**Janssen Research & Development ***

**Clinical Protocol**

**Protocol Title**

# A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Proof-of-concept Study Evaluating the Efficacy and Safety of Nipocalimab Administered Intravenously in Participants with Active Rheumatoid Arthritis Despite Standard Therapy

**Short Title**

A Proof-of-concept Study of the Efficacy and Safety of Nipocalimab in Participants with Active Rheumatoid Arthritis

**Protocol 80202135ARA2001; Phase 2a**
**AMENDMENT 3**

**JNJ-80202135 nipocalimab**

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

**Regulatory Agency Identifier Number(s):**

**IND: 154384**
**EudraCT Number: 2021-000510-42**

**Status:** Approved
**Date:** 12 January 2022
**Prepared by:** Janssen Research & Development, LLC
**EDMS number:** EDMS-RIM-220499, 6.0

Global Amendment to EDMS-RIM-220499

**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

**Confidentiality Statement**

The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 3 | 12 January 2022 |
| Amendment 2 | 30 June 2021 |
| Amendment 1 | 19 May 2021 |
| Original Protocol | 07 April 2021 |

### Amendment 3 (12 January 2022)

**Overall Rationale for the Amendment:** CCI [redacted]

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| CCI [redacted] | | |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| CCI [redacted] | | |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| CCI | [redacted] | [redacted] |

# TABLE OF CONTENTS

# LIST OF IN-TEXT TABLES AND FIGURES

## TABLES



## FIGURES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Proof-of-concept Study Evaluating the Efficacy and Safety of Nipocalimab Administered Intravenously in Participants with Active Rheumatoid Arthritis Despite Standard Therapy

**DESCRIPTION OF COMPOUND**

Nipocalimab (also referred to as JNJ-80202135 and M281) is a fully human aglycosylated immunoglobulin (Ig)G1 monoclonal antibody designed to selectively bind, saturate, and block the IgG binding site on the endogenous neonatal Fc receptor.

**OBJECTIVES AND ENDPOINTS**

| OBJECTIVES | ENDPOINTS |
|---|---|
| **Primary** | |
| To evaluate the efficacy of nipocalimab vs placebo in participants with moderate to severe active RA | **Primary Endpoint**:<br>• Change from baseline in DAS28-CRP at Week 12<br>**Secondary Endpoints**:<br>• Proportion of participants who achieve ACR20, ACR50, ACR70, and ACR90 responses at Week 12<br>• Proportion of participants achieving DAS28-CRP remission at Week 12<br>• Proportion of participants achieving DAS28-CRP LDA at Week 12<br>• Change from baseline in HAQ-DI score at Week 12 |
| **Secondary** | |
| To evaluate the safety and tolerability of nipocalimab vs placebo in participants with moderate to severe active RA | • Proportion of participants with treatment-emergent AE<br>• Proportion of participants with treatment-emergent SAEs<br>• Proportion of participants with treatment-emergent AEs leading to discontinuation of study intervention<br>• Proportion of participants with treatment-emergent AESIs<br>• Laboratory parameters and change from baseline in laboratory parameters over time<br>• Vital sign parameters and change from baseline in vital sign parameters over time |
| To evaluate the PK and immunogenicity of IV nipocalimab in participants with moderate to severe active RA | • Serum nipocalimab concentrations over time in participants receiving active study intervention<br>• Incidence and titers of antibodies to nipocalimab (ADA and NAbs) in participants receiving active study intervention |
| **Exploratory** | |
| To evaluate the impact of nipocalimab vs placebo on disease activity in participants with moderate to severe active RA | • Proportion of participants who achieve ACR20, ACR50, ACR70, and ACR90 responses over time<br>• Percent improvement from baseline in ACR components over time |

| | |
|---|---|
| | • Change from baseline in DAS28-CRP (or DAS28-ESR) over time<br>• Proportion of participants achieving DAS28-CRP (or DAS28-ESR) LDA over time<br>• Proportion of participants achieving DAS28-CRP (or DAS28-ESR) remission over time<br>• Change from baseline in CDAI over time<br>• Proportion of participants achieving CDAI LDA over time<br>• Proportion of participants achieving CDAI remission over time<br>• Change from baseline in SDAI over time<br>• Proportion of participants achieving SDAI LDA over time<br>• Proportion of participants achieving SDAI-based ACR/EULAR remission over time<br>• Proportion of participants achieving Boolean-based ACR/EULAR remission over time<br>• Change from baseline in the Tender/Painful and Swollen Joint Counts over time<br>• Change from baseline in duration of morning stiffness over time |
| To evaluate the impact of nipocalimab vs placebo on PROs in participants with moderate to severe active RA | • Change from baseline in the PtGA of Disease Activity score over time<br>• Change from baseline in the Pain VAS score over time<br>• Change from baseline in FACIT-Fatigue score over time<br>• Change from baseline in Joint Pain Severity score over time<br>• Change from baseline in HAQ-DI score over time<br>• The proportion of participants achieving a decrease of ≥0.22 points from baseline in HAQ-DI score over time<br>• Change from baseline in SF-36 PCS, MCS, and domain scores over time |
| To evaluate the effect of nipocalimab vs placebo on PD and disease biomarkers in participants with moderate to severe active RA | • Change from baseline in serum total immunoglobulin and albumin levels over time by treatment group<br>• Change from baseline in disease biomarkers (eg, autoantibodies, circulating immune complexes) over time in participants with abnormal levels at baseline<br>• Reduction of IgG level-clinical response relationship analysis |
| To evaluate changes in serological profiles in response to nipocalimab vs placebo treatment in participants with moderate to severe active RA | • Change from screening visit in serum ACPA and RF levels over time by treatment group, in participants seropositive at screening visit for ACPA and RF, respectively |
| CCI [redacted] | |

Abbreviations: ACPA=anti-citrullinated protein antibodies; ACR=American College of Rheumatology; ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; CDAI=Clinical Disease Activity Index; DAS28-CRP=Disease Activity Index Score 28 using C-reactive protein; DAS28-ESR=Disease Activity Index Score 28 using erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy Fatigue Scale; HAQ-DI=Health Assessment Questionnaire Disability Index; IgG=immunoglobulin G; LDA=low disease activity; MCS=mental component score; NAb=neutralizing antibody; PCS=physical

component score; PK=pharmacokinetic(s); PRO=patient-reported outcome; PtGA=Patient Global Assessment of Disease Activity; RA=rheumatoid arthritis; RF=rheumatoid factor; SAE=serious adverse event; SDAI=Simple Disease Activity Index (for Rheumatoid Arthritis); SF-36=36-item Short Form Health Survey; VAS=visual analog scale

### Hypothesis

The primary hypothesis is that treatment with nipocalimab 15 mg/kg intravenously (IV) every 2 weeks (q2w) is superior to placebo in participants with moderate to severe active rheumatoid arthritis (RA) as assessed by the mean change from baseline in the Disease Activity Index Score 28 using C-reactive Protein (DAS28-CRP) at Week 12.

## OVERALL DESIGN

This is a randomized, double-blind, parallel-group, placebo-controlled, proof-of-concept, multicenter study in participants between the ages of 18 and 75, inclusive, with moderate to severe active RA despite standard therapy, including anti-tumor necrosis factor (anti-TNF) agents.

The total duration of the study is up to 24 weeks, consisting of 3 study periods: a ≤6-week screening period (rescreening is permitted once per participant), a 12-week double-blind treatment period, and a 6-week safety follow-up period (8 weeks after the last administration of study intervention).

Participants who have had an inadequate response (IR) or were intolerant to at least one anti-TNF therapy will be enrolled. Depending upon the enrollment rate, the study population may be expanded to also include participants who have had an IR or intolerance to a conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD).

Participants will be randomly assigned into 1 of 2 treatment groups. A placebo comparator (in addition to standard-of-care background therapy) will be used to allow for blinded, placebo-controlled evaluation of the efficacy and safety of nipocalimab in participants with RA.

Efficacy, safety, pharmacokinetics (PK), immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA). Pharmacogenomic blood samples will be collected from participants who consent to the collection of these samples (where local regulations permit).

The primary endpoint (the change from baseline in DAS28-CRP compared with placebo at Week 12) will be evaluated after all participants have completed the Week 12 visit (or discontinued). An interim analysis is planned when 60% (30 participants) of the planned number of participants complete the Week 12 assessment. This analysis is for future planning purposes and will not impact the conduct of the current study.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol. Beginning at the screening visit, all concomitant therapies and all changes in concomitant therapies should be recorded throughout the study.

Key safety assessments include adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), laboratory parameters (hematology, chemistry, lipid panel), vital signs, and physical examination.

Serum samples will be used to evaluate PK and antibodies to nipocalimab. Blood-based biomarkers will be evaluated for inflammation-associated proteins and other analytes and will be used to better understand the biology of RA, to provide a biological assessment of the response of participants to treatment with nipocalimab, to analyze differences between responders and nonresponders, to assess loss of response, and to determine if the markers can be used to classify participants as potential responders prior to treatment.

Actigraphy data will utilize accelerometry measurements to assess physical activity, mobility, and sleep parameters. These measurements will be captured via wrist-worn actigraph devices, which have been validated against polysomnography to assess sleep-related variables.

Database locks are planned at Week 12 and at the end of the study. The end of the study is defined as the last follow-up assessment (8 weeks after the last infusion of study intervention) for the last participant.

A Data Monitoring Committee will be commissioned for this study.

## NUMBER OF PARTICIPANTS

A target of 50 participants will be enrolled in this study.

## INTERVENTION GROUPS AND DURATION

Participants will be randomly assigned into 1 of 2 treatment groups using a 2:3 randomization ratio, respectively:

- Group 1: Placebo IV q2w: Participants will receive placebo IV q2w through Week 10.
- Group 2: Nipocalimab 15 mg/kg IV q2w: Participants will receive nipocalimab 15 mg/kg IV q2w through Week 10.

Participants will remain on their assigned treatment through Week 10.

## EFFICACY EVALUATIONS

Patient-reported outcomes and clinician-reported outcomes of efficacy include the following:

- Patient-reported outcomes
  - Patient's Global Assessment of Disease Activity
  - Pain visual analog scale
  - Functional Assessment of Chronic Illness Therapy – Fatigue Scale
  - Joint Pain Severity Numeric Rating Scale
  - Health Assessment Questionnaire – Disability Index
  - 36-item Short Form Health Survey (Standard)
- Clinician-reported outcomes
  - joint assessment
  - duration of morning stiffness
  - Physician's Global Assessment of Disease Activity

## PHARMACOKINETIC EVALUATIONS

Serum samples will be used to evaluate the PK of nipocalimab.

## IMMUNOGENICITY EVALUATIONS

Antibodies to nipocalimab will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

## PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Samples for the analysis of pharmacodynamic (PD) biomarkers will be collected from all participants as specified in the SoA, where local regulations permit. Serum or plasma concentrations of immunoglobulin,

albumin, and disease biomarkers (eg, autoantibodies, circulating immune complexes) will be measured to assess the PD effect of nipocalimab.

Blood samples for serum and plasma biomarker analyses will be collected from all participants. Serum and plasma will be analyzed for levels of specific proteins, and other inflammation-related molecules and/or disease-associated serologies relevant to RA and treatment and response to nipocalimab.

## PHARMACOGENOMIC (DNA) EVALUATIONS

Participation in pharmacogenomic research is optional. A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit.

## SAFETY EVALUATIONS

Key safety assessments include AEs, SAEs, AESIs, clinical laboratory parameters (ie, hematology, chemistry, lipid panel), vital signs, and physical examination.

## STATISTICAL METHODS

### Sample Size Determination

Approximately 50 participants are planned to be randomized in a 2:3 ratio to the placebo and nipocalimab intervention groups, respectively, in the study. The sample size selection was determined based on the primary endpoint of the change from baseline in DAS28-CRP compared with placebo at Week 12. For this study, assuming a difference of 1 in the change from baseline in DAS28-CRP between a nipocalimab group and placebo, a sample size of 20 and 30 participants in the placebo group and nipocalimab 15 mg/kg group, respectively, will provide a power of approximately 80% to detect a significant treatment difference at a 2-sided significance level of $\alpha$=0.05 using a T-test.

### Statistical Analyses

#### *General Considerations*

In general, descriptive statistics, such as mean, standard deviation, median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

For binary response efficacy endpoints, treatment comparisons will generally be performed using a Chi-square test or a Cochran-Mantel-Haenszel test. For continuous efficacy endpoints, treatment comparisons will be performed using an analysis of covariance, a Mixed-Effect Model Repeated Measure (MMRM) model, or a constrained longitudinal data analysis model.

In general, all statistical tests will be performed using a 2-sided test at a significance level of 5%. No multiplicity adjustment will be made for secondary endpoints; nominal p-values will be reported.

#### *Primary Endpoint*

The primary endpoint is the mean change from baseline in DAS28-CRP compared with placebo at Week 12.

In the primary efficacy analysis, data from all participants who were randomized in the study and received at least 1 administration of study intervention (ie, the Full Analysis Set [FAS]) will be analyzed according to randomized treatment group regardless of the treatment received. Missing data will be assumed as Missing-At-Random. A MMRM will be used to test the difference between the nipocalimab group and the placebo group at Week 12. The explanatory variables of the MMRM model will include treatment group, and interaction terms of visit with treatment group, baseline score and randomization stratification factors.

An unstructured covariance matrix for repeated measure within a participant will be used. Other structured covariances matrix will be defined in the Statistical Analysis Plan (SAP) in case of lack of convergence. The Least Square Mean difference and 95% confidence intervals between each nipocalimab group versus the placebo group will be provided.

The comparison between the nipocalimab and placebo group for the primary endpoint will be tested at a 2-sided α level of 0.05.

Further details about the analysis of the primary endpoint, including sensitivity and subgroup analyses will be included in the SAP.

***Secondary Endpoints***

The secondary endpoints are listed above.

Data from all participants in the FAS will be analyzed according to randomized treatment group regardless of the treatment received.

Details of the analysis of the secondary endpoints will be included in SAP.

***Safety Analyses***

The following analyses will also be used to assess the safety of participants in the study:

- Proportion of participants with treatment-emergent AE
- Proportion of participants with treatment-emergent SAEs
- Proportion of participants with treatment-emergent AEs leading to discontinuation of study intervention
- Proportion of participants with treatment-emergent AESIs
- Laboratory parameters and change from baseline in laboratory parameters over time
- Vital sign parameters and change from baseline in vital sign parameters over time

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE. Listings of all participants with major adverse cardiovascular events (MACE; nonfatal myocardial infarction, stroke, and cardiovascular death) will be provided.

*Clinical Laboratory Tests*: Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for selected laboratory analytes at baseline and for changes over time.

*Vital Signs*: Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics. The percentage of participants with values beyond clinically important limits will be summarized.

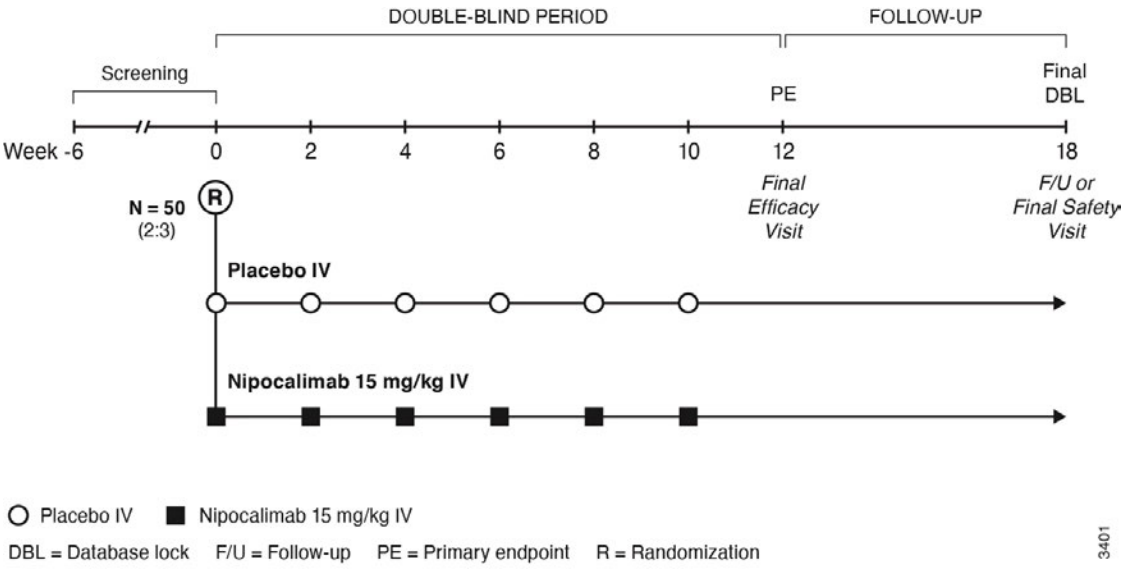
***Other Analyses***

- **Pharmacokinetic Analyses**: Serum nipocalimab concentrations over time will be summarized for each treatment group using descriptive statistics. Descriptive statistics will be calculated at each sampling timepoint. If sufficient data are available, a population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of nipocalimab. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate technical report.

- **Immunogenicity Analyses**: The incidence and titers of antibodies to nipocalimab will be summarized for all participants who received at least 1 administration of nipocalimab and have appropriate samples for detection of antibodies to nipocalimab (ie, participants with at least 1 sample obtained after their first dose of nipocalimab). The incidence of neutralizing antibodies (NAbs) to nipocalimab will be summarized for participants who are positive for antibodies to nipocalimab and have samples evaluable for NAbs.
- **Biomarkers Analyses**: Change in biomarkers over time may be summarized by treatment group. Associations between baseline levels and changes from baseline in select biomarkers and clinical response may be explored. Results of biomarker analyses will be summarized in a separate technical report.
- **Pharmacokinetic/Pharmacodynamic Analyses**: If data permit, the relationship between serum concentrations of nipocalimab and the efficacy measures and/or relevant PD biomarkers/endpoints may be explored when appropriate. If any visual pattern is observed, additional analysis may be conducted. Results of analyses will be summarized in a separate technical report.
- **Pharmacogenomic Analyses**: Genetic (deoxyribonucleic acid) analyses may be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory and results will be summarized in a separate technical report.
- **Actigraphy Analyses**: Associations between actigraphy endpoints and primary and secondary endpoints may be explored. All actigraphy-related analyses are considered exploratory and will be summarized in a separate technical report.

## 1.2. Schema

**Figure 1: Schematic Overview of 80202135ARA2001**



## 1.3. Schedule of Activities (SoA)

| Period | Screening [a] | Double-blind Study Intervention | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | ≤6 weeks | 0 | 2 | 4 | 6 | 8 | 10 | 12 / Final Efficacy Visit [b] | 18 or Final Safety Follow-Up Visit (8 weeks after last dose) [b] | |
| Visit Window | | ±3 days | | | | | | | ±7 days | |
| **Study Procedure** | | | | | | | | | | **Notes** |
| **Screening/Administrative** | | | | | | | | | | |
| ICF | X | | | | | | | | | Must be signed before first study-related activity. |
| ICF for optional pharmacogenomics (DNA) sample collection | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Review medical history requirements | X | | | | | | | | | |
| Preplanned surgery/procedure(s) | X | | | | | | | | | |
| HIV, HBV, HCV testing | X | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Pre-study RA therapy review | X | X | | | | | | | | |
| **Study Intervention Administration** | | | | | | | | | | |
| Randomization | | X | | | | | | | | |
| Administer study intervention | | X | X | X | X | X | X | | | |
| **Efficacy Assessments** | | | | | | | | | | |
| PROs | | | | | | | | | | To be conducted prior to study intervention administration and before any tests, procedures, or other consultations for that visit to prevent influencing participants' perceptions. PRO assessments should be conducted in the order shown here in the SoA. |
| PtGA of Disease Activity | | X | X | X | X | X | X | X | | |
| Pain VAS | | X | X | X | X | X | X | X | | |
| FACIT-Fatigue | | X | | X | X | X | | X | | |
| Joint Pain Severity NRS | | X | X | X | X | X | X | X | | |
| HAQ-DI | | X | X | X | X | X | X | X | | |
| SF-36 | | X | | X | | X | | X | | |
| ClinROs | | | | | | | | | | To be completed prior to administration of study intervention and should be conducted in the order shown here in the SoA. |
| Joint assessment | X | X | X | X | X | X | X | X | | |
| Duration of morning stiffness | | X | X | X | X | X | X | X | | |
| PGA of Disease Activity | | X | X | X | X | X | X | X | | |

| Period | Screening [a] | Double-blind Study Intervention | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | ≤6 weeks | 0 | 2 | 4 | 6 | 8 | 10 | 12 / Final Efficacy Visit [b] | 18 or Final Safety Follow-Up Visit (8 weeks after last dose) [b] | |
| Visit Window | | ±3 days | | | | | | | ±7 days | |
| **Study Procedure** | | | | | | | | | | **Notes** |
| **Safety Assessments** | | | | | | | | | | |
| Full physical examination | X | | | | | | | | | |
| Targeted physical examination | | X | X | X | X | X | X | X | | |
| Height | X | | | | | | | | | |
| Weight | X | X | X | X | X | X | X | X | | Needed for IV preparation (dose calculation). |
| Vital signs | X | X | X | X | X | X | X | X | X | |
| Urine pregnancy test | X | X | X | X | X | X | X | X | X | For females of childbearing potential only. Additional details are provided in Section 10.5 [Appendix 5]). |
| Concomitant therapy | X | X | X | X | X | X | X | X | X | |
| AEs | X | X | X | X | X | X | X | X | X | |
| Infusion reaction evaluation [c] | | X | X | X | X | X | X | | | |
| **Clinical Laboratory Tests** | | | | | | | | | | |
| Hematology | X | X | X | X | | X | | X | X | |
| Chemistry | X | X | X | X | | X | | X | X | |
| Coagulation | X | X | X | X | | X | | X | X | |
| Urinalysis | X | X | | X | | X | | X | X | |
| Lipid panel | X | X | | X | | | | X | X | • Nonfasting lipid panel (at screening only) includes total cholesterol, HDL, LDL (calculated), and triglycerides.<br>• Fasting lipid panel (at Week 0, Week 4, Final Efficacy Visit, and Final Safety Visit) includes: total cholesterol, HDL, LDL (calculated), and triglycerides. Fasting is recommended for at least 6 hours unless medically contraindicated. |
| CRP | X | X | X | X | X | X | X | X | X | |
| ESR | X | X | X | X | X | X | X | X | X | Local laboratory. |

| Period | Screening [a] | Double-blind Study Intervention | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | ≤6 weeks | 0 | 2 | 4 | 6 | 8 | 10 | 12 / Final Efficacy Visit [b] | 18 or Final Safety Follow-Up Visit (8 weeks after last dose) [b] | |
| Visit Window | | ±3 days | | | | | | | ±7 days | |
| **Study Procedure** | | | | | | | | | | **Notes** |
| ACPA | X | X | | X | | X | | X | X | |
| RF | X | X | | X | | X | | X | X | |
| Circulating immune complexes | | X | | X | | X | | X | X | |
| Immunoglobulin profile | X | X | | X | | X | | X | X | |
| **Clinical Pharmacology Assessments** | | | | | | | | | | |
| Serum nipocalimab concentrations [d] | | 2X | 2X | X | | 2X | | X | X | See footnote "d" for more details on Clinical Pharmacology assessments. |
| CCI | | | | | | | | | | |
| Antibodies to nipocalimab [d] | | X | X | X | | X | | X | X | |
| **Pharmacodynamics/Biomarkers** | | | | | | | | | | |
| Serum biomarkers | | X | X | X | | X | | X | X | |
| Plasma biomarkers | | X | X | X | | X | | X | X | |
| Whole blood (bulkRNAseq) | | X | | X | | | | X | | |
| PBMC (cellular flow analysis) | | X | | X | | | | X | | |
| **Pharmacogenomics (DNA)** | | | | | | | | | | Participation is optional |
| Blood sample collection (optional) | | X [e] | | | | | | X | | |
| **Digital Health (optional)** | | | | | | | | | | Participation is optional |
| Actigraph Watch [f] | X | X | X | X | X | X | X | X | | |
| Actigraph Watch Exit Survey [g] | | | | | | | | X | | |

**Abbreviations:** ACPA=anti-citrullinated protein antibodies; ADA=anti-drug antibody; AE=adverse event; PBMC=peripheral blood mononuclear cell; ClinRO=clinician-reported outcome; CRP=C-reactive protein; DBL=database lock; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; FACIT-fatigue=Functional Assessment of Chronic Illness Therapy-fatigue (scale); HAQ-DI=Health Assessment Questionnaire – Disability Index; HBV=hepatitis B virus; HCV=hepatitis C virus; HDL=high-density lipoprotein; HIV=human immunodeficiency virus; ICF=informed consent form; IgG=immunoglobulin G; IV=intravenous; LDL=low-density lipoprotein; NRS=numeric rating scale; PK=pharmacokinetic(s); PRO=patient-reported outcome; PGA=Physician Global Assessment; PtGA=Patient Global Assessment; RA=rheumatoid arthritis; RF=rheumatoid factor (test); RNA=ribonucleic acid; SF-36=36-item Short Form Health Survey; SoA=Schedule of Activities; VAS=visual analog scale

**Footnotes:**

a. Screening visit must be performed no more than 6 weeks prior to the randomization visit (Week 0).

b. Participants who discontinue study intervention administration but do not withdraw from study participation should be followed at all subsequent study visits through Week 12. Week 12 may serve as the final safety follow-up visit if study intervention was stopped on or before Week 4, but a full physical examination should be performed along with the other Week 12 assessments. Participants who discontinue study intervention administration and do not wish to continue in the study should complete their Week 12 visit assessments at their next scheduled visit and should return 8 weeks after their last administration of study intervention for the final safety visit.
c. Participants will be observed for safety 1 hour postinfusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions.
d. (i.) 2X means 2 samples will be collected (1 sample will be collected prior to IV infusion and the other collected 45 minutes after the end of the infusion) for all participants. The sample should be drawn from the opposite arm than the IV line. For all other visits, only a predose serum nipocalimab concentration sample will be collected.
(ii.) For visits with study intervention administration, all blood samples for assessing predose nipocalimab concentration and antibodies to nipocalimab MUST be collected BEFORE the administration of the study intervention.
CCI [redacted]
(iv.) When samples for both PK ("nipocalimab concentration") and ADA ("antibodies to nipocalimab") are collected, 1 sample (instead of 2) will be collected for both assays.
e. The sample should be collected at the specified time point, but it may be collected at a later time point without constituting a protocol deviation.
f. At screening at preselected sites, participants will be provided with an Actigraphy watch to be able to capture a baseline profile. Participants who will not prove eligible will return their Actigraphy watch to the study site.
g. At the preselected sites where Actigraphy watches are distributed, participants will be asked to fill an exit survey when returning their Actigraphy watch to the study site.

## 2. INTRODUCTION

Nipocalimab (also referred to as JNJ-80202135 and M281) is a fully human aglycosylated immunoglobulin (Ig)G1 monoclonal antibody (mAb) designed to selectively bind, saturate, and block the IgG binding site on the endogenous neonatal Fc receptor (FcRn). The primary role of FcRn in humans is to bind, salvage, and recycle IgG into circulation or transport IgG across the placenta, following nonspecific pinocytosis into endothelial cells and cells of the reticuloendothelial system. At homeostasis, FcRn recycles IgG to maintain serum IgG levels and extend IgG half-life, and it also regulates immune cell inflammatory responses to IgG complexes. By targeting the IgG binding site on FcRn, nipocalimab is expected to block the binding and, hence, recycling of pathogenic IgG, resulting in a decrease in circulating IgG antibody levels, including pathogenic IgG autoantibodies and alloantibodies, and potentially IgG immune complexes (ICs). FcRn has also been shown to contribute to the protection of circulating immune complexes (CICs) and the inhibition of FcRn results in more rapid elimination of CICs (Blumberg 2019). Clinical studies with other anti-FcRn mAbs or Fc fragments confirm that blockade of IgG binding to FcRn rapidly decreases IgG to low but predictable steady-state levels while also effectively decreasing circulating levels of pathogenic autoantibodies by increasing IgG catabolism (Peter 2020). In addition, it has been shown that induction of inflammatory pathways is dependent on FcRn and can be blocked by an FcRn inhibitor. Furthermore, this blockade of FcRn-IgG binding may also directly inhibit inflammatory immune cell responses to IgG that recruit and stimulate lymphocytes (Blumberg 2019; Hubbard 2020).

Administration of nipocalimab has not been observed to reduce levels of other immunoglobulins, including IgA, IgM, or IgE, or impact other aspects of immune system response to infection, considering FcRn blockage only affects IgG half-life and does not prevent IgG production.

To date, nipocalimab has not been approved in any therapeutic indication. Because of its mechanism of action, nipocalimab is being evaluated for the treatment of patients with diseases mediated by pathogenic IgG antibodies, including generalized myasthenia gravis (gMG) and warm autoimmune hemolytic anemia (wAIHA), as well as diseases of the fetus and newborn caused by maternofetal transfer of pathogenic IgG antibodies, such as early onset severe hemolytic disease of the fetus and newborn (EOS-HDFN).

Immunoglobulin G antibodies cause inflammation and organ damage in autoimmune diseases such as rheumatoid arthritis (RA). As nipocalimab use results in a decrease in circulating IgG antibody concentrations, including pathogenic IgG antibody concentrations, and associated inflammatory pathways, and considering that there remains unmet medical need in the treatment of RA, exploring the use of nipocalimab in the treatment of RA is believed to be useful.

For the most comprehensive nonclinical and clinical information regarding nipocalimab, refer to the latest version of the Investigator's Brochure (IB) for nipocalimab.

The term “study intervention” throughout the protocol, refers to study drug as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject."

## 2.1. Study Rationale

Rheumatoid arthritis is a chronic autoimmune inflammatory disorder of unknown etiology that occurs in approximately 1% of the population (Alamanos 2015). In all populations, RA is more prevalent among women than men and usually develops in the fourth or fifth decades of life, with 80% of the total cases occurring between the ages of 35 and 50. Synovial inflammation underlies the cardinal manifestations of this disease, which include pain, stiffness, swelling, and tenderness in the joints followed by cartilage destruction, bone erosion, and subsequent deformities, resulting in impaired physical function. There may also be associated morbidity from nonarticular manifestations of RA, including fever, malaise, and pulmonary, ocular, and hematologic effects. Patients with RA experience a shorter life expectancy than the general population, and the increased mortality rates in RA are associated with clinical disease activity.

### 2.1.1. Unmet Need in Rheumatoid Arthritis

While there has been some success in treating patients with moderate to severe RA using various targeted therapies, many patients continue to have refractory disease. In fact, between 20-50% of patients fail to achieve low disease activity (LDA; Keystone 2004; Lipsky 2000; Weinblatt 2003). Participants with inadequate response (IR) to various disease-modifying anti-rheumatic drug (DMARD) therapies including anti-tumor necrosis factor (anti-TNF) agents remain a top unmet need in RA.

### 2.1.2. Rationale for Targeting FcRn in Rheumatoid Arthritis

Nipocalimab has a unique mechanism of action whereby it blocks the IgG binding site on endogenous FcRn and is expected to decrease pathogenic IgG antibody concentrations. A significant involvement of pathogenic IgG antibodies has been demonstrated in autoimmune diseases including RA.

Autoantibody seropositivity is a defining characteristic of the majority of patients diagnosed with RA, particularly for anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF). ACPAs have an IgG isotype in almost all seropositive patients, and seropositivity is associated with more severe disease and predictive of progression of joint erosion (Jilani 2015). However, about 70% of ACPA seropositive patients also have ACPA with IgA and/or IgM isotypes (Sieghart 2018). By definition, RF is autoreactive to the Fc domain of IgG, with pathogenicity purported to be mediated by stabilizing IgG ICs, including IgG-ACPA ICs, to promote Fc-gamma receptor- and complement-dependent effector functions (Anquetil 2015).

ACPAs are central to the development and propagation in RA, as they have been shown to bind osteoclast precursor cells and directly promote their differentiation into bone-resorbing osteoclasts. Other results have shown that in ACPA-positive individuals, bone loss starts even before the onset of clinical disease; this is indicative of the independent effect of these antibodies

in initiating skeletal damage. Additionally, once bone resorption occurs as a result of ACPA binding generating osteoclasts, neoantigens can be generated by bone erosion that further augment the inflammatory process in the articular tissues resulting is joint swelling and synovitis (Kocijan 2013; Sun 2019). It is logical that by reducing levels of the pathologic antibodies with nipocalimab, the severity and progression of RA should be abrogated.

Seropositivity for ACPA and/or RF is associated with clinical response to rituximab and abatacept but not to TNF inhibitors (Courvoisier 2021). Given the IgG-lowering mechanism of action of nipocalimab, it is presumed that autoantibody seropositivity and immune complex formation are requisite for clinical impact. Although autoreactive antibodies and ICs are likely a feature of all patients with RA, ACPA and/or RF seropositivity will be an inclusion criterion for this study to provide the best opportunity for efficacy. In addition, the possible benefit of nipocalimab is supported by data from the trials with Prosorba, a therapy in which patient's serum is passed through a Staphylococcal protein A column that absorbs IgG and ICs. The Prosorba Trial was a randomized sham-controlled study demonstrating efficacy in American College of Rheumatology 20 (ACR20) response with the Prosorba column (31.9%) compared with sham treatment (11.4%) (Felson 1999). A noninterventional prospective study of refractory RA demonstrated a response rate of 53.8% measured as ACR20 response (Roth 2004).

Nipocalimab is administered intravenously and, depending on the amount of IgG reduction needed, may be administered every 2 weeks (q2w), which is supported by human pharmacokinetic (PK) studies. This is the first study of an FcRn inhibitor in patients with RA so it is believed to be prudent to study nipocalimab on top of standard-of-care (SOC) to achieve proof-of-concept and collect basic efficacy and safety data in patients with RA who will be on SOC background medications.

This Phase 2a, multicenter, randomized, double-blinded, placebo-controlled study is designed to evaluate efficacy and safety of nipocalimab administrated intravenously in participants with moderate to severe active RA.

## 2.2. Background

**Nonclinical Studies**

The nonclinical pharmacology, PK, and toxicity of nipocalimab have been adequately characterized in appropriately designed nonclinical studies that support the potential efficacy, safety, and mechanism of action. Pharmacologic studies showed that nipocalimab binds with high affinity to the IgG binding site of FcRn preventing FcRn-mediated IgG recycling and promoting IgG catabolism in vitro. In vivo, nipocalimab administered intravenously (IV) induced serum IgG decreases in rodents or nonhuman primates and ameliorated disease pathology in animal models of pathogenic IgG-driven autoimmune disease. Pharmacokinetic and pharmacodynamic (PD) evaluation of IV nipocalimab in cynomolgus monkeys and mice established consistent dose-, exposure-, and time-dependent relationships between PK, the PD effect on FcRn receptor occupancy (RO) and the lowering of serum IgG concentrations.

In repeat-dose toxicity studies of IV nipocalimab in the cynomolgus monkey, nipocalimab was administered once-weekly at doses up to the maximum feasible dose of 300 mg/kg for up to 6 months in duration. Pharmacokinetic and PD assessment indicated target effects of dose-dependent RO and reductions in serum IgG concentration occurred in a dose-dependent manner. Chronic administration of nipocalimab was well tolerated without adverse effects, including those associated with infection. Importantly, no immunotoxic effects were observed in a comprehensive evaluation of innate and humoral immunity. In a reproductive toxicology study in which pregnant cynomolgus monkeys received IV nipocalimab at doses of up to 300 mg/kg from the early second trimester (ie, gestational day 45) through parturition, serum IgG in dams, fetuses, and newborns was decreased with no evidence of nipocalimab-related developmental toxicity or impact on fetal or infant survival.

These nonclinical pharmacology and toxicology results support the potential safety and efficacy of nipocalimab and its clinical investigation in diseases caused by pathogenic IgG, including RA.

For the most comprehensive nonclinical information regarding nipocalimab, refer to the latest version of the IB for nipocalimab.

**Clinical Studies**

**Phase 1 Studies of IV Nipocalimab**

Safety, PK, and PD data are available from 3 completed Phase 1 studies in healthy adult participants: a first-in-human (FIH) study (MOM-M281-001) of single ascending doses (SAD) up to 60 mg/kg and multiple ascending doses (MAD) study up to 30 mg/kg weekly; a single dose infusion rate study (MOM-M281-007), and a single dose, dose escalating study conducted in Japanese adults (MOM-M281-010).

Pharmacokinetic parameters for IV nipocalimab showed dose dependency and likely target mediated disposition. Across the SAD dose groups (0.3-60 mg/kg), maximum concentration increased in a dose-proportional manner, whereas area under the concentration-time curve increased in a greater than dose-proportional manner. Serum clearance decreased nearly 50% from 10 to 60 mg/kg while half-life increased with increasing dose, from approximately 7.36 hours at 3 mg/kg to 32.2 hours at 60 mg/kg.

A close PK/PD relationship was observed, with the onset of PD effects (FcRn RO increases; IgG and albumin mean decreases) occurring rapidly following all dose levels of nipocalimab. Recovery of IgG and albumin toward baseline values following the last dose of nipocalimab was observed to occur later at higher dose levels.

In healthy participants, IV nipocalimab was well tolerated with no deaths or serious adverse events (SAEs) reported. The majority of the treatment-emergent adverse events (TEAEs) were transient, mild, or moderate in severity, resolved without intervention, and were assessed as unrelated to treatment. Infusions of IV nipocalimab were also well tolerated over infusion times from 15 minutes to 2 hours.

In the MAD portion of the MOM-M281-001 study, asymptomatic, dose dependent, reversible elevations in non-fasting mean total cholesterol were observed up to 25% of baseline. Retrospective analyses of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) data could not be performed from this study.

In SAD and MAD healthy participants, there was no clear relationship between nipocalimab dose and the presence of neutralizing antibodies (NAbs), anti-drug antibodies (ADA) or ADA titers.

**Phase 2 Studies of IV Nipocalimab**

In the Phase 2 study of nipocalimab in adults with gMG (Study MOM-M281-004), IV nipocalimab was administered for 8 weeks in 4 nipocalimab groups (5 mg/kg every 4 weeks [q4w], 30 mg/kg q4w, 60 mg/kg q2w, and 60 mg/kg single dose) and the IV placebo group. Study conduct has been completed and the final report is in preparation.

Consistent with its mechanism of action, nipocalimab produced dose-dependent, transient decreases in mean serum IgG concentrations. Infusions of IV nipocalimab were generally safe and well tolerated in this study with no deaths, discontinuations due to TEAEs, TEAEs of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ≥Grade 3, or adverse events of special interest (AESIs; events of infection or hypoalbuminemia ≥Grade 3). The overall incidence of TEAEs was similar between the combined nipocalimab group (83.3%) and placebo group (78.6%). Three SAEs were reported during the study; an SAE of musculoskeletal pain was reported for 1 nipocalimab-treated patient (30 mg/kg q4w) and 2 SAEs (ischemic stroke, myasthenia gravis) were reported in placebo-treated patients; none of the SAEs were considered by the investigator as related to study intervention.

In the MOM-M281-004 study, asymptomatic, dose dependent, reversible elevations in non-fasting mean total cholesterol were observed up to 25% of baseline. The elevations in total cholesterol appear to mirror the kinetics of the decreases in albumin observed with nipocalimab.

The Phase 2 study evaluating IV nipocalimab administered to pregnant women at high risk for EOS-HDFN (MOM-M281-003) is ongoing.

A preliminary review of the ongoing study data suggested a possible treatment-emergent increase in non-fasting cholesterol higher than published reference values expected during normal pregnancies (ie, physiologic increases for the appropriate gestational age). The cholesterol elevations observed in pregnant women decreased after nipocalimab discontinuation and returned to baseline values after delivery.

Preliminary safety data on a limited number of patients with gMG in an ongoing long-term extension study and in the wAIHA study have raised no safety concerns.

While a dose-dependent increase in the number of nipocalimab-treated patients with NAb was observed in gMG participants, NAb titers were low throughout the studies. Overall, IV administration of nipocalimab did not lead to a detectable clinically relevant immune response

against nipocalimab. No definitive conclusions can be made regarding the impact of immunogenicity on PK due to the low sample sizes.

For the most comprehensive information regarding nipocalimab, refer to the latest version of the IB for nipocalimab.

## 2.3. Benefit-Risk Assessment

CCI

[redacted]

### 2.3.1. Risks for Study Participation

**Table 1: Potential Risks of Nipocalimab for the Treatment of Rheumatoid Arthritis**

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

### 2.3.2. Benefits for Study Participation

CCI

[redacted]

CCI

[redacted]

### 2.3.3. Benefit-Risk Assessment for Study Participation

CCI

[redacted]

## 3. OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS |
|---|---|
| **Primary** | |
| To evaluate the efficacy of nipocalimab vs placebo in participants with moderate to severe active RA | **Primary Endpoint**:<br>• Change from baseline in DAS28-CRP at Week 12<br>**Secondary Endpoints**:<br>• Proportion of participants who achieve ACR20, ACR50, ACR70, and ACR90 responses at Week 12<br>• Proportion of participants achieving DAS28-CRP remission at Week 12<br>• Proportion of participants achieving DAS28-CRP LDA at Week 12<br>• Change from baseline in HAQ-DI score at Week 12 |
| **Secondary** | |
| To evaluate the safety and tolerability of nipocalimab vs placebo in participants with moderate to severe active RA | • Proportion of participants with treatment-emergent AEs<br>• Proportion of participants with treatment-emergent SAEs<br>• Proportion of participants with treatment-emergent AEs leading to discontinuation of study intervention<br>• Proportion of participants with treatment-emergent AESIs<br>• Laboratory parameters and change from baseline in laboratory parameters over time<br>• Vital sign parameters and change from baseline in vital sign parameters over time |
| To evaluate the PK and immunogenicity of IV nipocalimab in participants with moderate to severe active RA | • Serum nipocalimab concentrations over time in participants receiving active study intervention<br>• Incidence and titers of antibodies to nipocalimab (ADA and NAbs) in participants receiving active study intervention |

| | |
|---|---|
| **Exploratory** | |
| To evaluate the impact of nipocalimab vs placebo on disease activity in participants with moderate to severe active RA | • Proportion of participants who achieve ACR20, ACR50, ACR70, and ACR90 responses over time<br>• Percent improvement from baseline in ACR components over time<br>• Change from baseline in DAS28-CRP (or DAS28-ESR) over time<br>• Proportion of participants achieving DAS28-CRP (or DAS28-ESR) LDA over time<br>• Proportion of participants achieving DAS28-CRP (or DAS28-ESR) remission over time<br>• Change from baseline in CDAI over time<br>• Proportion of participants achieving CDAI LDA over time<br>• Proportion of participants achieving CDAI remission over time<br>• Change from baseline in SDAI over time<br>• Proportion of participants achieving SDAI LDA over time<br>• Proportion of participants achieving SDAI-based ACR/EULAR remission over time<br>• Proportion of participants achieving Boolean-based ACR/EULAR remission over time<br>• Change from baseline in the Tender/Painful and Swollen Joint Counts over time<br>• Change from baseline in duration of morning stiffness over time |
| To evaluate the impact of nipocalimab vs placebo on PROs in participants with moderate to severe active RA | • Change from baseline in the PtGA of Disease Activity score over time<br>• Change from baseline in the Pain VAS score over time<br>• Change from baseline in FACIT-Fatigue score over time<br>• Change from baseline in Joint Pain Severity score over time<br>• Change from baseline in HAQ-DI score over time<br>• The proportion of participants achieving a decrease of ≥0.22 points from baseline in HAQ-DI score over time<br>• Change from baseline in SF-36 PCS, MCS, and domain scores over time |
| To evaluate the effect of nipocalimab vs placebo on PD and disease biomarkers in | • Change from baseline in serum immunoglobulin and albumin levels over time by treatment group |

| | |
|---|---|
| participants with moderate to severe active RA | • Change from baseline in disease biomarkers (eg, autoantibodies, CICs) over time in participants with abnormal levels at baseline<br>• Reduction of IgG level-clinical response relationship analysis |
| To evaluate changes in serological profiles in response to nipocalimab vs placebo treatment in participants with moderate to severe active RA | • Change from screening visit in serum ACPA and RF levels over time by treatment group, in participants seropositive at screening visit for ACPA and RF, respectively |
| CCI | |

Abbreviations: ACPA=anti-citrullinated protein antibodies; ACR=American College of Rheumatology; ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; CDAI=Clinical Disease Activity Index; CICs=circulating immune complexes; DAS28-CRP=Disease Activity Index Score 28 using C-reactive protein; DAS28-ESR=Disease Activity Index Score 28 using erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy Fatigue Scale; HAQ-DI=Health Assessment Questionnaire Disability Index; IgG=immunoglobulin G; IV=intravenous; LDA=low disease activity; MCS=mental component score; NAb=neutralizing antibody; PCS=physical component score; PD=pharmacodynamics; PK=pharmacokinetic(s); PRO=patient-reported outcome; PtGA=Patient Global Assessment of Disease Activity; RA=rheumatoid arthritis; RF=rheumatoid factor; SAE=serious adverse event; SDAI=Simple Disease Activity Index (for Rheumatoid Arthritis); SF-36=36-item Short Form Health Survey; VAS=visual analog scale

Refer to Section 8, (Study Assessments and Procedures) for evaluations related to endpoints.

**HYPOTHESIS**

The primary hypothesis is that treatment with nipocalimab 15 mg/kg IV q2w is superior to placebo in participants with moderate to severe active RA as assessed by the mean change from baseline in the Disease Activity Index Score 28 using C-reactive Protein (DAS28-CRP) at Week 12.

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a randomized, double-blind, parallel-group, placebo-controlled, proof-of-concept, multicenter study in participants between the ages of 18 and 75, inclusive, with moderate to severe active RA despite standard therapy, including anti-TNF agents.

The total duration of the study is up to 24 weeks, consisting of 3 study periods: a ≤6-week screening period (rescreening is permitted once per participant), a 12-week double-blind treatment period, and a 6-week safety follow-up period (8 weeks after the last administration of study intervention).

A target of 50 participants will be enrolled in this study. Participants who have had an IR or were intolerant to at least one anti-TNF therapy will be enrolled. Depending upon the enrollment rate, the study population may be expanded to also include participants who have had an IR or intolerance to a conventional synthetic DMARD (csDMARD; see Section 5.1).

Participants will be randomly assigned into 1 of 2 treatment groups using a 2:3 randomization ratio, respectively:

- **Group 1: Placebo IV q2w**: Participants will receive placebo IV q2w through Week 10.
- **Group 2: Nipocalimab 15 mg/kg IV q2w**: Participants will receive nipocalimab 15 mg/kg IV q2w through Week 10.

A placebo comparator (in addition to SOC background therapy) will be used to allow for blinded, placebo-controlled evaluation of the efficacy and safety of nipocalimab in participants with RA.

Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA, Section 1.3). Pharmacogenomic blood samples will be collected from participants who consent to the collection of these samples (where local regulations permit).

The primary endpoint (the change from baseline in DAS28-CRP compared with placebo at Week 12) will be evaluated after all participants have completed the Week 12 visit (or discontinued). An interim analysis (IA) is planned when 60% (30 participants) of the planned number of participants complete the Week 12 assessment. This analysis is for future planning purposes and will not impact the conduct of the current study (Section 9.5).

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol (Section 6.8). Beginning at the screening visit, all concomitant therapies and all changes in concomitant therapies should be recorded throughout the study.

Key safety assessments include adverse events (AEs), SAEs, AESIs, clinical laboratory parameters (eg, hematology, chemistry, lipid panel), vital signs, and physical examination.

Serum samples will be used to evaluate PK and antibodies to nipocalimab. Blood-based biomarkers will be evaluated for inflammation-associated proteins and other analytes and will be used to better understand the biology of RA, to provide a biological assessment of the response of participants to treatment with nipocalimab, to analyze differences between responders and nonresponders, to assess loss of response, and to determine if the markers can be used to classify participants as potential responders prior to treatment.

Actigraphy data will utilize accelerometry measurements to assess physical activity, mobility, and sleep parameters. These measurements will be captured via wrist-worn actigraph devices, which have been validated against polysomnography to assess sleep-related variables.

Database locks (DBLs) are planned at Week 12 and at the end of the study. The end of the study is defined as the last follow-up assessment (8 weeks after the last infusion of study intervention) for the last participant.

A Data Monitoring Committee (DMC) will be commissioned for this study. Refer to Section 10.3.6 for details on the DMC.

A diagram of the study design is provided in Section 1.2, Schema.

## 4.2. Scientific Rationale for Study Design

This study is designed to examine the efficacy and safety of nipocalimab, the effects of nipocalimab on physical function, patient-reported outcomes (PROs), and population PK of nipocalimab in participants with moderate to severe active RA who are refractory to standard therapy.

A double-blind, placebo-controlled study design (allowing background SOC therapy to be continued) was selected, as a true placebo design (no treatment) would not be appropriate. The background SOC therapy is defined as being treated with any csDMARDs (eg, methotrexate [MTX], sulfasalazine [SSZ], hydroxychloroquine [HCQ], chloroquine [CQ], and leflunomide).

### 4.2.1. Blinding, Control, Study Phase/Periods, Intervention Groups

CCI

[redacted]

### 4.2.2. DNA and Biomarker Collection

CCI

[redacted]

CCI

[redacted]

### 4.2.3. Actigraphy Measurements

Digital health applications may help to objectively capture participant well-being. Wearable devices equipped with biometric sensors and self-reporting mobile applications are able to continuously track participant activities and may provide useful insights on disease progression, clinical response, or complications.

Digital sensing technologies will provide valuable data that supplement clinical data streams such as clinical endpoints, PROs, objective measures from clinical laboratory and biomarker assessments to better characterize the disease status and well-being of participants with RA when treated with nipocalimab compared with placebo.

### 4.2.4. Participant Input into Design

Historical data were collected from a 30-60 minute internet survey which was administered to 6 sample groups of patients with RA in the United States. Mobility and fatigue were identified by many as significant barriers to daily life. Actigraphy will be employed in this protocol (optional participation) to track mobility and sleep data related to study intervention.

Additionally, the lack of new therapies has been identified as a recurrent cause of frustration among patients with RA and rheumatologists. For this reason, the potential of nipocalimab to emerge as a new treatment would be considered a valuable contribution to the RA suffering population.

### 4.2.5. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

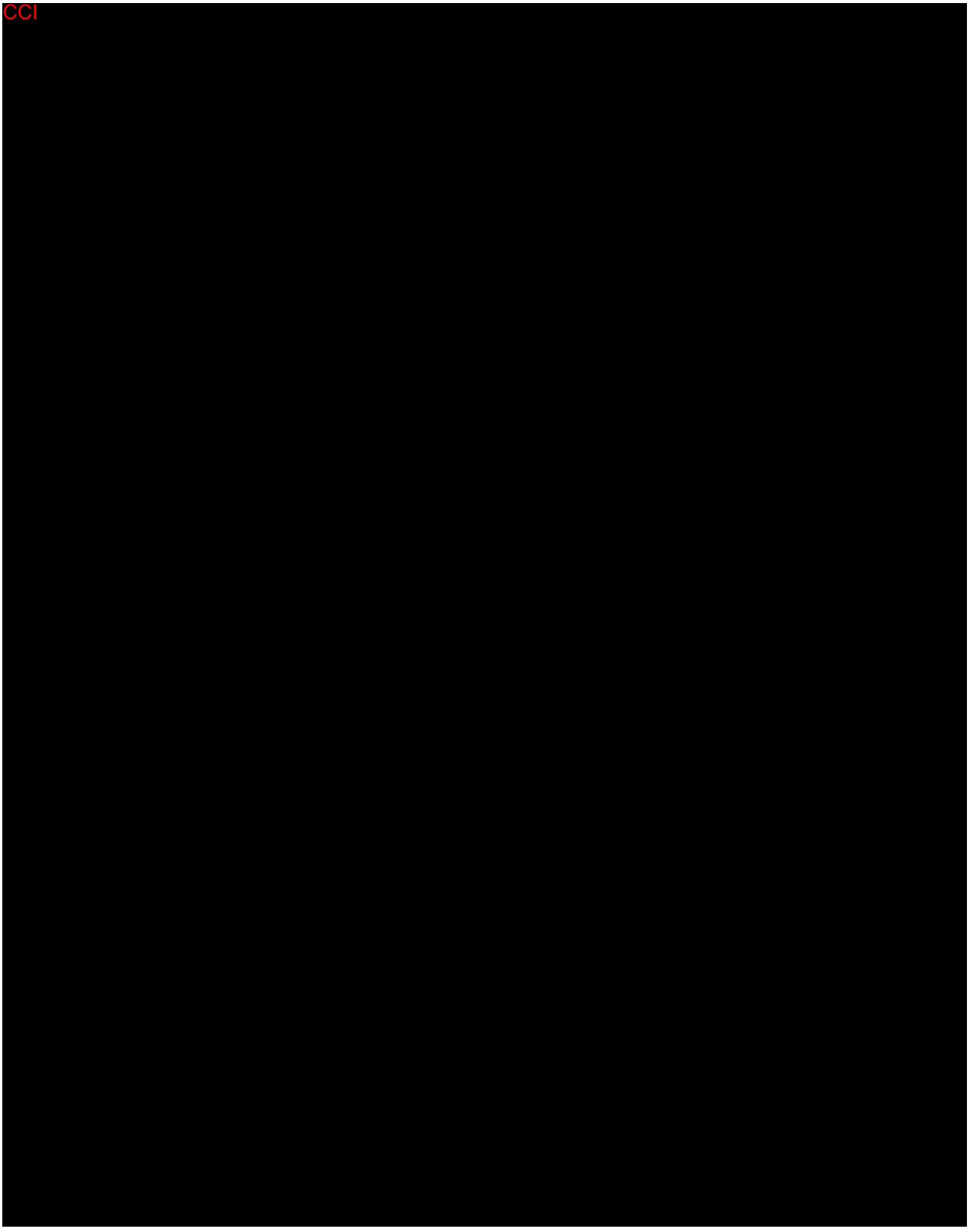
The primary ethical concern is that although targeting FcRn has shown promise of early efficacy in humans in several diseases (eg, myasthenia gravis, primary immune thrombocytopenia [Howard 2019, Kiessling 2017, Newland 2020]), efficacy has not been shown in RA, and response to nipocalimab in RA is theoretical at this time.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross standard limit for whole blood donation (approximately 475 mL every

8 weeks) and is, therefore, considered an acceptable amount of blood to be collected over this time. For more details regarding blood collection, see Blood Sample Collection in Section 8.

### 4.3. Justification for Dose

CCI



CCI

[redacted]

CCI

[redacted]

## 4.4. End of Study Definition

**End of Study Definition**

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

**Study Completion Definition**

A participant will be considered to have completed the study if he or she has completed assessments through Week 12 of the double-blind phase and the safety follow-up visit.

# 5. STUDY POPULATION

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.4 for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

## 5.1. Inclusion Criteria

Enrollment for this study will begin with participants who have demonstrated an IR or intolerance to at least 1 anti-TNF therapy. Depending upon the enrollment rate, sites will be informed to expand the participant population to also include those who are anti-TNF-therapy naïve and have demonstrated an IR or intolerance to at least 1 csDMARD.

Each potential participant must satisfy the following criteria to be enrolled in the study:

**Age**

1. 18 to 75 years of age (inclusive) at the time of consent. (In regions where the legal age of consent is older than 18 years and the participant is under the legal age, signed informed consent must be obtained from both the participant and his or her legally acceptable representative.)

**Disease Characteristics**

2. Diagnosis of RA and meeting the 2010 ACR / European League Against Rheumatism (EULAR) Criteria for RA for at least 3 months before screening.

3. Has moderate to severe active RA as defined by persistent disease activity with at least 6 swollen and 6 tender joints out of the 66/68-swollen and tender joint count at the time of screening and at baseline.

4. Is positive for ACPA and/or RF at screening.

5. Screening CRP ≥0.3 mg/dL by the central laboratory.

6. If has received prior anti-TNF agent (including biosimilars), has demonstrated IR or is intolerant to the anti-TNF therapy based on 1 of the following:

    a. IR to at least 1 anti-TNF agent including biosimilars, as assessed by the treating physician, after at least 12 weeks of etanercept, adalimumab, golimumab, or certolizumab pegol therapy and/or at least a 14-week dosage (ie, at least 4 doses) of infliximab. Documented IR may include inadequate improvement in joint counts or other parameters of disease activity.

    b. Intolerance to an anti-TNF agent (as assessed by the treating physician) including etanercept, adalimumab, golimumab, certolizumab pegol, or infliximab (including biosimilars). Documented intolerance includes side effects and or injection/infusion reactions.

7. If has not received prior anti-TNF agent (including biosimilars), has demonstrated IR or intolerance to csDMARDs based on 1 of the following:

    a. For participants receiving a csDMARD at the time of entry: has had regular use of the csDMARD for at least 12 weeks prior to randomization, with a continuous (nonchanging) dose for at least 8 weeks prior to randomization.

    b. For participants not receiving a csDMARD at the time of entry: has failed, was unable to tolerate, or had a contraindication to treatment with a csDMARD, as will be documented by the investigator in the participant's history.

**Concomitant or Previous Medical Therapies Received**

8. If using csDMARDs (eg, MTX, SSZ, HCQ, CQ, or leflunomide), has started treatment at least 12 weeks prior to the first administration of study intervention, is on a stable dosage for at least 8 weeks prior to the first administration of study intervention, and has no serious toxic side effects attributable to the csDMARD:

    a. If using MTX: on a stable dosage of no more than 25 mg/week (intramuscular [IM], subcutaneous [SC], or oral [PO])

    b. If using SSZ: on a stable dosage of 1000-2000 mg/day

    c. If using HCQ or CQ: on a stable dosage of 200-400 mg/day

    d. If using leflunomide: on a stable dosage of 10-20 mg/day

9. If currently not using csDMARDs (ie, MTX, SSZ, HCQ, CQ, or leflunomide), has not received these DMARDs for at least 4 weeks prior to the first administration of the study intervention.

10. If using MTX, is on a stable dosage of oral folic/folinic acid (>5 mg/week) for at least 4 weeks prior to the first administration of study intervention.

11. If using oral corticosteroids, is on a stable dosage equivalent to ≤10 mg/day of prednisone for at least 2 weeks prior to the first administration of study intervention. If not currently using corticosteroids, the participant must not have received oral corticosteroids for at least 2 weeks prior to the first administration of study intervention.

12. If using nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesics for RA, is on a stable dosage for at least 2 weeks prior to the first administration of study intervention.

**Sex and Contraceptive/Barrier Requirements**

13. Criterion deleted per Amendment 3.

14. A woman of childbearing potential must have a negative highly sensitive urine pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine (β-hCG) pregnancy test at Week 0 prior to administration of study intervention.

15. Criterion modified per Amendment 3.

    15.1. A woman must be (as defined in Section 10.5):

    a. Not of childbearing potential

    **OR**

    b. Of childbearing potential, and:

    Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days after last dose - the end of relevant systemic exposure. The investigator must evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.5.

16. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for 30 days after the last administration of study intervention.

17. A male participant who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal

foam/gel/film/cream/suppository if available in their local), during the study and for at least 90 days after receiving the last administration of study intervention.

18. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 90 days after receiving the last administration of study intervention.

**Vaccination History**

19. Criterion modified per Amendment 3.

    19.1. It is recommended to be up to date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labeling, guidelines, and standards-of-care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.8.4).

**General**

20. Criterion modified per Amendment 3.

    20.1. Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study. (In regions where the legal age of consent is older than 18 years, those under the legal age, must obtain signed informed consent from both the participant and his or her legally acceptable representative.)

21. Criterion modified per Amendment 3.

    21.1. Must sign a separate ICF if the participant agrees to provide optional DNA samples for research where local regulations permit. In regions where the legal age of consent is older than 18 years, those under the legal age must obtain signed informed consent from both the participant and his or her legally acceptable representative.

    Refusal to give consent for the optional DNA samples does not exclude a participant from participation in the study.

22. Must be willing and able to adhere to all specified requirements, including but not limited to completion of the required assessments, adherence to the visit schedule, and compliance with the lifestyle restrictions as specified in this protocol.

23. Must be able to read and write.

## 5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

**Coexisting Medical Conditions or Past Medical History**

1. Has any confirmed or suspected clinical immunodeficiency syndrome not related to treatment of his/her RA or has a family history of congenital or hereditary immunodeficiency unless confirmed absent in the participant.
2. Currently has a malignancy or has a history of malignancy within 3 years before screening (with the exception of localized basal cell carcinoma and/or squamous cell carcinoma skin cancer that has been adequately treated with no evidence of recurrence for at least 12 weeks before the first administration of study intervention or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first administration of study intervention).
3. Has known allergies, hypersensitivity, or intolerance to nipocalimab or its excipients (refer to the IB).
4. Is (anatomically or functionally) asplenic.
5. Has experienced myocardial infarction (MI), unstable ischemic heart disease, or stroke within 12 weeks of screening.
6. Has a history of severe, progressive, and/or uncontrolled liver, gastrointestinal, renal, pulmonary, cardiovascular, psychiatric, neurologic, or musculoskeletal disorder (with the exception of RA), hypertension, or any other medical disorder that, in the opinion of the investigator, might interfere with the participant's full participation in the study, or might jeopardize the safety of the participant or the validity of the study results.
7. Has other known inflammatory diseases that might confound the evaluations of benefit from nipocalimab therapy, including but not limited to ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus, Lyme disease.
8. Has screening laboratory test result as follows:
    a. Hemoglobin <8.0 g/dL (International system of Units [SI]: <80 g/L)
    b. White blood cells (WBCs) $<3.0\times10^3$ cells/µL (SI:$<3.0\times10^9$ cells/L)
    c. Neutrophils $<1.0\times10^3$ cells/µL (SI: $<1.0\times10^9$ cells/L)
    d. Platelet count $<75\times10^3$ cells/µL (SI: $<75\times10^9$/L)
    e. Estimated glomerular filtration rate <30 mL/min per 1.73 $m^2$
    f. Liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) results that are ≥2 × the upper limit of normal (ULN)
    g. CCI [redacted]

9. Poor tolerability of venipuncture or lacks adequate venous access for required blood sample collections during the study period.

10. Has shown a previous severe immediate hypersensitivity reaction, such as anaphylaxis, to therapeutic proteins (eg, mAbs).

**Concomitant or Previous Medical Therapies Received**

11. Is currently taking IgG Fc-related protein therapeutics.

12. Has received plasmapheresis, immunoadsorption therapy, or IVIg within 6 weeks prior to screening.

13. Criterion modified per Amendment 3.

    13.1. Has received a live vaccine within 3 months prior to screening or has a known need to receive a live vaccine during the study, or within at least 3 months after the last administration of study intervention in this study.

    Has had a Bacille Calmette-Guérin (BCG) vaccination within 1 year of first administration of study intervention.

14. Has taken any disallowed therapies (within the periods of time detailed in Section 6.8, Concomitant Therapies) prior to the planned first administration of study intervention.

15. Has received anti-TNF agent (or its biosimilars) within 30 days or 5 half-lives, whichever is greater, prior to the first administration of study intervention.

16. Has received biologic therapy or targeted synthetic DMARDs including but not limited to the below within 30 days or 5 half-lives, whichever is greater, prior to the first administration of study intervention:

    a. anti-interleukin (IL)-6 receptor mAb (eg, tocilizumab or sarilumab)
    b. anti-IL-1 blockers (eg, anakinra)
    c. Co-stimulatory inhibitors (eg, abatacept)
    d. Janus kinase inhibitors (JAKi, eg, tofacitinib, baricitinib, upadacitinib)

17. Has received rituximab within 6 months prior to first administration of study intervention.

18. Currently using MTX and leflunomide combination therapy.

19. Has used oral cyclophosphamide within 3 months or IV cyclophosphamide within 6 months prior to the first administration of study intervention.

20. Has received cyclosporine A, azathioprine, tacrolimus, mycophenolate mofetil, oral or parenteral gold, or D-penicillamine within 4 weeks prior to the first administration of study intervention.

21. Use of complementary therapies, including traditional/Chinese medicines, herbs, ointments, or procedures (eg, acupuncture), that have the potential to activate (eg, echinacea) or inhibit (eg, *Tripterygium wilfordii* Hook F) the immune system is prohibited within 6 weeks of first administration of study intervention. In addition, use of complementary therapies, including traditional/Chinese medicines and herbs, that have the potential to interact with antithrombotic agents (eg, St. John's Wort) is prohibited within 6 weeks of first administration of study intervention in those taking antithrombotic agents. Any questions or concerns with the use of these therapies should be discussed with the study sponsor and/or medical monitor.

**Prior/Concurrent Clinical Study Experience**

22. Criterion modified per Amendment 3.

    22.1. Has received an investigational intervention within 3 months or 5 half-lives (whichever is longer) or used an invasive investigational medical device within 3 months before the planned first administration of study intervention or is currently enrolled or plans to enroll in an investigational study.

23. Is currently breastfeeding, pregnant, intends to become pregnant during the study, or is planning egg donation during the study or within 30 days after the last administration of study intervention.

24. Is planning to father a child while enrolled in this study or donate sperm within 90 days after the last administration of study intervention.

**Infections or Predisposition to Infections**

25. Has a severe infection including opportunistic infections (eg, pneumonia, biliary tract infection, diverticulitis, *Clostridioides difficile* infection, cytomegalovirus, pneumocystosis, and aspergillosis) requiring parenteral anti-infectives and/or hospitalization, and/or is assessed as serious/clinically significant by the investigator, within 8 weeks prior to screening. The patient may be rescreened after the 8-week exclusionary period has passed.

26. Has a chronic infection (eg, bronchiectasis, chronic osteomyelitis, chronic pyelonephritis) or requires chronic treatment with anti-infectives (eg, antibiotics, antivirals).

27. Tests positive for hepatitis B virus (HBV) infection (see Section 10.7).

28. Is seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy 1 of the following conditions:

    a. Has a history of successful treatment, defined as being negative for HCV ribonucleic acid (RNA) at least 24 weeks after completing antiviral treatment, and has a negative HCV RNA test result at screening,

       **OR**

    b. While seropositive, has a negative HCV RNA test result at least 24 weeks prior to screening and a negative HCV RNA test at the screening.

29. Has a history of being HIV1 or HIV2 antibody-positive, or tests positive for HIV at screening.

30. Criterion modified per Amendment 3.

    30.1. COVID-19 infection:

    During the 6 weeks prior to baseline, has had **any** of the following (regardless of vaccination status): (a) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (test positive) **OR** (b) suspected SARS-CoV-2 infection (clinical features of COVID-19 without documented test results) **OR** (c) close contact with a person with known or suspected SARS-CoV-2 infection

    - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test
      i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, [eg, fever, cough, dyspnea])

      AND

      ii) with absence of all conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

    Note on COVID-related exclusion:

    - The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.

    Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

31. Criterion modified per Amendment 3.

    31.1. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening.

32. Has a history of an infected joint prosthesis, or has ever received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

**Diagnostic Assessments**

33. Had major surgery (eg, requiring general anesthesia [although not all procedures requiring general anesthesia would necessarily be major]) within 3 months before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

    **Note:** Participants with planned surgical procedures to be conducted under local anesthesia may participate.

**Other Exclusions**

34. History of moderate or severe substance or alcohol use disorder according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria, except nicotine or caffeine, within 1 year before screening.

35. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

36. Lives in an institution on court or authority order.

37. Currently participating or intends to participate in any other study using an investigational agent or procedure during the conduct of this study.

38. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

**NOTE:** Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study (refer to Section 5.4). The required source documentation to support meeting the enrollment criteria are noted in Section 10.3.10.

## 5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria.

3. Participants must follow contraceptive measures as outline in Section 5.1. Women should continue using these contraceptive measures for 30 days after the last dose of study intervention. Men should continue using these contraceptive measures for 90 days after the last dose of study intervention.

4. Criterion modified per Amendment 3.

   4.1. Must agree not to receive a live vaccine during the study and for 3 months after receiving the last dose of study intervention.

   Must agree not to receive a BCG vaccination during the study and for 1 year after receiving the last dose of study intervention.

5. Must be willing and able to complete study-related questionnaires and document clinical symptoms, AEs, and concomitant medications.

6. Avoid donating blood for at least 90 days after completion (ie, final follow-up visit) of the study.

## 5.4. Screen Failures

**Participant Identification, Enrollment, and Screening Logs**

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

**Retesting**

Retesting of abnormal laboratory values for safety that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening phase, as long as this is done

within the specified screening window of up to 6 weeks. In such cases, the first abnormal test result will not constitute a screen failure. If a laboratory abnormality occurs, the site is encouraged to wait for all laboratory tests to be completed to ensure other laboratory tests do not need to be repeated, as only 1 retest of laboratory tests is allowed. Participants who have laboratory values that do not meet entry criteria following the retest or do not meet disease activity inclusion criteria following the repeat procedure are to be deemed screen failures. A screening laboratory test(s) analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the screening period.

**Rescreening**

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time after discussion with the sponsor representative or their designee. Rescreened participants must be assigned new participant numbers, undergo the informed consent process, and then start a new screening phase.

### 5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.8. Criteria for temporary discontinuation of study intervention are described in Section 7.1.2.

## 6. STUDY INTERVENTION AND CONCOMITANT THERAPY

### 6.1. Study Interventions Administered

Participants will be randomized in a 2:3 ratio to 1 of 2 treatment groups as described below:

- **Group 1 – placebo IV q2w**: Participants will receive placebo IV q2w from Week 0 through Week 10.
- **Group 2 – nipocalimab 15 mg/kg IV q2w**: Participants will receive nipocalimab 15 mg/kg IV q2w from Week 0 through Week 10.

Participants will remain on their assigned treatment through Week 10. All participants will receive a planned total of 6 IV infusions over a 10-week period.

Intravenous study intervention should be prepared and administered according to the instructions specified in the Investigational Product Preparation and Administration Instructions (IPPI).

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Nipocalimab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients. Placebo will be a commercially available saline solution. Placebo will be centrally sourced and provided under the responsibility of the sponsor where required per local regulations. Nipocalimab and the centrally-sourced and supplied placebo are designated as Investigational Medicinal Product (IMP). In the United States of America, a site-sourced and locally-sourced saline placebo option will be available in addition to the centrally-sourced placebo.

These site and locally sourced commercial saline for placebo are designated as Non-Investigational Medicinal Product (NIMP) per US Food and Drug Administration (FDA) regulations.

For a definition of study intervention overdose, refer to Section 6.7.

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.8.

## 6.2. Preparation/Handling/Storage/Accountability

**Preparation/Handling/Storage**

CCI

The nipocalimab solution in the vial should be clear to slightly opalescent and colorless to slightly brown and may contain small translucent particles. Do not use nipocalimab if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material but direct exposure to sunlight should be avoided. Aseptic techniques must be used during the preparation and administration of the study intervention material.

Saline will be used as a placebo.

Refer to the site IPPI and Site Investigational Product Procedures Manual (SIPPM) for additional guidance on study intervention preparation, handling, and storage.

**Accountability**

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study.

The study intervention administered to the participant must be documented on the intervention accountability form or in the interactive web response system (IWRS) intervention accountability system as applicable. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers except as noted in the IPPI.

Study intervention must be handled in strict accordance with the protocol and as indicated on the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor or sponsor-designated destruction facility of unused study intervention will be documented on the intervention return form or in the IWRS intervention accountability system, as applicable. When the study site is an authorized destruction unit and study intervention supplies

are destroyed on site, this must also be documented on the intervention return form or in the IWRS intervention accountability system as applicable.

Potentially hazardous materials (eg, used needles and syringes) must be disposed of immediately in a safe manner and, therefore, will not be retained for intervention accountability purposes.

Study intervention must be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be administered only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study intervention are provided in the SIPPM.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

**Intervention Allocation**

***Procedures for Randomization and Stratification***

Dynamic central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on biased-coin algorithm implemented in the IWRS before the study. Dynamic central randomization targets to balance the distribution of participants to achieve the randomization ratio (2:3) at the study level and within the levels of each individual stratification factor: baseline MTX use, anti-TNF IR/intolerance, and swollen and tender joint counts level.

The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

**Blinding**

The participant, investigator, and sponsor will be blinded to study intervention for the duration of the study. The unblinded site pharmacist(s) or designee will be responsible for preparing the study intervention for infusion while the remainder of site personnel will remain blinded. To preserve blinding, the unblinded pharmacist(s) or designee will prepare the infusion material to be identical in appearance for administration, in accordance with the IPPI. Administration of study intervention to the participants will be performed by a blinded, qualified healthcare provider. Independent drug monitors will be used to monitor drug accountability and all unblinded study data.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Selected data will be handled with special care to minimize any potential impact on blinding/bias (see Section 4.2.1). This can include masking/segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding. If there is sufficient safety concern that local laboratory samples are drawn to check the level of any masked laboratory assessments, the medical monitor or sponsor should be notified immediately. The participant may be required to be discontinued from study intervention.

Under normal circumstances, the blind must not be broken until all participants have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency intervention/course of action would be dictated by knowing the intervention status of the participant. In such cases, the investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations and are not eligible to receive further study intervention.

Additionally, a given participant’s treatment assignment may be unblinded to the sponsor, the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs).

A separate code break procedure will be available for use by the sponsor’s Global Medical Safety group to allow for unblinding of individual participants to comply with specific requests from regulatory or health authorities.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, for the IA, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the IA.

The blind will be maintained until the last participant completes the safety follow-up assessments at Week 12 and the data are locked. At the Week 12 DBL, the data will be unblinded for analysis to some sponsor personnel while participants are still participating in the study. Identification of sponsor personnel who will have access to the unblinded participant-level data will be documented prior to unblinding. Investigative sites and participants will remain blinded to initial intervention assignment until the final DBL (Week 18).

## 6.4. Study Intervention Compliance

Study-site personnel will maintain a log of all study intervention administered. Study intervention supplies for each participant will be inventoried and accounted for.

Study intervention will be administered as an IV infusion by qualified study-site personnel and the details of each administration is to be conducted using the IPPI.

Additional details may be provided in the site SIPPM that is provided separately. Compliance with the treatment schedule is strongly encouraged.

## 6.5. Dose Modification

No study intervention dose adjustment will be permitted through the study.

## 6.6. Continued Access to Study Intervention After the End of the Study

There are no provisions for continued access to study intervention after the end of this proof-of-concept study.

## 6.7. Treatment of Overdose

For this study, any dose of nipocalimab greater than CCI above the highest dose at a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AEs and SAEs.
- Discuss with the medical monitor if one or additional serum sample for PK analysis will be required and at what timepoints.
- Document the quantity of the excess dose.

## 6.8. Concomitant Therapy

Detailed information of pre-study RA therapies, including dosage and frequency of administration, must be recorded for past history. Other pre-study therapies and any COVID-19 vaccinations, including vaccinations authorized for emergency use, administered at the time of screening or up to 60 days before first dose of study intervention, whichever is longer, must be recorded at screening. For any therapies that were discontinued, the reason for discontinuation (eg, non-response, loss of response, intolerance, safety concern) should be documented.

Concomitant therapies (including RA concomitant therapies, non-RA concomitant therapies, and any COVID-19 vaccinations [including vaccinations authorized for emergency use]) must be recorded throughout the study, beginning with screening to the final safety follow-up visit after the last dose of study intervention.

All concomitant therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosage, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

In participants with elevated lipids at any time during the study, it is recommended that the investigator initiates or continues appropriate therapy for dyslipidemia as per local health guidelines.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Every reasonable effort should be made to keep concomitant medications stable to avoid introducing non-protocol medications for RA disease activity through the final safety visit, or as specified in the sections below. Dose stabilization of all concomitant medications is required prior to randomization. All medications must meet study protocol guidelines (see Section 5.1, Section 5.2). It is recommended that all other concomitant medications be maintained at stable doses through the final safety visit, including for those discontinuing the study prematurely. If necessary, a concomitant medication may be reduced or temporarily discontinued because of abnormal laboratory values, safety and tolerability issues, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication change should be clearly documented in the participant's medical record. Adjustments in concomitant therapies that do not comply with the study protocol guidelines may cause a participant to be considered a treatment failure for the primary and secondary endpoints through Week 12.

During the entire study, investigators should consider whether increases in permitted background therapy due to increased RA disease activity warrant discontinuation of study intervention. If protocol-prohibited medication (detailed in Section 6.8.5) is needed, the participant should be considered for discontinuation from study intervention (see Section 7.1). This should be discussed with the medical monitor and/or sponsor.

Table 2 outlines permitted concomitant medication use and dose stabilization requirements prior to randomization.

**Table 2: Permitted Concomitant Medications for 80202135ARA2001, the Minimum Stabilization Period before Randomization, and the Maximum Allowed Doses at Study Randomization**

| Permitted Concomitant Medications for RA | Stabilization Period Prior to First Study Intervention Administration | Allowable Dosage |
|---|---|---|
| csDMARDs | Treated for ≥12 weeks with stable dosage for ≥8 weeks | • MTX: ≤25 mg/week<br>• SSZ: 1000-2000 mg/day<br>• HCQ or CQ: 200-400 mg/day<br>• Leflunomide: 10-20 mg/day |
| Oral corticosteroids | Stable dosage for ≥2 weeks | Equivalent to average of ≤10 mg/day of prednisone |
| NSAIDs and other analgesics | ≥2 weeks | No more than the usual marketed dosages approved in the country where the study is being conducted |

Abbreviations: CQ=chloroquine; csDMARD=conventional synthetic disease-modifying anti-rheumatic drugs; HCQ=hydroxychloroquine; MTX=methotrexate; NSAIDs=nonsteroidal anti-inflammatory drugs; RA=rheumatoid arthritis; SSZ=sulfasalazine

### 6.8.1. Disease-Modifying Antirheumatic Drugs and Systemic Immunosuppressives

If using csDMARDs (eg, MTX, SSZ, HCQ, CQ, or leflunomide), the participant:

- should have started treatment at least 12 weeks prior to the first administration of study intervention,
- should have no serious toxic side effects attributable to the DMARD,
- must be on a stable dosage for at least 8 weeks prior to the first administration of study intervention,
  - if using MTX: stable dosage of ≤25 mg/week (IM, SC, or PO)
  - if using SSZ: stable dosage of 1000-2000 mg/day
  - if using HCQ or CQ: stable dosage of 200-400 mg/day
  - if using leflunomide: stable dosage of 10-20 mg/day
- and must remain on the dosage throughout the study unless reduction or interruption is required for safety or tolerability reasons.

If not currently using MTX, SSZ, HCQ, CQ, or leflunomide, the participant must not have received these csDMARDs for at least 4 weeks prior to the first administration of the study intervention and must not initiate these csDMARDs during the study.

### 6.8.2. Corticosteroid Therapy

**Oral Corticosteroids**

Participants treated with oral corticosteroids should receive a stable dosage equivalent to ≤10 mg prednisone per day for at least 2 weeks prior to their first administration of the study intervention

and continue to receive this dosage through the end of the study. The dosage and the type of oral corticosteroid may be changed at the discretion of the investigator if the participant develops unacceptable side effects.

Initiation of oral corticosteroids is prohibited during the study for any indication.

**Intraarticular, Intramuscular, and Intravenous Corticosteroids**

Intraarticular, intramuscular, and IV administration of corticosteroids for the treatment of RA is not allowed within 4 weeks before the first administration of study intervention and throughout the study.

**Other Administration of Corticosteroids**

Other forms of corticosteroid administration (eg, topical/mucosal [including eye drops or creams], bronchial or nasal inhalation) for treatment of conditions other than RA may be given as needed throughout the course of the study.

### 6.8.3. Nonsteroidal Anti-inflammatory Drugs and Other Analgesics

Participants treated with NSAIDs, including aspirin and selective cyclooxygenase-2 inhibitors, and other analgesics should receive the usual marketed doses approved in the country where the study is being conducted. In this study, aspirin is considered an NSAID, except for low-dose aspirin prescribed for cardiovascular or cerebrovascular disease. Prescriptions of NSAIDs and other analgesics generally should not be adjusted for at least 2 weeks prior to the first administration of the study intervention and through Week 12. The dose and the type of NSAIDs or other analgesics may be changed at the discretion of the investigator if the participant develops unacceptable side effects or a contraindication to their use. Nonsteroidal anti-inflammatory drugs should not be used within 24 hours before a study visit involving joint counts and pain assessments.

### 6.8.4. Vaccinations (Including COVID-19)

When considering use of locally approved non-live vaccines (including emergency-use-authorized COVID-19 vaccines) in study participants, follow applicable local vaccine labeling, guidelines, and standards-of-care for participants receiving immune-targeted therapy.

For study participants receiving a locally-approved (including emergency use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to COVID-19 vaccine, it is recommended where possible that vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.

### 6.8.5. Prohibited Therapies

Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria (Section 5.1 and Section 5.2), are prohibited, including (but not limited to) the following:

- Systemic immunosuppressives or DMARDs (other than MTX, SSZ, HCQ, CQ, and leflunomide) including azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, oral or parenteral gold
- Anti-TNF therapy such as: infliximab, golimumab, etanercept, adalimumab, certolizumab, and biosimilars to those anti-TNFs
- Anti-IL-6 receptor mAb (eg, tocilizumab or sarilumab)
- IL-1 inhibitors (eg, anakinra)
- B-cell depleting biologic therapy (eg, rituximab)
- Co-stimulatory inhibitors (eg, abatacept)
- JAKi (eg, tofacitinib, baricitinib, upadacitinib)
- Cytotoxic drugs such as cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents
- Any other targeted biologic therapy
- Any investigational intervention or use of an invasive investigational medical device
- Live vaccinations
- The use of complementary therapies (eg, herbs, ointments, traditional Chinese medicine, acupuncture) that have the potential to activate or inhibit the immune system is prohibited (see Section 5.2). In addition, use of complementary therapies that have the potential to interact with antithrombotic agents is prohibited in those taking antithrombotic agents.

As these lists cannot be exhaustive, please consult the medical monitor to discuss prior to starting any biologic or other advanced therapies.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The participant becomes pregnant.
- The participant develops an infection that is unresponsive or worsening while on anti-infective therapy.
- The participant develops any serious infection (ie, meets AE seriousness criteria).
- The participant develops a moderate or severe opportunistic infection.
- The participant develops a severe infusion reaction/allergic reaction assessed by the investigator as related to study intervention (eg, anaphylaxis per Sampson's criteria [Section 10.9]).

- The participant develops clinical manifestations of hypoalbuminemia, including 3+ pedal edema, ascites, or pleural or pericardial effusions assessed by the investigator as related to study intervention.
- The investigator believes that, for safety or tolerability reasons (eg, AE), it is in the best interest of the participant to discontinue study intervention.
- CCI
- The participant initiates a prohibited therapy as described in Section 6.8.5.

**Discontinuation of a participant's study intervention should be considered under the following conditions:**

- Persistent IR or worsening of RA.

If a participant discontinues study intervention for any reason before the end of the double-blind phase, they may continue in the study. Participants who permanently discontinue study intervention but do not withdraw from study participation should be followed at all subsequent study visits through Week 12. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

If the participant wishes to discontinue the study, then the Final Efficacy and Safety Follow-up Visit assessments should be obtained as specified in the SoA (Section 1.3).

### 7.1.1. Liver Chemistry Stopping Criteria

Stopping of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Section 10.6 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

### 7.1.2. Study Stopping Rules

The study will be terminated if any of the following criteria are met:

- Death of any participant in which the cause of death is assessed by the investigator to be related to study intervention and the DMC and sponsor believe that participants would incur undue risk by continuing the study
- Three or more participants report serious infections assessed by the investigator to be related to study intervention and the DMC and sponsor believe that participants would incur undue risk by continuing the study.

## 7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, no additional assessments are allowed.

**Withdrawal of Consent**

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator must offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below. Participants will not be allowed to continue to receive study intervention if reduced follow-up is in place, but other study evaluations should continue as much as possible. Withdrawal of consent must be an infrequent occurrence in clinical studies (Rodriguez 2015); therefore, prior to the start of the study the sponsor and the investigator must discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

**Circumstances for Reduced Follow-up**

In the situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for reduced follow-up. These may include (as local regulations permit):

- Less frequent clinical visits
- Telephone, email, letter, social media, fax, or other contact with:
  - participant
  - relatives of the participant
  - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

### 7.2.1. Withdrawal from the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample

destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample have been destroyed.

**Withdrawal From the Optional Research Samples While Remaining in the Main Study**

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

**Withdrawal From the Use of Samples in Future Research**

The participant may withdraw consent for use of samples for research (refer to Section 10.3.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

## 7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

# 8. STUDY ASSESSMENTS AND PROCEDURES

**Overview**

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study.

All visit-specific PRO assessments must be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses. When multiple assessments are scheduled for the same timepoint, it is recommended that PROs be completed in the following sequence: Patient's Global Assessment (PtGA) of Disease Activity, Pain visual analog scale (VAS), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) assessment, Joint Pain Severity Numeric Rating Scale (NRS), Health Assessment Questionnaire – Disability Index (HAQ-DI), and 36-item Short Form Health Survey (SF-36).

It is recommended that clinician-reported outcome (ClinRO) assessments be performed in the following sequence: joint assessment, duration of morning stiffness, and Physician's Global Assessment (PGA) of Disease Activity. ClinRO assessments should be performed by an adequately trained assessor (see Section 8.1 for details).

Additional urine pregnancy tests may be performed (as determined necessary by the investigator or required by local regulation) to establish the absence of pregnancy at any time during the participation in the study.

**Screening Phase**

The screening phase is up to 6 weeks duration before randomization. After written informed consent has been obtained, all screening evaluations (eg, laboratory test results, clinical data, and concomitant medication data) that establish participant eligibility will be performed by the principal investigator or designee to confirm that the participant satisfies all inclusion criteria and does not violate any exclusion criteria. Participants who meet all of the inclusion and none of the exclusion criteria can be enrolled in the study. Every effort should be made to adhere to the SoA (Section 1.3) for each participant. The collection of AEs will start at the time informed consent is obtained.

Women of childbearing potential must have a negative urine pregnancy test result at screening and at each visit and before any study intervention administration. Participants must be reminded that they are required to use a highly effective method of contraception during the study and must continue taking such precautions for 30 days after receiving the last dose of study intervention (as described in Section 5.1 and Section 10.5). The method(s) of contraception used by each participant must be documented.

All screening evaluations establishing participant eligibility will be performed and reviewed by the investigator before a participant can be randomized. Participants must have received approval for study randomization following assessment of inclusion and exclusion criteria.

**Blood Sample Collection**

The total blood volume to be collected from each participant over 12 weeks will be approximately 300 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

**Sample Collection and Handling**

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the SoA for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

**Study-Specific Materials**

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and nipocalimab IB)
- Study SIPPM and IPPI
- Sample ICFs
- Laboratory Manual(s) and laboratory kits
- IWRS Manual
- eCRF completion instructions
- Electronic ClinRO and/or PRO equipment (tablet device questionnaires, completion instructions)
- Actigraphy device and instruction for use
- Patient recruitment materials
- Procedural Manual for major adverse cardiovascular events (MACE) Adjudication

## 8.1. Efficacy Assessments

Patient-reported outcomes and investigator assessments of efficacy are included in this section.

It is strongly recommended that the same clinical assessor perform the clinical assessments at every visit.

- The PRO instrument will be provided in the local language in accordance with local guidelines.

- The PRO instrument will be available for regulators and for IRB/IEC submissions and will be provided separately in a companion manual with the instruments that will be submitted with the protocol.
- The PRO and AE data will not be reconciled with one another.

### 8.1.1. Evaluations

#### 8.1.1.1. Patient's and Physician's Global Assessment of Disease Activity

The Patient's and Physician's Global Assessments of Disease Activity (Anderson 2011; Felson 1995) will be recorded on a VAS. The scale for the participant's assessment ranges from "very well" to "very poor." The scale for the physician's assessment ranges from "no arthritis activity" to "extremely active arthritis." The evaluating physician and participant must complete the global assessment independently of each other. The physician should preferably be the same person at every study visit for a given participant.

#### 8.1.1.2. Pain Assessment

Participants will be asked to assess their average pain during the past week on a VAS. The scale ranges from "no pain" to "the worst possible pain." This assessment should be completed prior to the joint examination. The validity of this assessment has been evaluated and reviewed extensively as it is a component of the ACR response score (Felson 1993; Hawley 1992).

#### 8.1.1.3. Functional Assessment of Chronic Illness Therapy-Fatigue

The FACIT-Fatigue assessment (version 4.0) is a 13-item questionnaire formatted for participant self-administration that assesses patient-reported fatigue and its impact upon daily activities and function over the past 7 days. Participants will be asked to answer each question using a 5-point Likert-type scale (0=Not at all; 1=A little bit; 2=Somewhat; 3=Quite a bit; and 4=Very Much). The interpretation of FACIT-Fatigue score is such that a higher score indicates less fatigue, with a range of possible scores of 0-52, with 0 being the worst possible score and 52 the best. The FACIT-Fatigue can generally be completed in 5 minutes (Cella 2002; Yellen 1997).

FACIT-Fatigue has been used in clinical trials of participants with RA and has demonstrated sensitivity to change in these participants (Smolen 2008; Yount 2007).

#### 8.1.1.4. Joint Pain Severity NRS

Participants' joint pain will be assessed using a single item that asks the participant to report the worst severity of their joint pain over the past 7 days on a 0 to 10 NRS. Responses range from 'No joint pain' (0) to 'Severe joint pain' (10).

#### 8.1.1.5. Health Assessment Questionnaire – Disability Index

The functional status of the participant will be assessed using the HAQ-DI (Fries 1980). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored from 0, indicating no difficulty, to 3,

indicating inability to perform a task in that area. A score change of (-0.22) is considered the minimum threshold for a clinically important improvement (Kosinski 2000; Pope 2009; Wells 1993).

#### 8.1.1.6. 36-item Short Form Health Survey (Standard)

The SF-36 version 2 Standard health survey is a self-administered, 36-item questionnaire measuring health-related quality of life, with a recall period of the past 4 weeks. It includes 8 domains that measure physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. The 8 domains can be aggregated into 2 summary scales that reflect physical and mental health: a physical component scale (PCS) and a mental component score (MCS). Responses to all items are rated on a 3-, 5- or 6-point Likert scale. The SF-36 version 2 Standard survey can generally be completed in 5 to 10 minutes (Quality Metric 2011).

#### 8.1.1.7. Joint Assessments

**Joint Assessor**

Each of 68 joints will be evaluated for tenderness, and each of 66 joints will be evaluated for swelling (hips are excluded for swelling). All joints will be examined at visits as indicated in the SoA (Section 1.3). It is recommended that the joint assessor should not be changed during the study.

The joint assessment should be performed by adequately trained joint assessor. Training on how the joint count will be performed will be provided by the sponsor. The joint assessor should be a rheumatologist or a health care provider with at least 1 year of experience in performing joint assessments. A health care provider with less than 1 year of experience may serve as a joint assessor based on the approval of the sponsor. The same assessor should perform joint assessments at every visit. It is recommended that the designated joint assessor identify an appropriate backup joint assessor in case the designated joint assessor is unavailable.

**Nonevaluable Joints**

Joints should only be designated as “non-evaluable” by the joint assessor on the Joint Assessment Worksheet *if it is physically impossible to assess the joint* (ie, joint inaccessible due to a cast, joint was replaced, joint not present due to an amputation, joint deformed so as to make it impossible to assess). In all other cases, the joint assessor should assess each joint for tenderness and swelling (hips are excluded for swelling) and complete the worksheet with their assessments. This should be completed regardless of any visual indications of prior surgical procedures (eg, scars) or knowledge they may have of a participant’s prior joint procedures/injections (eg, if the participant was the joint assessor’s patient prior to study participation).

#### 8.1.1.8. Duration of Morning Stiffness

The average duration of morning stiffness during the previous week in minutes will be assessed. If a participant has stiffness that lasts the entire day, this should be recorded as 1440 minutes of morning stiffness.

### 8.1.2. Definitions

#### 8.1.2.1. Disease Activity Index Score 28

##### 8.1.2.1.1. DAS28 Using C-reactive Protein

The DAS28-CRP is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP, and PtGA of Disease Activity (van Riel 2000). The DAS28-CRP is a continuous parameter and is defined as follows:

DAS28-CRP = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.36 × ln (CRP+1) + 0.014 × GH + 0.96 where:

- The set of 28 joint count is based on evaluation of the shoulder, elbow, wrist, metacarpophalangeal (MCP) 1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP) 1, PIP2, PIP3, PIP4, PIP5 joints of both the upper right extremity and the upper left extremity as well as the knee joints of lower right and lower left extremities
- TEN28 is 28-joint count for tenderness
- SQRT(TEN28) is square root of TEN28
- SW28 is 28-joint count for swelling
- SQRT(SW28) is square root of SW28
- Ln (CRP+1) is natural logarithm of (CRP value [mg/L] + 1)
- GH is PtGA of Disease Activity on a VAS of 100 mm

##### 8.1.2.1.2. DAS28 Using Erythrocyte Sedimentation Rate

The Disease Activity Index Score 28 using erythrocyte sedimentation rate (DAS28-ESR) is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), erythrocyte sedimentation rate (ESR), and GH (Prevoo 1995). It is a continuous parameter and is defined as follows:

DAS28-ESR = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.70 × ln (ESR) + 0.014 × GH

- The set of 28 joint count is based on evaluation of the shoulder, elbow, wrist, MCP1, MCP2, MCP3, MCP4, MCP5, PIP1, PIP2, PIP3, PIP4, PIP5 joints of both the upper right extremity and the upper left extremity as well as the knee joints of lower right and lower left extremities
- TEN28 is 28-joint count for tenderness
- SQRT(TEN28) is square root of TEN28
- SW28 is 28-joint count for swelling
- SQRT(SW28) is square root of SW28
- Ln (ESR) is natural logarithm of ESR
- GH is PtGA of Disease Activity on a VAS of 100 mm

#### 8.1.2.1.3. DAS28 Response

DAS28 response is defined in Table 3 (van Riel 2000).

**Table 3: DAS28 Response Criteria**

| | Improvement from Baseline | | |
|---|---|---|---|
| **DAS28 at the visit** | **>1.2** | **>0.6 and ≤1.2** | **≤0.6** |
| ≤3.2 | Good response | Moderate response | No response |
| >3.2 and ≤5.1 | Moderate response | Moderate response | No response |
| >5.1 | Moderate response | No response | No response |

Abbreviation: DAS28= Disease Activity Index Score 28

#### 8.1.2.1.4. DAS28 Low Disease Activity

DAS28 LDA is defined as a DAS28 value of ≥2.6 and ≤3.2 at a visit.

#### 8.1.2.1.5. DAS28 Remission

DAS28 remission is defined as a DAS28 value of <2.6 at a visit.

### 8.1.2.2. American College of Rheumatology Response

ACR responses are presented as the numeric measurement of improvement in multiple disease assessment criteria. For example, an ACR20 response (Felson 1995) is defined as:

1. ≥20% improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints)

   AND

2. ≥20% improvement from baseline in 3 of the following 5 assessments:
   - Patient's Global Assessment of Disease Activity (VAS)
   - Patient's assessment of pain (VAS)
   - Patient's assessment of physical function as measured by HAQ-DI
   - Physician's Global Assessment of Disease Activity (VAS)
   - CRP

ACR50, ACR70, and ACR90 are similarly defined except improvement threshold from baseline is 50%, 70%, and 90%, respectively.

### 8.1.2.3. Clinical Disease Activity Index Score

The Clinical Disease Activity Index (CDAI) score is a derived score combining tender joints (28 joints), swollen joints (28 joints), PtGA of Disease Activity, and PGA of Disease Activity (Aletaha 2006).

The CDAI score is defined as follows:

CDAI = TEN28 + SW28 + GH + PGH where:

- TEN28 and SW28 were defined the same as in Section 8.1.2.1
- GH is PtGA of Disease Activity (VAS)
- PGH is PGA of Disease Activity (VAS)

**CDAI Low Disease Activity**

CDAI LDA is defined as a CDAI score of ≤10 at a visit.

**CDAI Remission**

CDAI remission is defined as a CDAI score of <2.8 at a visit.

### 8.1.2.4. Simplified Disease Activity Index Score

The Simplified Disease Activity Index (SDAI) for RA score is a derived score combining tender joints (28 joints), swollen joints (28 joints), PtGA of Disease Activity, PGA of Disease Activity, and CRP (Aletaha 2006).

The SDAI score is defined as follows:

SDAI = TEN28 + SW28 + GH + PGH + CRP (mg/dL) where:

- TEN28 and SW28 were defined the same as in Section 8.1.2.1
- GH is Patient's Global Assessment of Disease Activity (VAS)
- PGH is Physician's Global Assessment of Disease Activity (VAS)

*Note*: SDAI is the same as CDAI, except that CRP is included.

**SDAI Low Disease Activity**

SDAI LDA is defined as a SDAI score of ≤5.5 at a visit.

### 8.1.2.5. ACR/EULAR Remission

**Simple Disease Activity Index-based ACR/EULAR Remission**

SDAI-based ACR/EULAR remission is defined as a SDAI value of ≤ 3.3 at a visit (Felson 2011).

**Boolean-Based ACR/EULAR Remission**

A participant is considered as having achieved the Boolean-based ACR/EULAR remission at a visit if he/she meets all of the following 4 criteria at that visit (Felson 2011):

- Tender joint count (68 joints) ≤1
- Swollen joint count (66 joints) ≤1

- CRP ≤1 mg/dL
- PtGA of Disease Activity on VAS ≤1 (on a 0 to 10 scale)

## 8.2. Safety Assessments

Details regarding the DMC are provided in Section 10.3.6.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Section 10.4.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3).

### 8.2.1. Physical Examinations

Physical examinations will be performed by the investigator or designated physician, nurse practitioner or physician assistant as specified in the SoA (Section 1.3). Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

The full physical examination will be performed including: the head and neck, chest, abdomen, and extremities, as well as including examinations based on the individual's medical history and manifestations of RA.

The targeted physical examination (performed at visits not specified for full physical exams) based on a participant's RA history and manifestations should also include evaluation of signs or symptoms of infection.

Specific assessment of RA-related signs and symptoms will be performed by a clinical assessor as described in Section 8.1 and at timepoints specified in the SoA (Section 1.3).

Assessment of the participants for safety may require some physical examination by an investigator.

**Height and Weight**

Height and weight will be measured as specified in the SoA (Section 1.3). Participants will be instructed to remove shoes and outdoor apparel and gear prior to this measurement.

### 8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, and blood pressure (BP) will be assessed at each visit.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

If feasible, BP and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

At a study intervention administration visit, vital signs should be obtained before and 30 minutes after completion of the IV infusions, or if the participant reports any symptoms.

### 8.2.3. Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed at screening. Subsequent ECGs can be performed locally based on investigator's judgment.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

### 8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, coagulation, serology, lipid panel, and other safety laboratory assessments will be collected as noted in Section 1.3. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor or designee:

- Hematology assessments
- Blood chemistry assessments
- Urine assessments
- Coagulation assessment
- Serology assessments
- Lipid panel assessments

A medical monitor or designee and the clinical site will be notified if pre-specified abnormal laboratory values defined in the Laboratory Manual are identified in any participant during the conduct of the study.

### 8.2.5. Pregnancy Testing

Urine pregnancy testing will be done for women of childbearing potential only (performed locally), see definition in Section 10.5. Additional urine pregnancy tests may be performed, if applicable, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

### 8.2.6. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

### 8.2.7. Adverse Events Temporally Associated with Infusion

Any AE (except laboratory abnormalities) that occurs during or within the observation period after the IV infusion of study intervention will be carefully evaluated. Participants will be observed for safety for 1 hour postinfusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed with these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions.

### 8.2.8. Infusion Reactions

An infusion reaction is defined as any AE that is reported by investigator to represent an infusion reaction.

Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study intervention is interrupted because of an AE that, in the opinion of the investigator, is not severe or does not result in an SAE, the infusion may be restarted with caution.

### 8.2.9. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications (eg, antihistamines, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension). Potential cases of anaphylaxis should be assessed according to Sampson's criteria (Section 10.9).

In the case of a severe allergic reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available when study intervention is being administered. Participants who experience a severe infusion reaction/allergic reaction, assessed by the investigator as being related to study intervention, must be discontinued from further study intervention administrations.

### 8.2.10. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits. Study intervention administration should not be given to a participant with a clinically significant, active infection. Study intervention must be discontinued if a participant

develops any serious infection (ie, that meets criteria for a serious AE), or develops a moderate or severe opportunistic infection or develops an infection that is unresponsive or worsening while on anti-infective therapy (Section 7.1).

#### 8.2.11. Increased Lipids

Lipids levels are routinely monitored in participants throughout the study.

In participants with elevated lipids at any time during the study, it is recommended that investigators initiate or continue appropriate therapy for dyslipidemia per local health guidelines. In participants with persistently elevated lipids (above LDL threshold of 190 mg/dL or the triglyceride threshold of 1000 mg/dL), it is strongly recommended that investigators initiate appropriate therapy or modify current therapy for dyslipidemia per local health guidelines.

### 8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and Product Quality Complaints (PQCs), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQCs can be found in Section 10.4.

#### 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

**All Adverse Events**

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

All AEs with an onset date after the signing of the ICF and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the eCRF.

**Serious Adverse Events**

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within by the final safety visit after the last dose of study intervention, must be reported. The sponsor will

evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All SAEs occurring after signature of the ICF up to 30 days after study treatment discontinuation must be reported on AE pages in the eCRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study mandated procedures.

A **possible Hy's Law Case** is defined by the occurrence of ALT/AST ≥3×ULN, alkaline phosphatase <2×ULN together with total bilirubin ≥2×ULN or International Normalized Ratio (INR) >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported to the sponsor within 24 hours, even before all other possible causes of liver injury have been excluded.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and signed by a physician from the study site and transmitted to the sponsor immediately, but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

Selected events including potential MACE will undergo adjudication by an Event Adjudication Committee (EAC). For such events, Investigators will be asked to provide specific package of information for evaluation. Further details will be provided in a procedural manual. The EAC will assess such events according to the committee's charter and will independently classify the events while blinded to treatment assignment.

### 8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 8.3.3. Follow-up of Adverse Events and Serious Adverse Events

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

Adverse events and the special reporting situation of pregnancy, will be followed by the investigator as specified in Section 10.4.

### 8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the

appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, the following SAE will be considered an anticipated event: worsening of RA.

This anticipated event will be periodically analyzed by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group, and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated event is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated event according to the requirements of the countries in which the studies are conducted.

### 8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of a male participant and his partner, and any postnatal sequelae in the infant will be required (see Section 10.5 and Section 10.4).

### 8.3.6. Adverse Events of Special Interest

Treatment-emergent AEs associated with the following situations are considered to be AESIs:

1. Infections that are severe or require IV anti-infective or operative/invasive intervention.
2. CCI [redacted]

These AEs occurring after the first administration(s) of study intervention in participants in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Section 10.4. These events are to be considered serious only if they meet the definition of an SAE.

**Observation Time After Each Infusion**

Participants will be observed for safety 1-hour postinfusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions.

## 8.4. Pharmacokinetics

Serum samples will be used to evaluate the PK of nipocalimab as well as the immunogenicity of nipocalimab (antibodies to nipocalimab). Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

### 8.4.1. Evaluations

Venous blood samples will be collected at the time points shown in the SoA (Section 1.3) for measurement of serum nipocalimab concentrations and antibodies to nipocalimab.

Serum samples will also be collected at the final visit from participants who terminate study participation early. At visits where PK and immunogenicity will be evaluated, 1 blood draw of sufficient volume can be used. Each sample will be split into 3 aliquots (1 aliquot for serum nipocalimab concentration, 1 aliquot for antibodies to study intervention, and 1 aliquot as a backup). Samples must be collected before study intervention administration at visits when a study intervention administration is scheduled. At Week 0, Week 2, and Week 8, a blood sample before study intervention administration and another blood sample 45 minutes after the end of infusion will be collected. The sample should be drawn from the opposite arm than the IV line.

CCI [redacted]

The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

### 8.4.2. Analytical Procedures

**Pharmacokinetics**

Serum samples will be analyzed to determine serum nipocalimab concentrations using a validated, specific, and sensitive immunoassay method by the sponsor's bioanalytical facility or under the supervision of the sponsor. The sponsor, or its designee, under conditions in which the participants' identity remains blinded, will assay these samples.

### 8.4.3. Pharmacokinetic Parameters and Evaluations

**Parameters**

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of nipocalimab will be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant.

## 8.5. Genetics and Pharmacogenomics

Participation in pharmacogenomic research is optional. A pharmacogenomic blood sample may be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit.

Genetic (DNA) variation may be an important contributory factor to interindividual variability in drug response and associated clinical outcomes. Genetic and epigenetic factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to an intervention.

The optional pharmacogenomic samples may be analyzed for identification of genetic and epigenetic factors that may be associated with the disease and/or the response to the treatments. This research may consist of the analysis of one or more candidate genes, or the analysis of genetic and epigenetic markers throughout the genome, or analysis of the entire genome (as appropriate) in relation to the disease and the treatments. CCI [redacted]

## 8.6. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to nipocalimab treatment and/or RA, where local regulations permit. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, plasma, whole blood, and urine collected as specified in the SoA (Section 1.3), where local regulations permit.

Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of nipocalimab.
2. To understand RA pathogenesis.
3. To understand why individual participants may respond differently to nipocalimab.
4. To understand the impact of treatment with nipocalimab on RA or systemic inflammation.
5. To develop diagnostic tests to identify RA populations that may be responsive or nonresponsive to treatment with nipocalimab.

**Stopping Analysis**

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

### 8.6.1. Pharmacodynamics

Samples for the analysis of PD biomarkers will be collected from all participants, where local regulations permit. Serum concentrations of total IgG, IgG1, IgG2, IgG3, IgG4, albumin, ACPA, RF, and CICs will be measured to assess the PD effect of nipocalimab.

### 8.6.2. Serum and Plasma Biomarkers

Blood samples for serum and plasma biomarker analyses will be collected from all participants. Serum and plasma will be analyzed for levels of specific proteins, and other inflammation-related molecules and/or disease-associated serologies relevant to RA and treatment and response to nipocalimab.

### 8.6.3. Whole Blood Gene Expression Profile

CCI

[redacted]

### 8.6.4. Peripheral Blood Mononuclear Cells

CCI

[redacted]

### 8.6.5. Exploratory Biomarkers

CCI

[redacted]

CCI

[redacted]

## 8.7. Immunogenicity Assessments

Antibodies to nipocalimab will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to nipocalimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to nipocalimab and/or further characterize the immunogenicity of nipocalimab (such as for the incidence of NAbs).

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

**Analytical Procedures**

The detection and characterization of antibodies to nipocalimab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to nipocalimab will also be evaluated for serum nipocalimab concentrations to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored up to 1 month after approval of the final Clinical Study Report (CSR) (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to nipocalimab.

## 8.8. Medical Resource Utilization and Health Economics

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

# 9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

## 9.1. Statistical Hypotheses

Treatment with nipocalimab 15 mg/kg q2w is superior to placebo in participants with moderate to severe active RA as measured by the mean change from baseline in DAS28-CRP at Week 12.

## 9.2. Sample Size Determination

CCI

[redacted]

**Table 4: Statistical Power for Treatment Difference in Change from Baseline in DAS28-CRP at Week 12**

CCI

[redacted]

## 9.3. Populations for Analysis Sets

CCI

[redacted]

## 9.4. Statistical Analyses

The SAP will be finalized prior to the Week 12 DBL 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.

### 9.4.1. General Considerations

In general, descriptive statistics, such as mean, standard deviation, median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

For binary response efficacy endpoints, treatment comparisons will generally be performed using a Chi-square test or a Cochran-Mantel-Haenszel test. For continuous efficacy endpoints, treatment comparisons will be performed using an analysis of covariance, a Mixed-Effect Model Repeated Measure (MMRM) model, or a constrained longitudinal data analysis model.

In general, all statistical tests will be performed using a 2-sided test at a significance level of 5%. No multiplicity adjustment will be made for secondary endpoints; nominal p-values will be reported.

### 9.4.2. Primary Endpoint

**Definition of the Primary Endpoint**

The primary endpoint is the mean change from baseline in DAS28-CRP compared with placebo at Week 12.

**Primary Estimand**

The primary endpoint will be analyzed based on the composite estimand defined by the following 5 components:

- **Population:**

  Participants between the ages of 18 and 75, inclusive, with moderate to severe active RA despite standard therapy, including anti-TNF agents.

- **Treatment:**
  - Control: Placebo IV q2w
  - Nipocalimab (experimental treatment/intervention) 15 mg/kg IV q2w
- **Variable:**

  Change from baseline in DAS28-CRP at Week 12. A participant who initiates or adjusts medication or discontinues or experiences an intercurrent event (ICE) in categories 1, 2, or 3 (defined below) during treatment prior to the Week 12 visit will be considered a treatment failure and will be assigned a zero change from baseline in the DAS28-CRP score, regardless of the observed change. For a participant who experiences an ICE in category 4 (defined below), the observed change from baseline in the DAS28-CRP score will not be used and will be assumed to follow a Missing-at-Random (MAR) assumption.

- **Intercurrent Events and Corresponding Strategies:**

1. Initiated protocol-prohibited medications/therapies for RA
2. Initiation or increased the dose of csDMARDs (such as MTX, SSZ, HCQ, CQ or leflunomide) or oral corticosteroid therapy above the baseline dose for RA
3. Discontinued study intervention infusion due to any reason, including COVID-19 infection but excluding other COVID-19 reasons
4. Treatment discontinuation due to study conduct affected by other COVID-19 reasons such as site closure/restricted access

ICEs in categories 1, 2, and 3 will be considered treatment failures and will be handled with the composite strategy to be include in the variable. ICE category 4 will be handled with the hypothetical strategy as if the ICE would not have occurred. For participants experiencing multiple ICEs, an ICE in category 1, 2, or 3 will supersede an ICE in category 4. For participants experiencing multiple ICEs, an ICE in category 1 will supersede an ICE in category 4.

- **Population-level summary:**

  Difference in mean between the nipocalimab group and the placebo group.

**Primary Efficacy Analysis**

In the primary efficacy analysis, data from all participants in the FAS will be analyzed according to randomized treatment group regardless of the treatment received. Missing data will be assumed as MAR. A MMRM model will be used to test the difference between the nipocalimab group and the placebo group at Week 12. The explanatory variables of the MMRM model will include treatment group, and interaction terms of visit with treatment group, baseline score and randomization stratification factors. An unstructured covariance matrix for repeated measure within a participant will be used. Other structured covariances matrix will be defined in the SAP in case of lack of convergence. The Least Square Mean difference and 95% confidence intervals between each nipocalimab group versus the placebo group will be provided.

The comparison between the nipocalimab and placebo group for the primary endpoint will be tested at a 2-sided α level of 0.05.

To evaluate the robustness of the primary endpoint analysis, sensitivity/supplementary analyses will be conducted. Details will be specified in SAP.

Subgroup analysis will be performed to evaluate consistency in the primary efficacy endpoint by demographic characteristics, baseline disease characteristics, and prior and baseline medications. Interaction test between the subgroups and treatment group will also be provided if appropriate.

### 9.4.3. Secondary Endpoints

The secondary endpoints are listed in Section 3.

Data from all participants in the FAS will be analyzed according to randomized treatment group regardless of the treatment received.

Details of the analysis of the secondary endpoints will be included in SAP.

### 9.4.4. Other Secondary Endpoints

#### 9.4.4.1. Pharmacokinetic Analyses

Serum nipocalimab concentrations over time will be summarized for each treatment group using descriptive statistics. All concentrations below the lowest quantifiable sample concentration of the assay or missing data will be labeled as such in the concentration data listing or statistical analysis dataset. The lowest quantifiable sample concentration of the assay will be treated as zero in the summary statistics. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention, missing information of dosing and sampling times).

If sufficient data are available, a population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of nipocalimab. The apparent total systemic clearance and apparent volume of distribution values will be estimated. The influence of important variables (eg, body weight, antibodies to nipocalimab, and concomitant medications if relevant) on the population PK parameter estimates may be evaluated. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate technical report.

#### 9.4.4.2. Immunogenicity Analyses

The incidence and titers of antibodies to nipocalimab will be summarized for all participants who received at least 1 administration of nipocalimab and have appropriate samples for detection of antibodies to nipocalimab (ie, participants with at least 1 sample obtained after their first dose of nipocalimab). The incidence of NAbs to nipocalimab will be summarized for participants who are positive for antibodies to nipocalimab and have samples evaluable for NAbs.

A listing of participants who are positive for antibodies to nipocalimab will be provided. The maximum titers of antibodies to nipocalimab will be summarized for participants who are positive for antibodies to nipocalimab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

### 9.4.5. Safety Analyses

All safety analyses will be made on the Safety Analysis Set population (Section 9.3). Participants will be summarized by the treatment they actually received.

**Adverse Events**

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Any AE occurring at or after the initial administration of study intervention through the safety follow-up visit is considered to be treatment-emergent. All reported TEAEs will be included in the analysis. For each AE, the

percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparison between intervention groups will be provided if appropriate.

The following analyses will also be used to assess the safety of participants in the study:

- Proportion of participants with treatment-emergent AEs
- Proportion of participants with treatment-emergent SAEs
- Proportion of participants with treatment-emergent AEs leading to discontinuation of study intervention
- Proportion of participants with treatment-emergent AESIs
- Laboratory parameters and change from baseline in laboratory parameters over time
- Vital sign parameters and change from baseline in vital sign parameters over time

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE. Listings of all participants with MACE (nonfatal MI, stroke, and cardiovascular death) will be provided.

**Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for selected laboratory analytes at baseline and for changes over time.

**Vital Signs**

Vital signs including temperature, pulse/heart rate, respiratory rate, and BP (systolic and diastolic) will be summarized over time, using descriptive statistics. The percentage of participants with values beyond clinically important limits will be summarized.

### 9.4.6. Exploratory Endpoints

All exploratory endpoints are listed in Section 3.

### 9.4.7. Other Analyses

**Biomarkers Analyses**

CCI

CCI

[redacted]

## 9.5. Interim Analysis

CCI

[redacted]

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Abbreviations

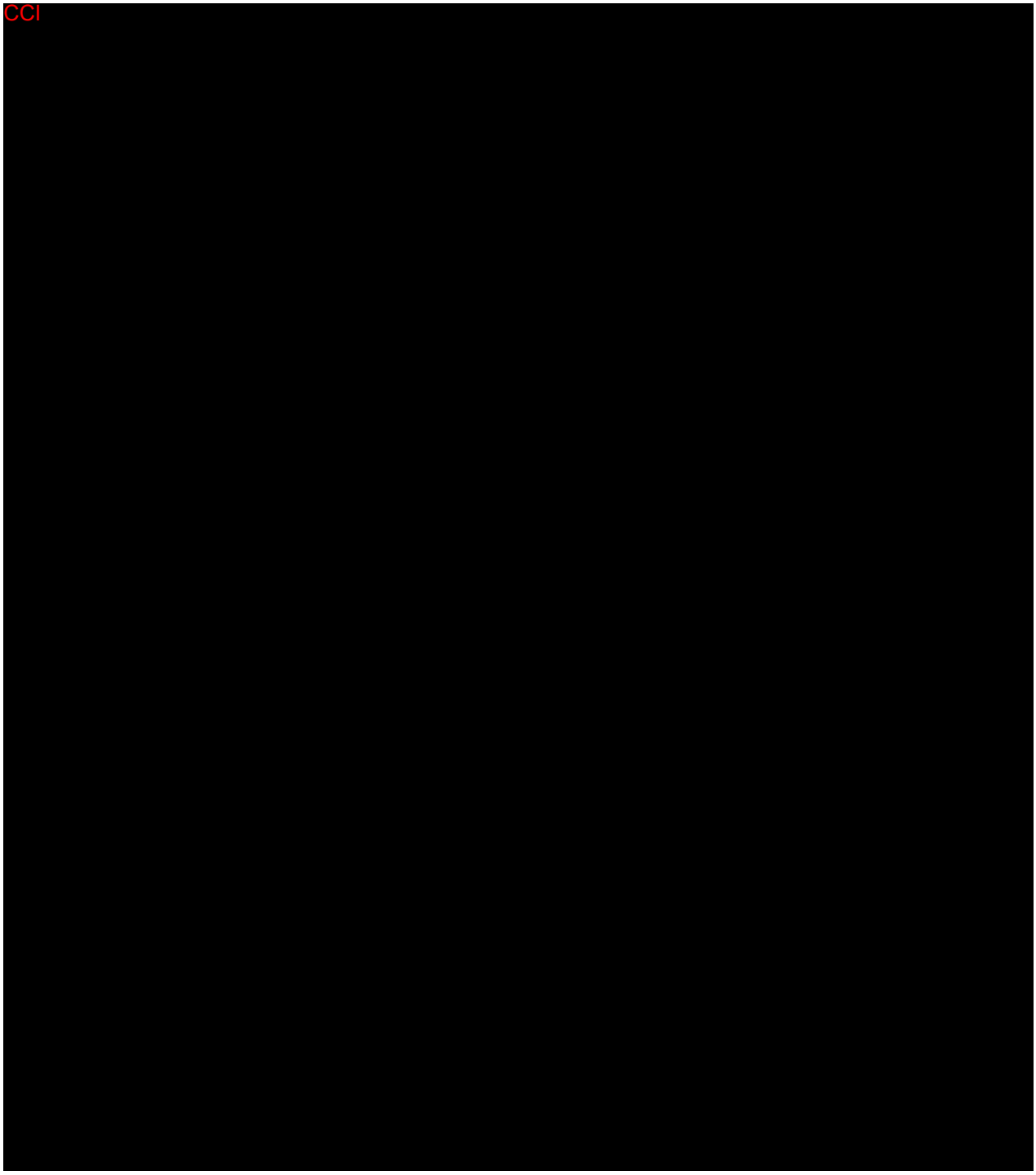
| | |
|---|---|
| ACPA | anti-citrullinated protein antibodies |
| ACR | American College of Rheumatology |
| ADA | anti-drug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| β-hCG | β-human chorionic gonadotropin |
| BP | blood pressure |
| CDAI | Clinical Disease Activity Index |
| CIC | circulating immune complex |
| ClinRO | clinician-reported outcome |
| COVID-19 | Coronavirus (Disease) 2019 |
| CPK | creatine phosphokinase |
| CQ | chloroquine |
| CRP | C-reactive protein |
| csDMARD | conventional synthetic disease-modifying anti-rheumatic drug |
| CSR | clinical study report |
| DAS28-CRP | Disease Activity Index Score 28 using C-reactive protein |
| DAS28-ESR | Disease Activity Index Score 28 using erythrocyte sedimentation rate |
| DBL | database lock |
| DMARD | disease-modifying anti-rheumatic drug |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eDC | electronic data capture |
| EOS-HDFN | early onset severe hemolytic disease of the fetus and newborn |
| ESR | erythrocyte sedimentation rate |
| EULAR | European League Against Rheumatism |
| FACIT-Fatigue | Functional Assessment of Chronic Illness Therapy – Fatigue Scale |
| FAS | Full Analysis Set |
| FcRn | neonatal Fc receptor |
| FIH | first-in-human |
| FOIA | Freedom of Information Act |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| gMG | generalized myasthenia gravis |
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| HBV | hepatitis B virus |
| HCQ | hydroxychloroquine |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HRT | hormone replacement therapy |
| IA | interim analysis |
| IAC | Interim Analysis Committee |
| IB | Investigator's Brochure |
| IC | immune complex |
| ICE | intercurrent event |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |

| | |
|---|---|
| Ig | immunoglobulin |
| IL | interleukin |
| IM | intramuscular |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |
| IPPI | Investigational Product Preparation and Administration Instructions |
| IR | inadequate response |
| IRB | Institutional Review Board |
| IV | intravenous(ly) |
| IWRS | interactive web response system |
| JAKi | janus kinase inhibitors |
| LDA | low disease activity |
| LDL | low-density lipoprotein |
| mAb | monoclonal antibody |
| MACE | major adverse cardiovascular event |
| MAD | multiple ascending dose(s) |
| MAR | Missing-at-Random |
| MCP | metacarpophalangeal |
| MCS | mental component score |
| MG-ADL | Myasthenia Gravis – Activities of Daily Living |
| MI | myocardial infarction |
| MMRM | Mixed-Effect Model Repeated Measure |
| MTX | methotrexate |
| NAb | neutralizing antibody |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NIMP | Non-Investigational Medicinal Product |
| NRS | Numeric Rating Scale |
| NSAID | nonsteroidal anti-inflammatory drug |
| PCC | protocol clarification communication |
| PCS | physical component score |
| PD | pharmacodynamic(s) |
| PEF | peak expiratory flow |
| PGA | Physician's Global Assessment (of Disease Activity) |
| PIP | proximal interphalangeal |
| PK | pharmacokinetic(s) |
| PO | oral (by mouth) |
| PQC | Product Quality Complaint |
| PRO | patient-reported outcome |
| PtGA | Patient's Global Assessment (of Disease Activity) |
| q2w | every 2 weeks |
| q4w | every 4 weeks |
| RA | rheumatoid arthritis |
| RBC | red blood cell |
| RF | rheumatoid factor |
| RNA | ribonucleic acid |
| RO | receptor occupancy |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SC | subcutaneous(ly) |
| SDAI | Simple Disease Activity Index (for Rheumatoid Arthritis) |
| SF-36 | 36-item Short Form Health Survey |
| SI | International System of Units |
| SIPPM | Site Investigational Product Procedures Manual |
| SoA | Schedule of Activities |
| SOC | standard-of-care |
| SSZ | sulfasalazine |

| | |
|---|---|
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TNF | tumor necrosis factor |
| ULN | upper limit of normal |
| VAS | visual analog scale |
| wAIHA | warm autoimmune hemolytic anemia |
| WBC | white blood cell |

## 10.2. Appendix 2: Clinical Laboratory Tests

CCI



CCI

[redacted]

## 10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

### 10.3.1. Regulatory and Ethical Considerations

**Investigator Responsibilities**

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

**Protocol Clarification Communications**

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

**Protocol Amendments**

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree

on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

**Regulatory Approval/Notification**

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

**Required Pre-study Documentation**

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

**Independent Ethics Committee or Institutional Review Board**

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

**Country Selection**

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.5, Study-Specific Ethical Design Considerations.

**Other Ethical Considerations**

For study-specific ethical design considerations, refer to Section 4.2.5.

### 10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations 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.

Refer to Required Pre-study Documentation (above) for details on financial disclosure.

### 10.3.3. Informed Consent Process

Each participant (or a legally acceptable representative) must give consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent must be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

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

Participants will be asked for consent to provide optional samples for research where local regulations permit. After informed consent for the study is appropriately obtained, the participant or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

Where local regulations require, a separate ICF will be used for the required DNA component of the study.

### 10.3.4. Data Protection

**Privacy of Personal Data**

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory DNA, PD, biomarker, PK, and immunogenicity] research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

### 10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand nipocalimab to understand RA, to understand differential intervention responders, and to develop tests/assays related to nipocalimab and RA. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

### 10.3.6. Committees Structure

**Interim Analysis Committee**

An internal unblinded IAC will be established to review IA data, as specified in Section 9.5. This committee will consist of physicians, statisticians, clinical pharmacologists, and pharmacometricians unaffiliated with the study; committee membership responsibilities, authorities, and procedures will be documented in its charter.

Further details of the interim analysis will be provided in the IAC SAP/Charter.

**Data Monitoring Committee**

An external DMC will be established to monitor data on an ongoing basis. This committee will consist of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician; committee membership responsibilities, authorities, and procedures will be documented in the combined DMC charter. The committee will meet periodically to review interim data through the Week 18 DBL. For the scheduled safety reviews, the DMC will make a recommendation to the sponsor whether the study should continue, be modified, or stopped for safety concerns.

Further details of the safety reviews will be provided in the DMC SAP/Charter.

### 10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding nipocalimab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of nipocalimab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a CSR generated by the sponsor and will contain data from all study sites that participated in the study per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses

performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Registration of Clinical Studies and Disclosure of Results**

The sponsor will register and disclose interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of the study to ensure the statistical analyses are relevant.

### 10.3.8. Data Quality Assurance

**Data Quality Assurance/Quality Control**

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and

study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor may review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

### 10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

### 10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents must be identifiable. Given that PROs are reports of a participant's health condition that come directly from the participant, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Information collected at unscheduled visits should be documented as described for scheduled visits.

The minimum source documentation requirements for Section 5.1 and Section 5.2 that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data are electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

### 10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

### 10.3.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

### 10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

### 10.3.14. Study and Site Start and Closure

**First Act of Recruitment**

The first participant screened is considered the first act of recruitment and it becomes the study start date.

**Study/Site Termination**

The sponsor 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:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

## 10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.4.1. Adverse Event Definitions and Classifications

**Adverse Event**

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal product (IMP or NIMP), whether or not related to that medicinal product (IMP or NIMP). (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

**Serious Adverse Event**

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment must be exercised in deciding whether expedited reporting is also 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 intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

**Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For nipocalimab, the expectedness of an AE will be determined by whether or not it is listed in the IB. For SOC background therapies with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

### 10.4.2. Attribution Definitions

**Assessment of Causality**

The causal relationship to study intervention is assessed by the investigator. The following selection must be used to assess all AEs.

**Related**

There is a reasonable causal relationship between study intervention administration and the AE.

**Not Related**

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

### 10.4.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

**Mild**: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Moderate**: Sufficient discomfort is present to cause interference with normal activity.

**Severe**: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

### 10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Special reporting situations must be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the eCRF.

### 10.4.5. Procedures

**All Adverse Events**

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

**Serious Adverse Events**

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves

- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience, the investigator may choose to hospitalize the participant for the duration of the intervention period.

The cause of death of a participant in a study within 8 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

### 10.4.6. Product Quality Complaint Handling

**Definition**

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

**Procedures**

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

### 10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues, PQCs, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

## 10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4.

**Definitions**

***Woman of Childbearing Potential (WOCBP)***

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

***Woman Not of Childbearing Potential***

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently** sterile (for the purpose of this study)
  - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

**Examples of Contraceptives**

| **EXAMPLES OF CONTRACEPTIVES[a] ALLOWED FOR FEMALE PARTICIPANTS DURING THE STUDY INCLUDE:** |
|---|
| **USER INDEPENDENT**<br>**Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.* |
| • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] |
| • Intrauterine device |
| • Intrauterine hormone-releasing system |
| • Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation) |
| • Azoospermic partner *(vasectomized or due to medical cause)*<br>*(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)* |
| **USER DEPENDENT**<br>**Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.* |
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal<br>– injectable |
| • Progestogen-only hormone contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| • Sexual abstinence<br>*(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)* |
| **NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)** |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. |
| • Male or female condom with or without spermicide[c] |
| • Cap, diaphragm, or sponge with spermicide |
| • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c] |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods) |
| • Withdrawal (coitus-interruptus) |
| • Spermicides alone |
| • Lactational amenorrhea method |

a) Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom must not be used together (due to risk of failure with friction).

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

### 10.6.1. Stopping Algorithm

CCI

### 10.6.2. Follow-up Assessments

#### 10.6.2.1. Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

CCI

[redacted]

CCI

[redacted]

### 10.6.2.2. Phase 2 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

CCI

## 10.7. Appendix 7: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for HBV. At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of HBV DNA. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol.

These eligibility criteria based on HBV test results are also represented in Table 1 below. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

**Table 1: Eligibility Based on Hepatitis B Virus Test Results**

| HEPATITIS B TEST RESULT | | | |
|---|---|---|---|
| **Hepatitis B surface antigen (HBsAg)** | **Hepatitis B surface antibody (anti-HBs)** | **Hepatitis B core antibody (anti-HBc total)** | **STATUS** |
| negative | negative | negative | **Eligible** |
| negative | (+) | negative | |
| negative | (+) | (+) | |
| (+) | negative *or* (+) | negative *or* (+) | **Not eligible** |
| negative | negative | (+) | **Require testing for presence of HBV DNA*** |

*If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of HBV infection is recommended.

## 10.8. Appendix 8: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation or quarantine of participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

If, as a result of the COVID-19 pandemic, visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted, after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the CSR.

**ADDITIONAL ELEMENTS, WHERE APPLICABLE:**

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures (eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration [including training where pertinent])
  - procurement of study intervention by patients (or designee) or shipment of study intervention from the study site directly to patients for at home administration

  - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
  - other procedures may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.
  - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in eCRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

## 10.9. Appendix 9: Criteria for Assessing Potential Cases of Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled (Sampson 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   *AND AT LEAST ONE OF THE FOLLOWING:*

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that participant (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

## 10.10. Appendix 10: Protocol Amendment History

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

### Amendment 2 (30 June 2021)

**Overall Rationale for the Amendment:** To include additional stopping criteria for the study and for individual participants. Additionally, minor updates of a clarifying nature were made throughout the protocol.

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| CCI [redacted] | | |

CCI

[redacted]

## Amendment 1 (19 May 2021)

**Overall Rationale for the Amendment:** C [redacted]
CI
[redacted]

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| CCI [redacted] | | |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| CCI | | |

# 11. REFERENCES

Alamanos Y (2005), Drosos A. Epidemiology of adult rheumatoid arthritis. Autoimmunity Reviews. 2005;4(3):130-136.

Aletaha D (2006), Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheum Dis Clin North Am. 2006;32(1):9-44, vii.

Anderson JK (2011), Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score With 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Cl. Arthritis Care Res. 2011;63(S11):S14–36.

Anquetil F (2015), Clavel C, Offer G, Serre G, Sebbag M. IgM and IgA rheumatoid factors purified from rheumatoid arthritis sera boost the Fc receptor- and complement-dependent effector functions of the disease-specific anti-citrullinated protein autoantibodies. J Immunol. 2015;194(8):3664-3674.

Blumberg LJ (2019), Humphries JE, Jones SD, et al. Blocking FcRn in humans reduces circulating IgG levels and inhibits IgG immune complex–mediated immune responses. Science Advances. 2019;5(12):eaax9586.

Cella D (2002), Lai J, Chang C, et al. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002; 94(2):528-538.

Courvoisier DS (2021), Chatzidionysiou K, Mongin D, et al. The impact of seropositivity on the effectiveness of biologic anti-rheumatic agents: results from a collaboration of 16 registries. Rheumatology. 2021;60(2):820-828.

Felson DT (1993), Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993;36(6):729-740.

Felson DT (1995), Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-735.

Felson DT (1999), LaValley MP, Baldassare AR, et al. The Prosorba column for treatment of refractory rheumatoid arthritis: a randomized, double-blind, sham-controlled trial. Arthritis Rheum. 1999;42(10):2153–2159.

Felson DT (2011), Smolen JS, Wells G, et al. American College of Rheumatology; European League Against Rheumatism. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011;63(3):573-586.

Fries JF (1980), Spitz P, Kraines RG, Holman HR. Measurement of patient outcomes in arthritis. Arthritis Rheum. 1980;23:137-145.

Hawley DJ (1992), Wolfe F. Sensitivity to change in the Health Assessment Questionnaire (HAQ-DI) and other clinical and health status measures in rheumatoid arthritis. Arthritis Care Res. 1992;5(3):130-136.

Howard JF (2019), Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. Neurology. 2019 04;92(23):e2661–2673.

Hubbard JJ (2020), Pyzik M, Rath T, et al. FcRn is a CD32a coreceptor that determines susceptibility to IgG immune complex-driven autoimmunity. J Exp Med. 2020;217(10):e20200359.

Jilani AA (2015), Mackworth-Young CG. The role of citrullinated protein antibodies in predicting erosive disease in rheumatoid arthritis: a systematic literature review and meta-analysis. Int J Rheumatol. 2015;2015:728610.

Kiessling P (2017), Lledo-Garcia R, Watanabe S, et al. The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study. Sci Transl Med. 2017 01;9(414).

Keystone EC (2004), Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004;50(2):353–363.

Kocijan R (2013), Harre U, Schett G. ACPA and bone loss in rheumatoid arthritis. Curr Rheumatol Rep. 2013;15(10):366.

Kosinski M (2000), Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum. 2000;43(7):1478-1487.

Lipsky PE (2000), van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. N Engl J Med. 2000;343(22):1594-1602.

Newland AC (2020), Sánchez-González B, Rejtő L, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. Am J Hematol. 2020;95(2):178–187.

Peter HH (2020), Ochs HD, Cunningham-Rundles C, et al. Targeting FcRn for immunomodulation: Benefits, risks, and practical considerations. J Allergy Clin Immunol. 2020;146(3):479-491.

Pope JE (2009), Khanna D, Norrie D, Ouimet JM. The minimally important difference for the health assessment questionnaire in rheumatoid arthritis clinical practice is smaller than in randomized controlled trials. J Rheumatol. 2009;36(2):254-259.

Prevoo ML (1995), van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44–48.

Quality Metric Inc. (2011) User's Manual for the SF-36v2 Health Survey. 3rd edition;2011: http://www.qualitymetric.com/WhatWeDo/ManualsUserGuides/UsersManusalfortheSF36v2HealthSurvey/tabid/328/Default.aspx.

Rodriguez F (2015), Harrison RW, Wojdyla D, Mahaffey KW. Lost to Follow-up and Withdrawal of Consent in Contemporary Global Cardiovascular Randomized Clinical Trials. Crit Pathways in Cardiol. 2015;14:150-153.

Roth S (2004). Effects of Prosorba column apheresis in patients with chronic refractory rheumatoid arthritis. J Rheumatol. 2004;31(11):2131-2135.

Sampson HA (2006), Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Sieghart D (2018), Platzer A, Studenic P, et al. Determination of autoantibody isotypes increases the sensitivity of serodiagnostics in rheumatoid arthritis. Front Immunol. 2018;9:876.

Smolen JS (2008), Beaulieu A, Rubbert-Roth A, et al, for the OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-997.

Sun M (2019), Rethi B, Krishnamurthy A, et al. Anticitrullinated protein antibodies facilitate migration of synovial tissue-derived fibroblasts. Ann Rheum Dis. 2019;78(12):1621-1631.

van Riel PL (2000), van Gestel AM, Scott DL. EULAR Handbook of Clinical Assessments in Rheumatoid Arthritis. Alphen Aan Den Rijn, The Netherlands: Van Zuiden Communications B.V.; 2000:40.

Weinblatt ME (2003), Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35–45.

Wells GA (1993), Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol. 1993;20(3):557-560.

Yellen SB (1997), Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Sympt Manage. 1997; 13;63-74.

Yount S (2007), Sorensen MV, Cella D, Sengupta N, Grober J, Chartash EK. Adalimumab plus methotrexate or standard therapy is more effective than methotrexate or standard therapies alone in the treatment of fatigue in patients with active, inadequately treated rheumatoid arthritis. Clin Exp Rheum. 2007; 25(6):838-846.

## INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): PPD MD, PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

# Signature

| User | Date | Reason |
|---|---|---|
| PPD | 12-Jan-2022 18:14:42 (GMT) | Document Approval |