ADA-positive patients.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to peresolimab may be assessed. Additional details may be provided in the SAP.

9.3.8. Other Analyses

9.3.8.1. Subgroup Analyses

Summary of subgroups will be provided. Subgroup analyses may be conducted for the primary endpoint ACR20 at CCI using the mITT population.

Subgroups that may be evaluated include previous RA therapy population, gender, race, geographic region, and disease duration.

Detailed description of the summaries and/or statistical analyses are provided in the SAP.

9.3.8.2. Supplemental Analyses

Supplemental analyses may be performed as deemed necessary.

9.4. Interim Analysis

Analyses for the primary database lock will be conducted as described in Section 9.3, when all participants have completed the CCI visit or have discontinued study intervention.

Potential prespecified interim analyses

Any of the predefined interim analyses may be not conducted at the discretion of the sponsor.

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An interim analysis prior to the analysis of the primary database lock may be conducted when approximately CCI of participants have completed CCI or have discontinued intervention, for the purpose of supporting planning activities associated with the peresolimab clinical development program. The analysis may assess safety, PK, or efficacy measures. No adjustments to study conduct and no adjustment of type I error will be performed.

An interim analysis prior to the analysis of the primary database lock may be conducted to review the safety and efficacy data when approximately CCI of participants have completed CCI or have discontinued intervention, for the purpose of supporting planning activities associated the peresolimab clinical development program. The analysis may assess safety, PK, and/or efficacy measures. No adjustments to study conduct and no adjustment of type I error will be performed.

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An interim analysis after the primary database lock may be conducted to review the safety and efficacy data when all participants have completed CCI or have discontinued intervention, for the purpose of supporting planning activities associated the peresolimab clinical development program. The analysis may assess safety, PK, and/or efficacy measures. No adjustments to study conduct and no adjustment of type I error will be performed.

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An interim analysis after the primary database lock may be conducted to review the safety and efficacy data when CCI of participants have completed CCI or have discontinued intervention, for the purpose of supporting planning activities associated the peresolimab clinical development program. The analysis may assess safety, PK, and/or efficacy measures. No adjustments to study conduct and no adjustment of type I error will be performed.

Assessment of unblinded interim data

Assessment of unblinded interim data will be conducted by an IAC with a limited number of prespecified team members who do not have direct site contact or data entry or validation responsibilities (see Section 10.1.5). Only the IAC will be authorized to evaluate unblinded interim efficacy and safety analyses.

Prior to the interim or final database lock, a limited number of preidentified individuals may gain access to the unblinded data to initiate the final population PK/PD model development processes for interim or final analyses.

To minimize bias, the SAP and PK/PD analysis plan will be finalized and approved before any unblinding.

Unblinding details will be specified in a separate unblinding document. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the prespecified milestone for unblinding of study results. Study sites will receive information about interim results only if they need to know for the safety of their participants.

9.5. Sample Size Determination

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines, and
- Applicable laws and regulations.

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/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 clinical trial agreement.

10.1.2. Financial Disclosure

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

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

10.1.3. Informed Consent Process

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

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 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

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

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. 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.

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

The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

10.1.5.1. Adjudication Committee

An independent committee with membership external to the sponsor will be responsible for adjudication of CCI [redacted] in a blinded fashion.

10.1.5.2. Internal Assessment Committee

An IAC will review the interim efficacy and safety data in an unblinded fashion.

The IAC will consist of a limited number of prespecified members not part of the blinded study team who do not have direct site contact or data entry or validation responsibilities. Details about IAC membership, purpose, responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

Participant safety will be continuously monitored by the sponsor's blinded internal safety review team, which includes safety signal detection at any time during the study.

All safety data collected will be summarized and reviewed by the sponsor's internal safety review committee for agreement of next steps.

10.1.6. Dissemination of Clinical Study Data

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor, for example, underpowered, or compromise the integrity of the overall analyses, for example, study 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

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.

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

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

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

The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

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

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

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

Data capture system

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

An electronic data capture 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 electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, electronic Clinical Outcome Assessment data (participant-focused outcome instrument) will be directly recorded by the participant and investigator site personnel, into an instrument, for example a tablet. The electronic Clinical Outcome Assessment data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) 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 system(s). Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

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

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

10.1.8. Source Documents

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

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

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

10.1.9. Study and Site Start and Closure

First act of recruitment

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

The first act of recruitment is the first site open.

Study or site termination

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB/IEC, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

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

10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of peresolimab or after peresolimab become(s) commercially available for rheumatoid arthritis.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or by the local laboratory as specified in the table below.

Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

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

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

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

Investigators must document their review of the laboratory safety results.

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


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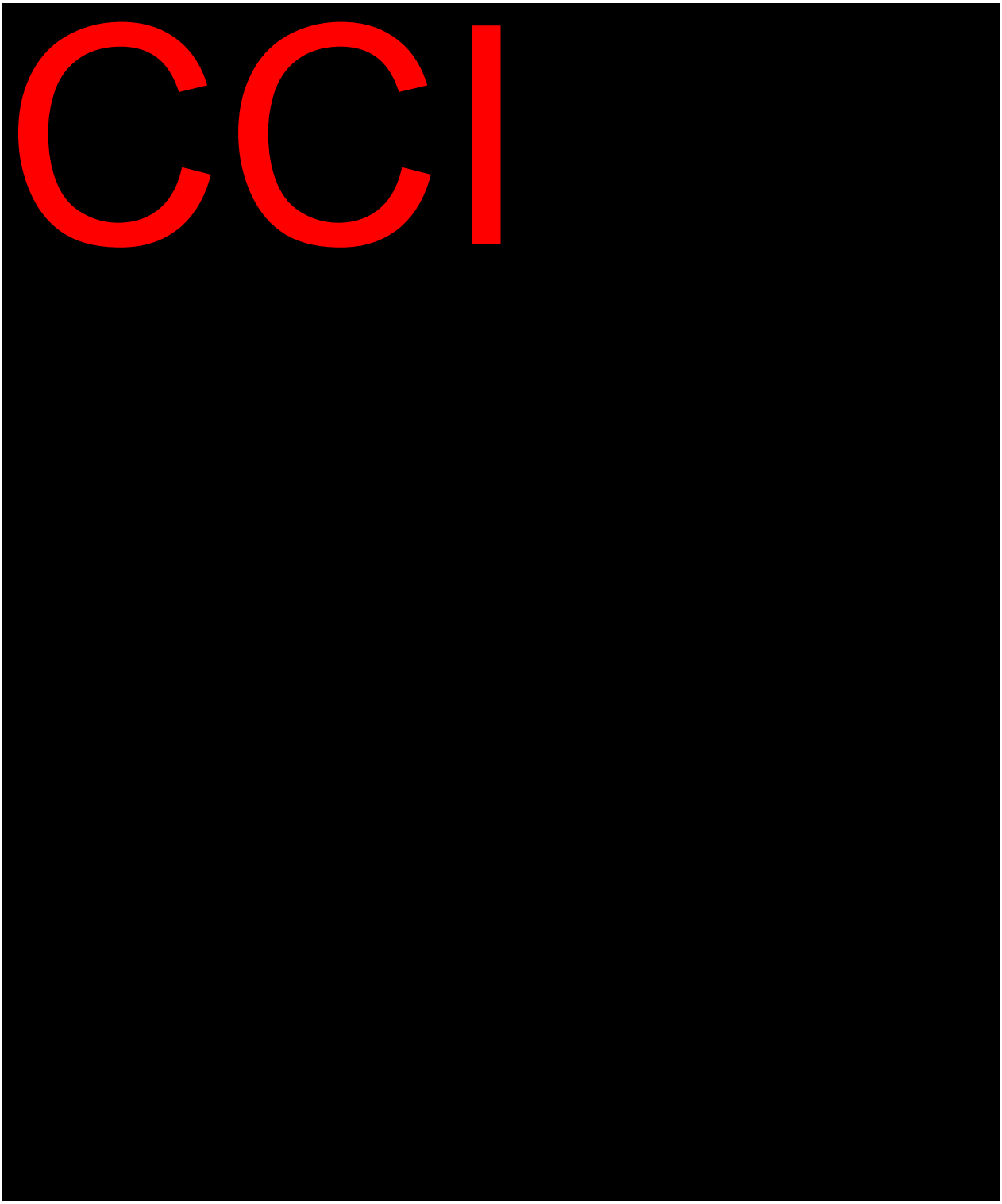
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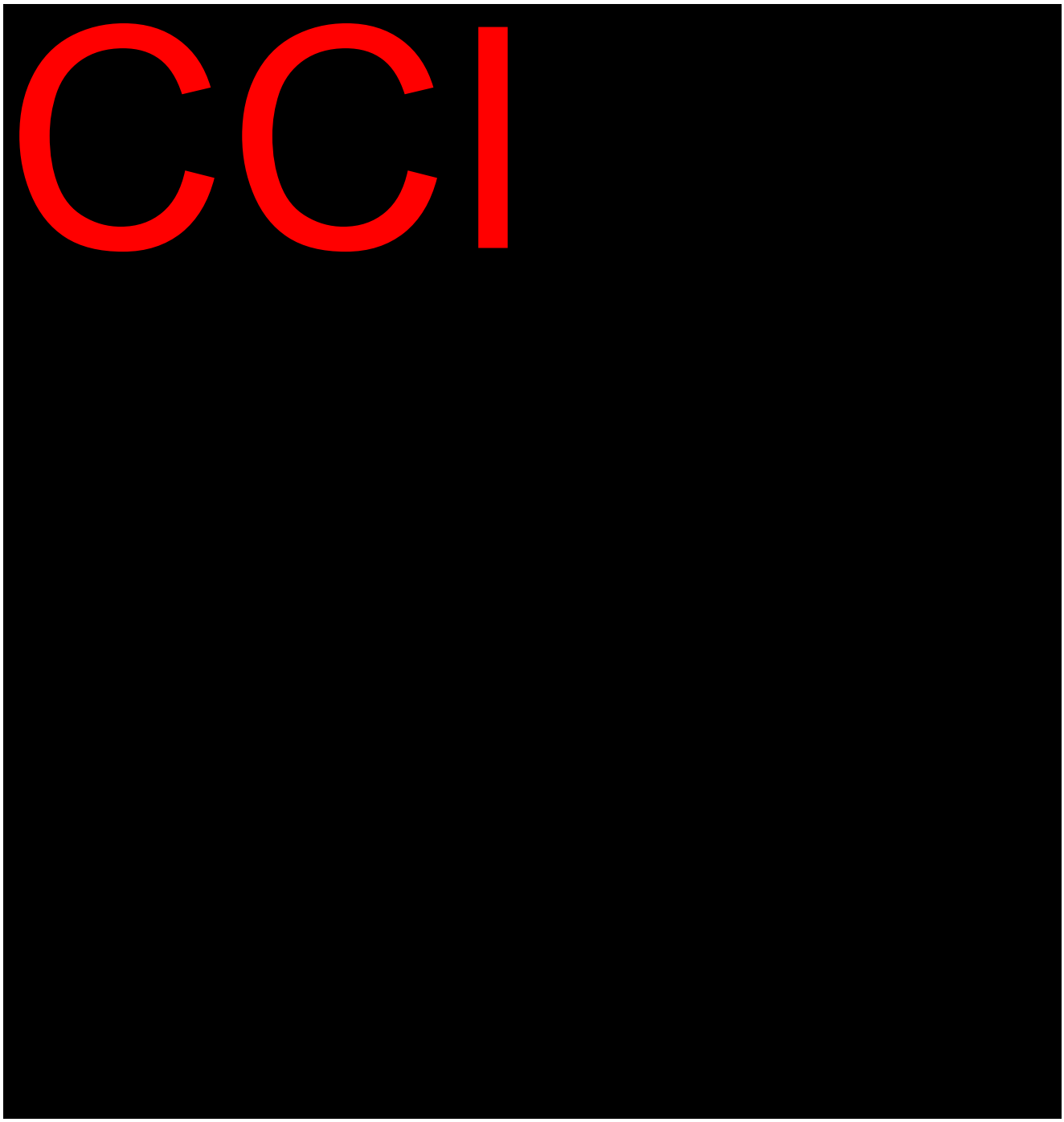
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10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events 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, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 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 pre-existing 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, ectopic pregnancy) are considered SAEs.

f. Other situations

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

10.3.3. Definition of Product Complaints

Product Complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical studies are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

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

AE, SAE, and PC Recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical

practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs 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 one of the following categories:

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB for peresolimab in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found on the SAE paper form.

SAE Reporting via Paper Form
• Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor. • 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 on the SAE paper form.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
• Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. • The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. • An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. • Consistent with the EU Clinical Trial Regulation (536/2014), the sponsor has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs. Upon an investigator's report of an SAE, the sponsor will evaluate the data, including confirmation of relatedness and assessment of expectedness. The sponsor will submit any qualifying reports to the EudraVigilance database within the required time frame. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and will be forwarded to investigators as necessary.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they meet the definition of 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 total 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 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Women

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle need to adhere to the rules in this table.

Must…	Must not…

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

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must adhere to the rules in this table.

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to first dose of study intervention. See the SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 highly effective method of contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least CCI after the last dose of the study intervention.

Men

The table below describes contraception guidance for all men.

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

Examples of different forms of contraception:

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

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide
	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective.

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to peresolimab or RA and related diseases. They may also be used to develop tests or assays including diagnostic tests related to peresolimab and RA. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome, as appropriate.

DNA samples will be analyzed for genetic variants thought to play a role in RA. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to peresolimab or study interventions of this class to understand study disease or related conditions.

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

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

The samples will be retained while research on peresolimab or study interventions of this class, or RA continues but no longer than 15 years or other period as per local requirements.

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

Hepatic Evaluation Testing

See Section 8.2.7 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)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (HBsAb)
Neutrophils, segmented	Hepatitis B core total antibody (HBcAb)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA [a]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA [a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	**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/confirmation dependent on regulatory requirements, testing availability, or both.

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

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

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/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: Examples of Infections Considered Possibly Opportunistic

This table is provided to aid the investigator in recognizing infections that may be considered opportunistic. This list is not exhaustive.

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

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

10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in "***Remote Visits***" below
- a change in the method of study intervention administration, or
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner may include, but are not limited to, AE collection, concomitant medication review, or administration of PROs if validated for these types of visits.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits may include, but are not limited to, AE collection, concomitant medication review, blood sample collection, physical assessments, study intervention administration, or administration of PROs if validated for these types of visits.

Other alternative locations: Local laboratories may be used to collect laboratory samples only for safety assessments.

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

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for hsCRP. The 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
- 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 healthcare visit or at an alternate location such as an infusion center.

These requirements must be met before action is taken:

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

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, only authorized study personnel may supply, prepare or administer study intervention.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit are valid for a maximum of 42 days.

If screening is interrupted for more than 42 days from randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by the randomization visit.

Adjustments to visit windows

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

For Visit 3 through Visit 18, the allowed tolerance is ±7 days.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.9. Appendix 9: Country-Specific Requirements

10.9.1. EU Member States

For sites in EU Member States, inclusion criterion 9 is revised as shown here.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
Abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ACR	American College of Rheumatology ACR20 – 20% improvement in the ACR core set values ACR50 – 50% improvement in the ACR core set values ACR70 – 70% improvement in the ACR core set values
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
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 labelling 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 labelling 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 study 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 study, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical study and not relevant for the design of the clinical study
Blinding	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.
CDC	Centers for Disease Control and Prevention
CCI	
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product

Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each study participant.
C-SSRS	Columbia-Suicide Severity Rating Scale
CCI	
DMARDs	Disease-modifying antirheumatic drugs
bDMARDs	Biologic DMARDs include, but are not limited to, tumor necrosis factor (TNF) inhibitors, T-cell inhibitors, B-cell inhibitors, or interleukin-6 inhibitors.
csDMARDs	Conventional synthetic DMARDs include, but are not limited to methotrexate, sulfasalazine, hydroxychloroquine, or gold salts.
tsDMARDs	Targeted synthetic DMARDs include, but are not limited to, Janus kinas (JAK) inhibitors, tofacitinib and baricitinib.
ECG	Electrocardiogram
ED	early discontinuation
Enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EU	European Union
EULAR	European League Against Rheumatism
GCP	good clinical practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus

IAC	internal assessment committee
IB	Investigator's Brochure
ICEs	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
IGRA	Interferon gamma release assay
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 study.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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."
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 a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
LDA	Low disease activity
LTBI	latent TB infection

medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MedDRA	Medical Dictionary for Regulatory Activities
Misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMRM	mixed-effect model for repeated measures
CCI	
NIMP	Non-investigational Medicinal Product See AxMP. A medicinal product used for the needs of a clinical study 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 study, or background treatment.
NRS	Numeric rating scale
NSAIDs	nonsteroidal anti-inflammatory drugs
CCI	
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical study, either as recipient of an investigational medicinal product or as a control
PaGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PC	product complaint
PD-1	programmed cell death protein 1
PK/PD	pharmacokinetics/pharmacodynamics
PPD	Purified protein derivative

PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT-INR	prothrombin time/international normalized ratio
CCI	
RA	Rheumatoid arthritis
CCI	
SAE	serious adverse event
SAP	statistical analysis plan
CCI	
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDAI	Simplified Disease Activity Index
SF-36	Short Form-36 version 2 health survey acute form
SJC	Swollen Joint Counts
SUSAR	suspected unexpected serious adverse reaction
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TJC	Tender Joint Counts
TSJC	Tender Joint Counts and Swollen Joint Counts
TST	Tuberculin skin test
ULN	upper limit of normal
VAS	Visual analog scale
WHO	World Health Organization
WOCBP	Women of childbearing potential

10.11. Appendix 11: Protocol Amendment History

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

Amendment [d]: 7 March 2023

This amendment is considered to be substantial.

The amendment is considered to be substantial because it may have an impact on the robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to address regulatory feedback. Changes and rationale are summarized in this table. Editorial or formatting changes to maintain document consistency are not shown in this table.

Amendment [c]: 31 January 2023

This amendment is considered to be nonsubstantial.

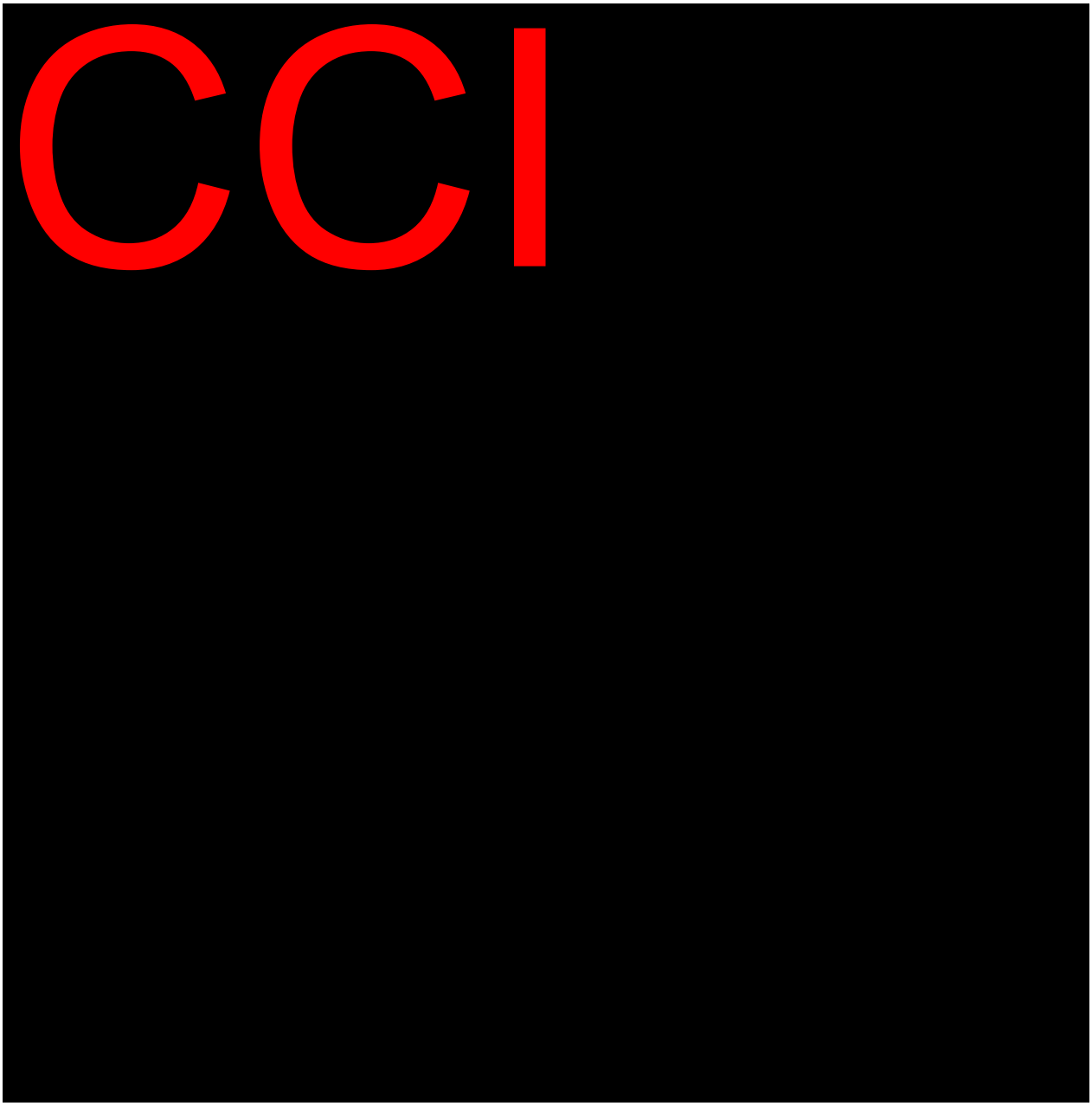
Overall Rationale for the Amendment:

The primary rationale for this amendment is to address regulatory feedback. Changes and rationale are summarized in the table below.

Amendment [b]: 07 October 2022

Overall Rationale for the Amendment:

This amendment addresses changes requested by the Food and Drug Administration (FDA).



Amendment [a]: 11 August 2022

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment

Added a clarification that if a participant randomly assigned to 400 mg or 1000 mg peresolimab receives rescue medication prior to Week 24, they will not be eligible for the Q12W dosing schedule.

11. References

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Approval	PPD Medical Director 31-May-2023 13:46:41 GMT+0000

Approval	PPD Statistician 31-May-2023 14:10:15 GMT+0000

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